TECHNISCHE UNIVERSITÄT MÜNCHEN

Lehrstuhl für Ernährungsphysiologie

Flavone effects on the proteome and transcriptome of colonocytes *in vitro* and *in vivo* and its relevance for cancer prevention and therapy

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Vollständiger Abdruck der von der Fakultät Wissenschaftszentrum Weihenstephan für Ernährung, Landnutzung und Umwelt der Technischen Universität München zur Erlangung des akademischen Grades eines

Doktors der Naturwissenschaften

genehmigten Dissertation.

Vorsitzender:	Univ.-Prof. Dr. D. Haller
Prüfer der Dissertation:	1. Univ.-Prof. Dr. H. Daniel
	2. Univ.-Prof. Dr. U. Wenzel (Justus-Liebig-Universität Giessen)
	3. Prof. Dr. E.C.M. Mariman (Maastricht University, Niederlande) schriftliche Beurteilung

Die Dissertation wurde am 24.08.2009 bei der Technischen Universität München eingereicht und durch die Fakultät Wissenschaftszentrum Weihenstephan für Ernährung, Landnutzung und Umwelt am 25.11.2009 angenommen.

Die Forschung ist immer auf dem Wege,
nie am Ziel.
(Adolf Pichler)

1. Introduction

According to the World Health Organization (WHO) cancer is the second leading cause of death (26.6% in 2005*)* in Germany after cardiovascular diseases (47.4% in 2005), with a predicted increasing incidence. In 2002 there were 424.250 new diagnosed cancer cases in Germany, while 209.576 people died from cancer [1].

According to that high amount of cancer deaths and to the extended spectrum of cancer types, which require different kind of treatments, it is obvious that the efforts in cancer research still have to be broadened. It is assumed that about 40-60% of the all cancer cases could be prevented due to the changing of deleterious habits. Mainly the incidences of bronchial carcinoma could be reduced by quit smoking. Likewise many colon cancer cases could be prevented by avoiding obesity through a healthier living style, for example by training and a diet containing more vegetarian food [2-7].

Apart from the manifold prevention possibilities concerning different cancer types, which should be tapped to full potential, the research is focusing on the development of new treatment methods for present cancer cases, currently consisting of using chemotherapy following the surgery. The main problems using chemotherapy are the general toxic effects on all tissues, even on the non-carcinogenic ones. Therefore the normal tissue is stressed by the need of regenerating very fast, which gives rise to possible new mutations in the fast growing cells, and creating a new cancer cell. There are many attempts to create or find substances, which are able to destroy the cancer cells significantly, without harming the surrounding non-cancerous cells.

Many studies show the protective effects of nutritional substances derived from edible plants, where protection against arteriosclerosis, inflammation and cancer can be demonstrated, respectively [8-10]. Recently, Newsweek announced “a new miracle drug” against cancer, which lead to apoptosis in cancer cells and was effective against lung cancer in animal studies with rats [11, 12]. But the substance dichloroacetate (DCA) was still in an early testing phase, showing its positive impacts solely in cell culture and animal studies. However, a controlled clinical trial with DCA had to be terminated due to unanticipated toxic effects on the peripheral nervous system [13]. On that account it is very interesting that epidemiological studies show that flavonoids, occurring ubiquitously in edible plants, play a major role in the effects of human health [14-16].

1.1. Cancer and carcinogenesis

Cancer describes an unimpeded and abnormal proliferation of cells arising from genetical disorders. The genome of a cancer cell is degenerated and somatically inherited by the daughter cells. Tumors are monoclonal, which means that they derive from one single neoplastic degenerated cell. Cancer comprises a group of more than 100 diseases that can affect any part of the body and occurs because of changes of the genes responsible for cell growth and repair [17-19]. These changes are the result of the interaction between internal factors (e.g. genetic host factors, hormones, digestion of nutrients) and external factors, which can be categorized as:

- physical carcinogens (ultraviolet (UV) and ionizing radiation)
- chemical carcinogens (tobacco smoke, asbestos, exhaust fumes)
- biological carcinogens (infections by virus (Hepatitis B Virus, Human Papilloma Virus), by bacteria (Helicobacter pylori) or parasites (schistosomiasis), and contamination of food by mycotoxins (aflatoxins))

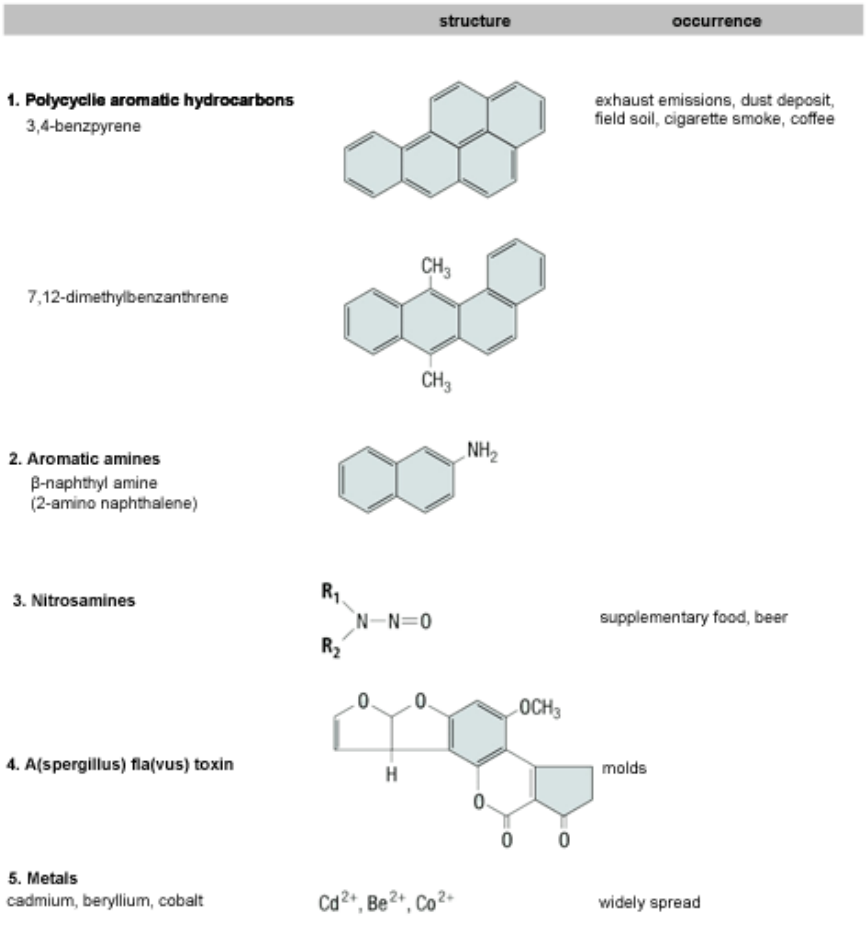

Figure 1: Chemical cancerogens occurring in nature (according to [19])

The transformation from a normal cell into a tumor cell is a multistage process, typically a progression from a pre-cancerous lesion to malignant tumors [20], when the accumulation of mutations in certain tumor suppressor genes and proto-oncogenes reaches a critical amount leading to cancer initiation [21]. The multistage theory of cancer, established in the 1950s, helps to explain the time lapse (sometimes several decades) between exposure to carcinogenic substances and the development of a tumor. Beneath the inherited genetic and the external factors mentioned above, the development of cancer is also initiated by ageing. The incidence of cancer rises dramatically with age, most likely due to risk accumulation over the life course combined with the tendency for cellular repair mechanisms to be less effective as a person grows older [22, 23].

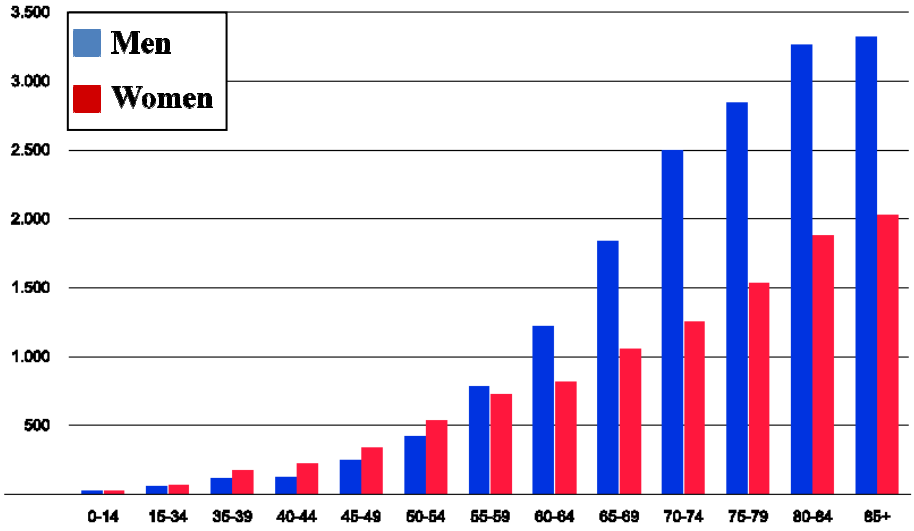

Figure 2: Age-specific estimation of the incidence of cancer in Germany in 2002

New cancer cases per 100000 showed in age cohorts (according to [24]).

After initiation, progression and proliferation, the tumor progression is followed by invasion in adjacent tissue and metastasis. A characteristic feature of cancer is the rapid creation of abnormal cells which grow beyond their usual boundaries, and which can invade adjoining parts of the body and spread to other organs, a process referred to as metastasis. Metastases are the major cause of death from cancer [25, 26].

1.2. Colorectal Cancer

Colorectal cancer is the second leading cause of cancer deaths in Germany as well as in whole Europe, in men and women, respectively [7, 24, 27]. The following figures show the percental distribution of new cancer cases and cancer deaths according to different types of cancer in Germany in 2002.

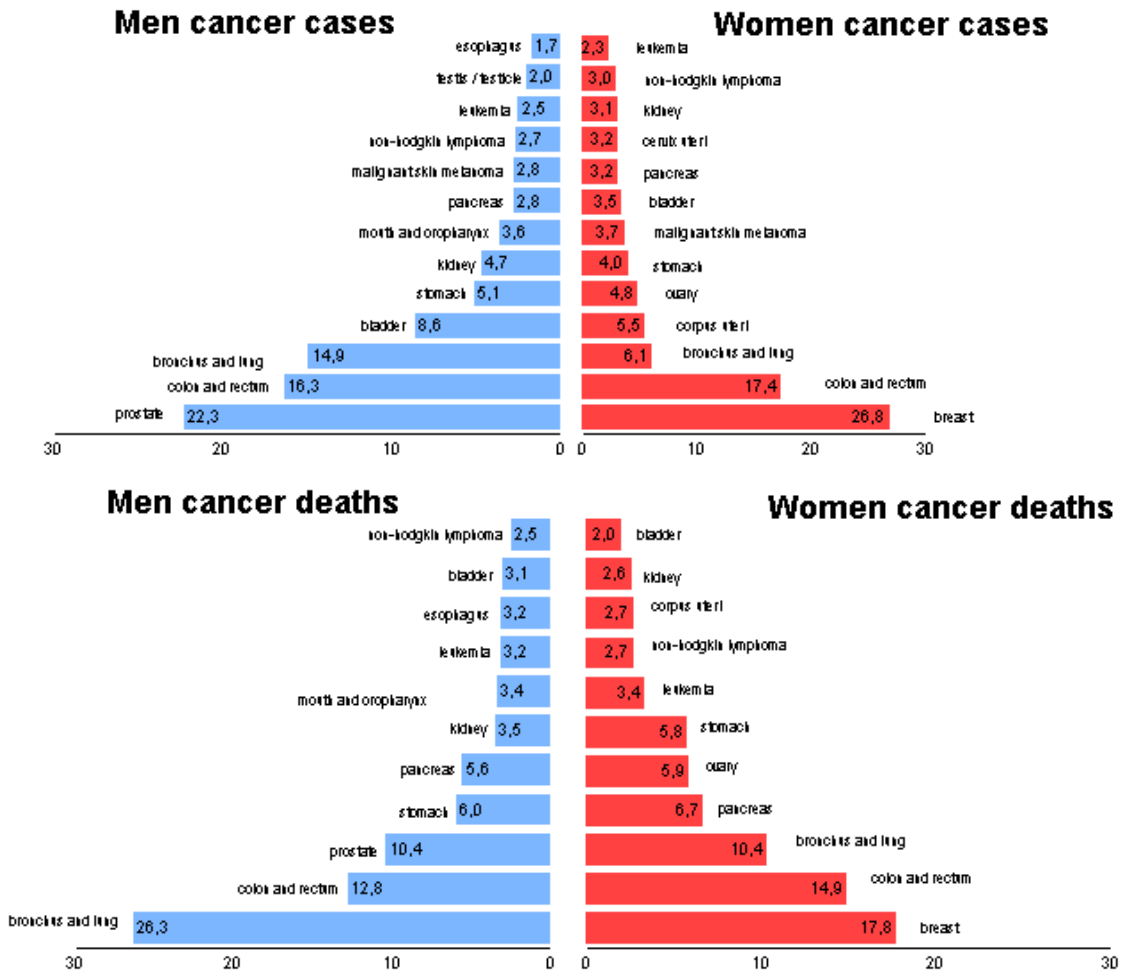

Figure 3: Cancer cases and deaths in Germany in 2002

Percentage of estimated new cancer cases in Germany in 2002 and percentage of cancer-related deaths in Germany in 2002 (according to [24]).

Colorectal cancer (CRC) is a term used to refer to cancerous growths starting in the rectum, colon or appendix. Most of the CRCs arise from adenomatous polyps, according to the current standard of knowledge, starting as non-cancerous, benign polyps, which develop on the lining of the colon or rectum [28-30]. Only 10-15% of these cancers are hereditary, the main part is of sporadic origin [31, 32].

1.2.1. Hereditary forms of CRC

If a genetical disposition exists, where abnormalities in the germline are present by birth, the relative risk to come down with CRC is increased. People suffering from chronic ulcerative diseases in the hindgut, like Colitis Ulcerosa, are also at higher risks of developing CRC. The most frequent hereditary CRC forms are the familial adenomatous polyposis (FAP) and the hereditary nonpolyposis colorectal carcinoma (HNPCC).

FAP is inherited in an autosomal dominant manner, when a deletion or mutation of the tumor suppressor gene APC has taken place on the chromosome 5q 21 or 22. Germline mutation of the APC gene and subsequent somatic mutation of the second APC allele causes this syndrome. If the MUTYH gene is involved the inheritance is autosomal recessive. This kind of hereditary CRC type represents only 1% of diagnosed CRC cases. From early adolescence and onwards, patients will develop hundreds of adenomatous polyps, mainly in the epithelium of the large intestine, which start out benign, but without treatment the probability that one of these numerous polyps will transform into a malignant form is increasing. Without prevention methods, like removal of polyps (polypectomy) or resection of the mainly affected parts of the colon (colectomy), the patients will surely develop malignant tumors from the age of 40 years on. After a partial colectomy the colonoscopic surveillance of the remaining colon is essential, because the patient still is at high risk of developing CRC. A total colectomy is indicated when the occurrence of polyps is exceeding a hundred exemplars or multiple polyps bigger than 1 cm are present. [19, 33-36]

HNPCC is an autosomal dominant inheritable disease and also known as Lynch syndrome. It is characterized by an increased risk of developing colorectal cancer (Lynch syndrome I) or other cancers of the gastrointestinal or reproductive system (Lynch syndrome II). HNPCC is associated with mutations of genes involved in the DNA mismatch repair pathway and patients bear about an 80% lifetime risk of colon cancer, while approximately 66% of them will occur in the proximal colon. HNPCC is accountable for about 5-15% of all diagnosed colon cancer cases. [19, 36-38]

1.2.2. Sporadic forms of CRC

Sporadic colorectal tumors evolve from the accumulation of multiple somatic mutations in genes, particularly in proto-oncogenes and tumor suppressor genes, playing a role in cell cycle control, differentiation or apoptosis. Gene products of suppressor genes defend cells from malignancy by driving them into apoptosis when the cells are severely damaged, which would lead to undamped growth, and therefore negatively regulate the cell proliferation. Demonstrated molecular genetic abnormalities in CRC involve the tumor suppressor genes APC, MCC, DCC and p53, as well as the oncogenes ras, src and myc [39]. The principal tumor suppressor genes, being involved in colorectal carcinogenesis, will be described in more detail, after showing the multistep theory of that disease.

1.2.3. Genetical conditions for CRC development

According to Fearon and Vogelstein the **multistep process** from the normal colonic epithelium towards the carcinoma in colon carcinogenesis can be described as follows. After the loss of function of the APC (and perhaps MCC) gene the colonic epithelium reaches a hyperproliferative state. Hypomethylations (altered DNA methylation) lead to early, tubular adenomas with genomic instability [40]. The chromosome condensation is impeded and after ras and DCC mutations the adenomas become tubuvillous and villous, potentially accompanied by activated oncogenes like c-myc or c-myb. Loss of activity of the p53 tumor suppressor gene leads to selective growth advantages of the affected cell, which can result in ongoing and undamped mutations of other genes. The accumulation of the genetical modifications will result in the progression from adenoma to carcinoma [19, 41].

Fearon and Vogelstein also state, that even if there are characteristic phases of tumor progression, the most important step in colorectal tumor development is the progressive accumulation of mutations and chromosome deletions, rather than their order of occurrence.

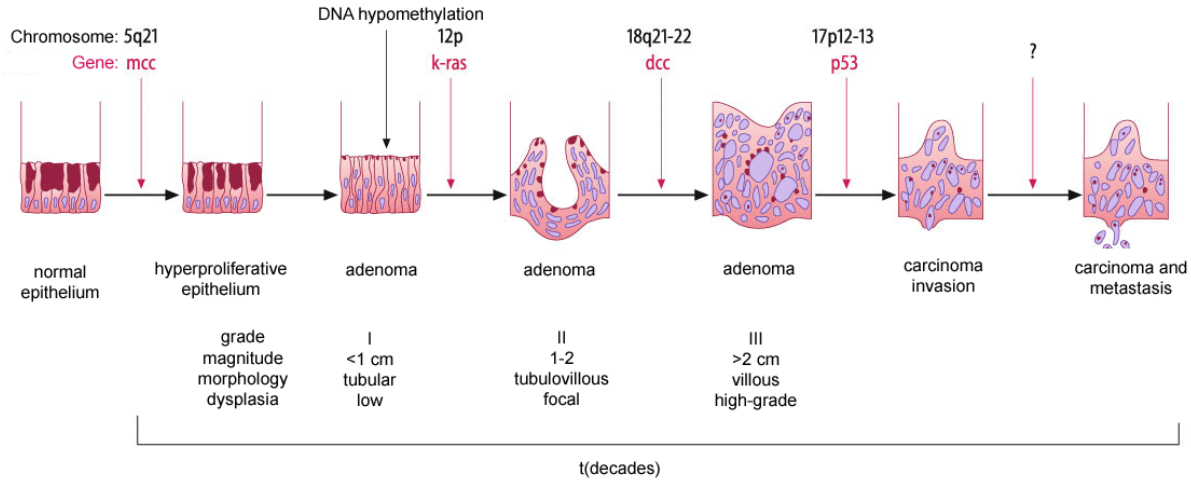

Figure 4: Multistep process in colorectal cancer

Genetical modifications during the progression of the colonic adenoma towards carcinoma (model according to [19]).

Mutations of the **APC** (Adenopolyposis coli) tumor suppressor gene were initially identified to be responsible for FAP. Subsequently, the APC gene was also found to be mutated in about 60-80% of the sporadic CRC cases, obviously playing a major role in the early stages of tumor initiation [42-44]. The functioning APC gene codes for a cytoplasmic multifunctional protein, which binds at cellular transcription factors and the protein beta-catenin. The mutated form is not able anymore to bind at beta-catenin and thereby regulate its

activity. Elevated levels of stabilized beta-catenin, being a component of the Wnt signaling pathway, translocate to the nucleus to interact with transcription factors, resulting in an augmented transcription of various genes (C-myc, COX-2, Cyclin D1, vascular endothelial growth factor, T cell factor, etc.) involved in tumorigenesis [45, 46].

The **MCC** (mutated in colorectal cancer) gene is closely located to the APC gene on the chromosome 5q21. Within the tumors of sporadic colorectal cancer patients both of the genes were found to be somatically altered by point mutation, deletion or insertion, respectively [47-49]. According to the Bioinformatics Harvester this gene is supposed to negatively regulate cell cycle progression. The orthologous gene in the mouse expresses a phosphoprotein associated with the plasma membrane and membrane organelles, while overexpression of the mouse protein is able to inhibit the entry into the S-phase.

The **DCC** (deleted in colorectal cancer) gene is located on the 18q21 chromosome and encodes a 170- to 190-kDa protein, which belongs to the Immunoglobulin superfamily. It is implicated as a tumor suppressor gene [50, 51] and acts as a dependence receptor required for apoptosis induction when not associated with netrin ligand [52].

P53 plays a role in the late phase of carcinogenesis, because deletions or mutations of the gene are considerably more often detected in carcinomas than in adenomas [53]. The gene encodes for a 53 kDa nuclear phosphoprotein, which binds to specific DNA sequences to regulate cell proliferation and apoptosis, and is functionally inactivated in over 50% of human cancers [18]. Therefore p53, located on the chromosome 17p is a tumor suppressor and its inactivation is associated with a poor prognosis for (colon) cancer patients [54, 55]. It can act as transcription factor for pro-apoptotic genes like APAF-1, p21Cip/WAF, Bax, PUMA, NOXA, p53-AIP1, 14-3-3, Gadd45 or IGF-BP3, and shows repressor activity towards Bcl-2, cyclin B or Cdc-2, respectively [56-59]. Besides its function as a transcription factor, p53 shows also exonuclease activity during DNA reparation [60, 61]. On account of its essential role in the regulation of the cell cycle, inducing growth arrest or apoptosis, and therefore acting as a tumor suppressor, P53 is entitled as the guardian of the genome [62, 63].

About 50% of the sporadic CRC cases develop mutations in the **K-ras** oncogene [64-67]. Its product, a 21 kDa GTPase, is a protein for signal transduction, activated by complex formation with GTP and deactivated by hydrolysis. Ras proteins are able to regulate proliferation and differentiation in mammalian cells [19, 68, 69]. The mutation alleviates the sensitivity of the protein for hydrolysis through inhibiting the binding of the GAP protein (GTPase activating protein), which precludes the inactivation of Ras [19, 69]. The hyperactive protein induces cell proliferation and inhibits the cytochrome-c generated

apoptosis by phosphorylating caspase 9, which suppresses the apoptosome formation [70]. The following table shows the discussed genes and supplementary ones, which are involved in colon carcinogenesis.

Table 1: Genes associated with colorectal Cancer (according to [17, 71])

Genes associated with CRC			
Gene	Gene description	Locus	Function
Oncogenes			
K-ras	Kirsten rat sarcoma virus	12p12.1	signal transduction, GTP binding
H-ras	Harvey rat sarcoma viral oncogene	11p15.5	signal transduction, nucleotide binding
c-myc	Myelocytomatosis virus	8q24ter	DNA replication/replicating factor
c-src	Rous sarcoma virus	20q13	protein kinase
Tumor suppressor genes			
APC	Adenopolyposis coli	5q21-22	signal transduction
MCC	Mutated in colon carcinoma	5q21-22	signal transduction
DCC	Deleted in colon carcinoma	18q21.3	cell adhesion, apoptosis induction
p53	Cellular tumor antigen p53	17p13.1	transcription factor, apoptosis, cell cycle checkpoint
TGF beta	Transforming growth factor	19q13.1-2	cytokine
Mismatch repair genes			
hMSH2	MutS homolog 2	2p21-22	DNA binding and repair
hMLH1	MutL protein homolog 1	3p21.3	DNA binding and repair
hPMS1	Postmeiotic segregation increased 1	2q31-33	DNA binding and repair
hPMS2	Postmeiotic segregation increased 2	7p22.2	DNA binding and repair

Some of the genes, mentioned in the table above, play a prominent role in apoptosis induction. And as the evasion from apoptosis is a hallmark of cancer [18], the importance of identifying anti-apoptotic survival pathways is obvious.

1.3. Apoptosis

The maintenance of tissue homeostasis and repair is disturbed by cancerous growth because of the imbalance between cell proliferation, cell differentiation and apoptosis.

Apoptosis describes a type of programmed cell death involving a biochemical cascade including caspases (**c**ysteine containing **asp**artate-specific prote**ase**) and proteins such as Bcl-2, Bax, Apaf-1 or apoptotic protease activating factor-1, as well as proteins involved in the digestion of proteins or the degradation of DNA. This program is activated when cells are no longer needed within an organism or when they become a threat to its health. Therefore

apoptosis describes an inherent part of biological processes like embryonic development, differentiation, tissue homeostasis and the defense against pathogens. It is a normal cellular process and essential for the proper development and maintenance of an organism, while its deregulation, both increase and decrease, plays a role in many diseases [72, 73]. Approximately 50 to 70 billion cells die each day due to apoptosis in an average human adult. The detailed description of the morphological changes associated with apoptosis was first published by Kerr et. al. in 1972 [74]. In contrast to the process called necrosis, the cells are shrinking instead of swelling and they do not induce inflammatory processes. The morphological changes include chromatin condensation with nucleus shrinkage, nuclear and chromosomal DNA fragmentation and formation of membrane-bound apoptotic bodies, which can be phagocytosed by adjacent cells and degraded within lysosomal vacuoles. The decision of a cell to undergo apoptosis depends upon the balance between positive signals keeping the cell alive (e.g. growth factors and interleukins such as IL-2) and negative signals that call for cellular suicide. The latter can be represented by oxidative stress, DNA damage, improper protein folding, as well as by specific molecules like tumor necrosis factor alpha or beta, the FAS ligand binding to the Fas receptor, or CD95, respectively. The mechanisms of apoptosis can be initiated by an extrinsic pathway through ligands interacting with surface-exposed death receptors (FAS, TNFR, TRAIL-RI/II), or by an intrinsic one that comprises central death machinery located at mitochondria (triggered by cellular stressors) or endoplasmatic reticulum (unfolded protein response-UPR or Ca^{++} signaling) [17, 19, 71, 75-80].

1.4. Treatment of cancer

Colorectal cancer (CRC) is mostly curable if diagnosed at an early stage and thus identification of a possible predisposition to the disease and optimization of prevention methods are very important. The mainly used treatment methods concerning cancer in general are surgery, chemotherapy, radiation therapy, immunotherapy and monoclonal antibody therapy. The elimination of the cancerous tissue without damaging the rest of the body is the aim of the treatment.

Studies show that adjuvant chemotherapy of CRC patients after surgery, for example with fluorouracil, can lead to an increase in the overall survival after 5 years [81, 82]. But the problems emerging by using chemotherapy are the direct cytotoxic effects affecting the whole tissue, and negative indirect effects on the body, which are mediated through the immune system. Modern drugs should be able to stimulate the immune system and perhaps operate

already in low dose ranges, which could contribute to lower the adverse reactions by the cytotoxic effects on the surrounding tissue.

Immune stimulation or immunochemotherapy seem to improve the survival rates and the disease-free survival of CRC patients [83]. Recent success using targeted therapeutics shows the importance of the investigations made in the therapeutical research field. Good results were achieved in metastatic CRC treatment by using monoclonal antibodies against vascular endothelial growth factor (bevacizumab) or the epidermal growth factor receptor (cetuxmab) [84]. Also combinations of the treatment methods show promising results [85].

One of the best methods would be the prevention of cancer, which could be supported by healthy diets containing secondary plant metabolites, like flavonoids for example. Alternative methods, using flavonoids as therapeutical substances or adjuvants, have to be validated.

1.5. Flavonoids

Flavonoids are secondary plant metabolites belonging to the class of polyphenols. More than 6500 of these substances have been detected and are known by structure until now, and it is speculated that their number may exceed 8000 [86-88]. They are classified into 6 subclasses: flavones, flavonols, flavanones, flavanols (catechins), anthocyanidins and the isoflavones.

1.5.1. Structure of flavonoids

Flavonoids share a common structure consisting of two aromatic rings (A and B), which are bound together by three carbon atoms forming an oxygenated heterocycle (ring C). This results in a typical C_6-C_3-C_6 flavan backbone.

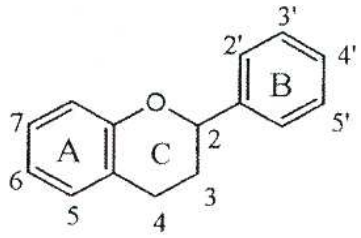

Figure 5: The generic structure of flavonoids (according to Liu [89])

Oxidative decarboxylation of pyruvate towards the activated acetyl-CoA represents the very first step in flavonoid biosynthesis. Acetyl-CoA itself serves on the one hand to form malonyl-CoA, and on the other hand to build up the phenylalanine through the shikimate

pathway. During the phenylpropanoid metabolic pathway the amino acid phenylalanine is used to form 4-coumaroyl-CoA. Three activated molecules malonyl-CoA and a 4-coumaroyl-CoA molecule are used for the generation of chalcone, representing the precursor of all flavonoids and containing two phenyl rings [90]. The metabolic pathway continues through a series of enzymatic modifications to yield flavanones, flavanonols and anthocyanins. Along this pathway, many products can be formed, including the flavonols, flavanols (flavan-3-ols), proanthocyanidins (tannins) and many other polyphenolics. The different subclasses of the flavonoids are distinguished by the oxidation state of their C-ring, while their representatives vary on account of number and arrangement of their substituent distribution of alkyl and hydroxyl groups, as well as of their sugar groups. The cytochrome P450 2-hydroxy-isoflavanone synthase (IFS) catalyzes the hydroxylation associated with aryl migration of flavanone to form the isoflavonoid skeleton. The aromatic B-ring of the isoflavonoids is bound to position C_3, in contrast to the other flavonoids at C_2 [17, 91-93].

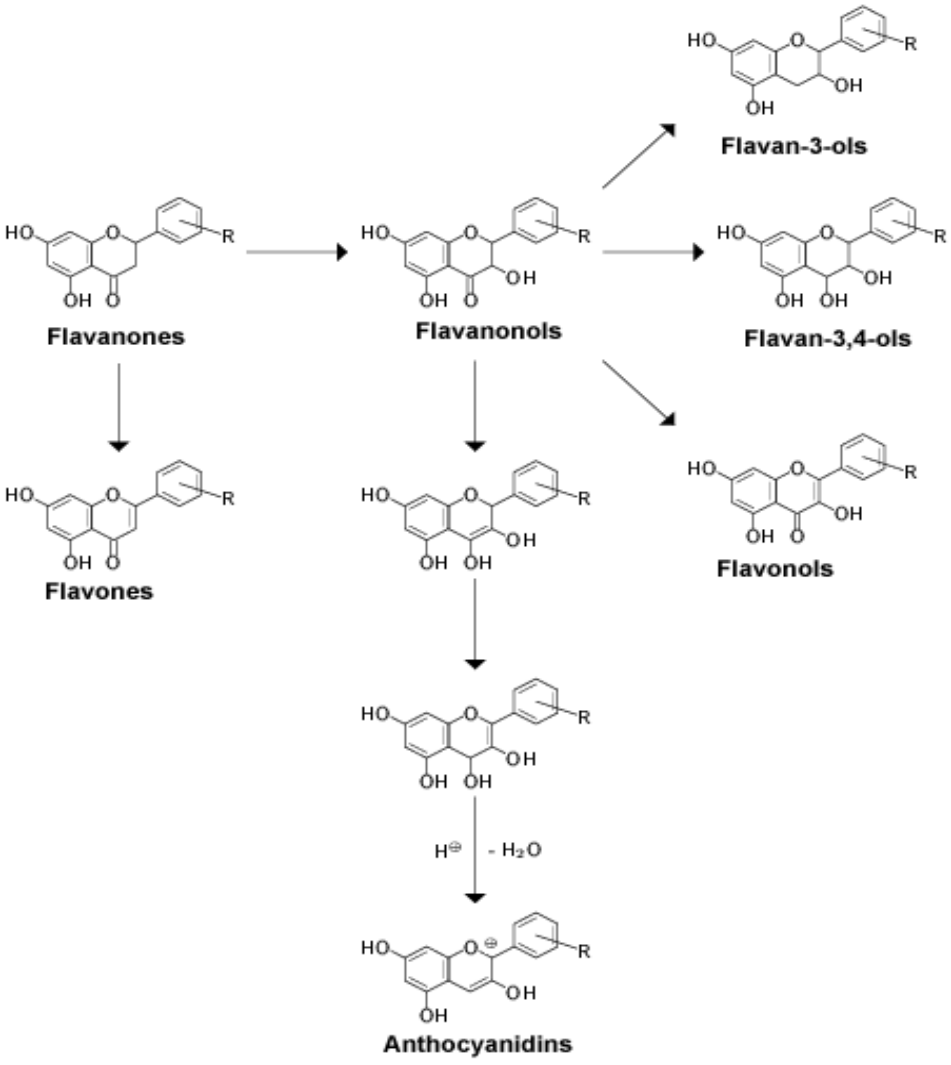

Figure 6: Chemical structures of the most common flavonoid subclasses

1.5.2. Sources of flavonoids

Flavonoids are nearly ubiquitous in plants, representing the most common secondary plant metabolites in angiosperms, and they are primarily recognized through their coloring of the flowers, leaves and other aerial parts of plants. The flavonoid content in different plant species varies enormously [94], even within one plant species, being influenced by internal and external factors. The internal factors are represented by the genetic constitution and the ripeness of edible parts of the plant at harvesting, while external factors can be determined by the cultivation technique (conventional or ecological), fertilization or the climate during the period of growth, for example [95].

Flavanones are characteristic for citrus fruits [96, 97], while flavones can be mostly found in umbelliferous plants [98]. Higher amounts of isoflavones can be detected in legumes, like soy beans for example [99, 100]. Flavanols are mostly found in tea, red wine and fruits [94, 101] and anthocyanidins in stone and soft fruits [102].

Table 2: Representatives of flavonoid subclasses and their sources/occurrences (according to [95])

Flavonoid subclass	Flavonoid	Source
flavones	luteolin	celery stalks, sweet pepper, sage
	apigenin	celery stalks, parsley, mint
flavonols	quercetin	blueberries, raspberries, dill, shallots
	kaempferol	raisins, tea, onions
	myricetin	cranberries, wine, broad beans
flavanones	hesperetin	grapefruit, orange
	naringenin	lemon, lime
flavanols (catechins)	catechin	chocolate, wine, plums, apricots
	epicatechin	tea, wine, grapes, apple
	epigallocatechin	tea, wine, cherries
anthocyanidins	cyanidin	cherries, elderberries, blackcurrants
	pelargonidin	strawberries, raspberries
	malvidin	bilberries, blueberries, grapes
isoflavones	daidzein	soy beans
	genistein	soy beans

Most of the flavonoids found in edible plants, like fruits (grape, plums, different soft fruits) or vegetables (curly kake, aubergine, onions), herbs, tea or cocoa, are found predominantly as glycosides, with the exception of the flavanols (catechins) [93]. The glycosylated form favors the solubility of the flavonoids within the plant and protects them from light and enzymatic degradation [103, 104].

1.5.3. Flavonoid functions in plants

Flavonoids do not only affect the color of the plants but they are essential for diverse defense and protection mechanisms, for reproduction and early plant development and they play a role as chemical messengers.

The potential of flavonoids showing defending properties against pathogenic microbes and fungi is shown in different studies [105-108]. The antimicrobial effects of 3-deoxyflavonoid controlling fire blight, a ruinous bacterial disease in pome fruits, which already caused severe economic losses worldwide, are very promising for example [109]. The utilization of these chemical defenders within the plants can be grouped into different modes of action, like constitutive flavonoids [110] and inducible flavonoids [105, 111, 112]. Flavonoids in plants can be seen as biological stress metabolites, inducible by wounding or biological attack, insect and mammalian herbivory or parasitic plants [113, 114]. UV radiation or oxidative stress is also able to induce flavonoid production in plants [115, 116]. The presence of anthocyanins in plants is often a stress response against biotic and abiotic stressors, like temperature extremes, heavy metals or water stress [87, 117-121].

Aside from their defense and protection mechanisms flavonoids can also serve as attractants for pollination and seed dispersal. To attract pollinating insects or birds, the pigmentation can contribute to the flower color, or an UV-absorbing zone in the center of a flower can serve as nectar guide for insects [122, 123]. As chemoattractants for nitrogen-fixing bacteria they are able to enhance the legume nodulation through their capability to induce the nodulation genes of symbiotic Rhizobium bacteria [124]. As the capacity for nitrogen fixation through nodulating bacteria is limited to relatively few plant species, flavonoids are also able to stimulate the arbuscular mycorrhizal fungi associations with roots, occurring in about 80% of plant species [125-127]. Some flavonoids are used as allelopathic agents by influencing growth and development of neighboring plants [128-131].

1.5.4. Flavonoids as dietary components and their proposed impacts on health

Hundreds of substances of different classes have been tested already in various systems to assess if they could have positive effects concerning various diseases in mankind. Epidemiological studies and associated meta-analyses lead to the assumption that a long-term consumption of diets rich in fruits and vegetables is able to protect against chronic diseases, especially cancer [132-134]. Apart from the studies showing negative effects after dietary intake, flavonoids are considered as dietary substances with health beneficial effects, like antioxidative, anti-inflammatory, anticarcinogenic, cardiopreventive, antimicrobial, antiviral, anti-asthmatic, anti-allergen, immune system stimulating and neuro-protective activities [135-142].

Cell culture studies Besides the antiproliferative effects of many flavonoids shown in several cancer cell lines, some studies were able to outline their mechanisms of action, like reactions with DNA bases, intercalation in DNA, inhibition of topoisomerases, inhibition of protein kinases, induction of apoptosis or cell cycle arrest by covalent binding to/modulation of enzymes of biological importance [143-150]. Green tea catechines, for example, are discussed to have cancer preventive potential. They are able to protect keratinocytes against the oxidative cellular and genotoxic damage of UVA radiation and may act as chemical chaperones [151-153].

Animal studies In several studies flavonoid consumption was inversely related to risk factors and the formation of preneoplastic lesions, adenomas or tumors, chemically or genetically induced, respectively [154-157]. Animal studies with isoflavone administration from soybeans showed cancer and cardiac protective, as well as antiatherogenic effects [158].

Studies in human beings Epidemiological studies concerning the effects of flavonoids towards cancer prevention are contradictory. Some studies could not find any association between the consumption of secondary plant metabolites and the risk of cancer, while other studies showed a lower incidence of cancer in people consuming diets rich in edible plants [98, 134, 156, 159-163]. For instance, some studies reveal that higher isoflavone intake through soy products is inversely related to cancer incidences of several cancer types, like breast, prostate and colon, as well as to inflammation-mediated chronic diseases [158, 164-167].

In the beginnings of this field of research the radical scavenging and radical suppressing capacities of the substances found in edible plants were the main focus, but besides their antioxidative capability, many different types of experimental and observational studies showed, that quite different mechanisms of action can lead to the protective effects of these

substances [168]. Within the flavonoid subclasses different laboratory investigations demonstrate their interaction potential concerning various enzyme systems, transport proteins, cell adhesion or heat shock proteins, as well as their capability to simulate hormones or neurotransmitters, or their impacts on gene expression [15, 16, 169-171].

Estimations of flavonoid intake on a population level led to enormous variations. The mostly cited reference concerning average daily intake of polyphenols is the data set published more than three decades ago by Kühnau et al [172]. Here it was estimated that the average daily polyphenol intake by U.S. citizens is about 1 g per day, also noted by Middleton [173], while Havsteen [170] estimated an average dietary flavonoid intake of 1-2 g per day. Scalbert et al [94] showed that it would be possible to reach 1 g of daily polyphenol intake by calculating the contents in foodstuffs and beverages, which could be consumed during one day. In this estimation flavonoids account for approximately two thirds of the total polyphenols, and phenolic acids account for one third. However, the authors clearly point out, that the evaluation of polyphenol dietary intake still lacks precision, and that it depends to a large extent on the different cultural or individual dietary habits and preferences, respectively. For instance, other authors are suggesting much lower average flavonoid intake, like Hertog et al [174] with 25.9 mg/day in the Zutphen Elderly Study, which was carried out with 805 men, and like de Vries [175] reporting a lowest daily flavonoid intake of 3.6 mg and a highest of 77 mg.

There is obviously an immense variability in the dietary uptake of these substances depending on the prevalent food source of an individual or an epidemiological group. Quercetin, for example, is the most common flavonol in the diet and the significance of different foods as quercetin sources varies amongst countries. Flavonol intakes were calculated by Hertog et al [160] from the Seven Countries Study, which was started in the late 1950s, and they reported that tea was the major source of quercetin in the Netherlands and in Japan. Onions and apples were the predominant sources in the United States, Finland and Greece, while red wine contributed most in Italy. The following table shows reported dietary sources and intakes of flavonoids in different countries according to Aherne et al [103]. But it has to be mentioned that the values shown here are mostly based on the main flavonols (quercetin, myricetin, kaempferol) and flavones (apigenin, luteolin), and not on the total flavonoid content.

Table 3: Dietary flavonoid intake and their main sources in different countries (according to Aherne et al [103])

Reported dietary sources and intakes of flavonoids		
country	dietary intake [mg/day]	main dietary sources
Denmark	26	tea, onions, apples
Finland	0-41; 3-10	apples, onions; fruit and vegetables
Greece	15	fruit and vegetables
Italy	23-34; 35	red wine; fruit, vegetable soups
Japan	60-68	green tea
The Netherlands	33	tea, onions, apples
United States	20	onions, black tea

Apart from the great variability in the dietary uptake of flavonoids, it is essential to elucidate their bioavailability, which can be altered by different factors.

1.6. Proteomics in nutritional sciences and cancer research

The term ***Proteome*** was created at the 2D-Gelelectrophoresis conference in Siena during the year 1994 by Marc Wilkins [176], and describes the whole **prote**in pattern expressed by the gen**ome** at a special time point. In contrary to the genome, the proteome is not a continuum, but it varies within different cell types or tissues and underlies the influence towards exogenic factors (e.g. stress, disease, temperature, pharmaceuticals). Proteins may be synthesized de novo, catabolized, or activated and deactivated by posttranslational modification, respectively.

The mostly used proteomic technologies are the two-dimensional polyacrylamide gel electrophoresis (2D-PAGE) for protein separation [177-179] followed by matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) for protein identification [180, 181]. By the use of this technique complex protein mixtures can be separated within two steps. In the first dimension, called isoelectric focusing (IEF), the proteins are separated according to their isoelectric points (pI). The second dimension is a SDS-polyacrylamide gel-electrophoresis (SDS-PAGE), where the proteins are separated according to their molecular mass (Mr). The proteins can be visualized through different staining methods (Coomassie, silver, DIGE/fluorescence) and each originated protein spot on the gel represents at least one special protein. The reproducibility and resolution was enhanced through the development of immobilized gel strips and pH gradients [182].

Identification of the protein spots is very often done with MALDI-TOF mass spectrometry via peptide mass fingerprint (PMF). Protein degradation by residue-specific cleavage into peptides is performed mainly enzymatically. The peptide masses can be acquired and afterwards matched against theoretical peptide libraries generated from the proteins as deposited in protein sequence databases. Due to the increasing demand for high-throughput proteome analysis, automated mass analysis and protein identification tools are already available [183-185].

The proteomic approach is a very promising tool for the identification of biomarkers. The possibility to display special proteins in tissues and in the better understanding of molecular pathways could lead to early disease detection, and therefore towards increasing the survival chance of people affected by CRC dramatically.

2. Aims of this study

Cancer incidences and cancer deaths will most likely increase within the next years. Dietary habits are supposed to play an essential role in the majority of the increasing incidences of CRC cases, and secondary plant metabolites, like flavonoids for example, have clearly shown their chemopreventive effects.

Concerning putative cancer prevention activities of flavonoids, different modes of action are known, like anti-oxidative activities, induction of apoptosis or the promotion of antiproliferative effects, respectively. To ascertain the molecular mechanisms involved in the selective apoptosis induction of the flavonoid flavone in cancer cells, *in vitro* experiments were carried out with HT-29 human colorectal cancer cells. To study the differences and possible similarities in their modes of action, a parallel study was done with the classical anti-tumor drug camptothecin. This chemotherapeutical agent is a topoisomerase inhibitor and leads to apoptosis in the cancer cells. For revealing the mechanisms of the different effectors, the proteome of the treated cells was analyzed via 2D-PAGE followed by MALDI-TOF mass spectrometry to exhibit the differentially expressed proteins. Preliminary studies revealed that flavone is a potent apoptosis inducer in HT-29 cells *in vitro* whereas non-transformed colonocytes remained unaffected by this flavonoid. It was also shown that flavone is able to increase the uptake of monocarboxylates into mitochondria, followed by their oxidation. The so-called Warburg effect, describing aerobic glycolysis, is overcome by flavone in tumor cells and the increased delivery of energy substrates to the respiratory chain in turn increases the production of reactive oxygen species in mitochondria that promotes a very efficient route of apoptosis induction.

In many animal studies flavonoids proved to have protective effects when colon tumors were induced chemically, and in cell culture the flavonoid flavone was able to drive transformed cells into apoptosis while not affecting non-transformed ones. To take these studies further, we investigated whether flavone ingestion was able to prevent and/or reduce carcinogen-induced preneoplastic lesions and microadenomas *in vivo*. To gain more insight into the mechanisms underlying potential anti-cancer activities *in vivo* a proteomic study of the intestinal tissue from DMH-treated C57BL/6J mice was conducted, and additionally transcriptomic and histological analyses were performed. These studies were realized with three different treatment groups representing different stages in carcinogenesis (blocking, suppressing, and therapy group).

3. Materials and Methods

3.1. Cell culture

The human colon cancer cell line HT-29 was obtained from the American Type Culture Collection (ATCC, Rockville, Maryland, USA) and passages 156-158 were used for the experiments. Cell culture handling was generally performed under sterile conditions. The cells were cultured at 37°C in a humidified atmosphere with 5% CO_2 in 25 cm^2 or 75 cm^2 culture flasks. This cell line represents the first human colon cancer cell line and was isolated by J. Fogh out of a primary tumor in 1964 [186]. The cells are able to grow in monolayers and do not differentiate in standard medium.

3.1.1. Cultivation of the cell line HT-29

The RPMI 1640 standard medium was supplemented with 10% heat-inactivated fetal bovine serum albumin, 2.5 mM HEPES, 100 U/ml penicillin and 100 µg/ml streptomycin. Cells were subcultivated at 80-90% confluence. They were washed with PBS and incubated in trypsin/EDTA buffer (0.05% w/v trypsin and 0.5 mM EDTA in PBS buffer, pH 7.4) at 37°C until they detached from the ground. The digestion process was stopped with culture medium and used in aliquots for further passages. The cell density was acquired by using a Neubauer counting cell chamber.

3.1.2. Experimental Treatment and harvesting of HT-29

The treatment of the cells with different testing substances was performed at 70% confluence for 24 hours each. The different substances were dissolved in DMSO while its total concentration did not exceed 1.5% in the medium. There were two different substances in use for the experiments. The flavonoid flavone and the topoisomerase-inhibitor camptothecin were applied in different end concentrations, which were determined in earlier experiments avoiding cytotoxic impacts on the cells. Therefore flavone was added at concentrations of 150 µM and camptothecin with 50 µM, while the associated controls solely received 1.5% DMSO without compounds. The fractionated cellular compartment analyses were accomplished only from cells treated with flavone. The two different preparation methods for the cell culture experiments are described in chapter 3.3.1.

3.2. Animals

The laboratory animals are represented by female C57BL/6J mice purchased from Harlan Winkelmann at 4 weeks of age. We used female mice due to the description that ACF are reliably inducible by 1,2-DMH in female mice [187]. They were kept on a 12 hour light- and 12 hour dark-cycle in a controlled temperature and humidity room with 4-5 animals per cage. Diet (V1534, Ssniff, Soest, Germany) was supplied ad libitum and animals had free access to tap water. Animal handling and experimentation were performed in accordance to the German Animal protection law and approved by the Animal Care und Use Committee of Bavaria (AZ 211-2531-37/00).

3.2.1. Experimental procedures

For the induction of ACF all animals were treated with 40 mg/kg body weight DMH by intraperitoneal injection once a week for six weeks. The test chemicals were applied by gavage in 4 ml/kg of body weight vehicle. For the application of flavone by gavage, it was vigorously pulverized and suspended in 0.9% saline solution containing 0.1% of the cosurfactant Myrj 53. All mice were weighed weekly and before sacrifice. The mice were killed by cervical dislocation under ether anesthesia.

3.2.2. Experimental arrangements

All animals were divided into three main groups. The “blocking group” animals received flavone either at 15 mg/kg body weight (low dose, n = 23) or at 400 mg/kg body weight (high dose, n = 23) five days a week over six weeks in parallel to the DMH-application. The “suppressing group” animals obtained low (n = 23) or high doses of flavone (n = 23) 5 times a week over four weeks starting one week after the last DMH-application. The flavone treatment for the “therapy group” animals started four weeks after the last DMH injection, leaving enough time for the progression of the lesions. Control animals received the vehicle alone (n = 23 for each control group), respectively. All animals from the blocking and suppressing group were sacrificed 5 weeks after the last injection of DMH, always between 9-11 am, the therapy group following four weeks later (see Figure 7).

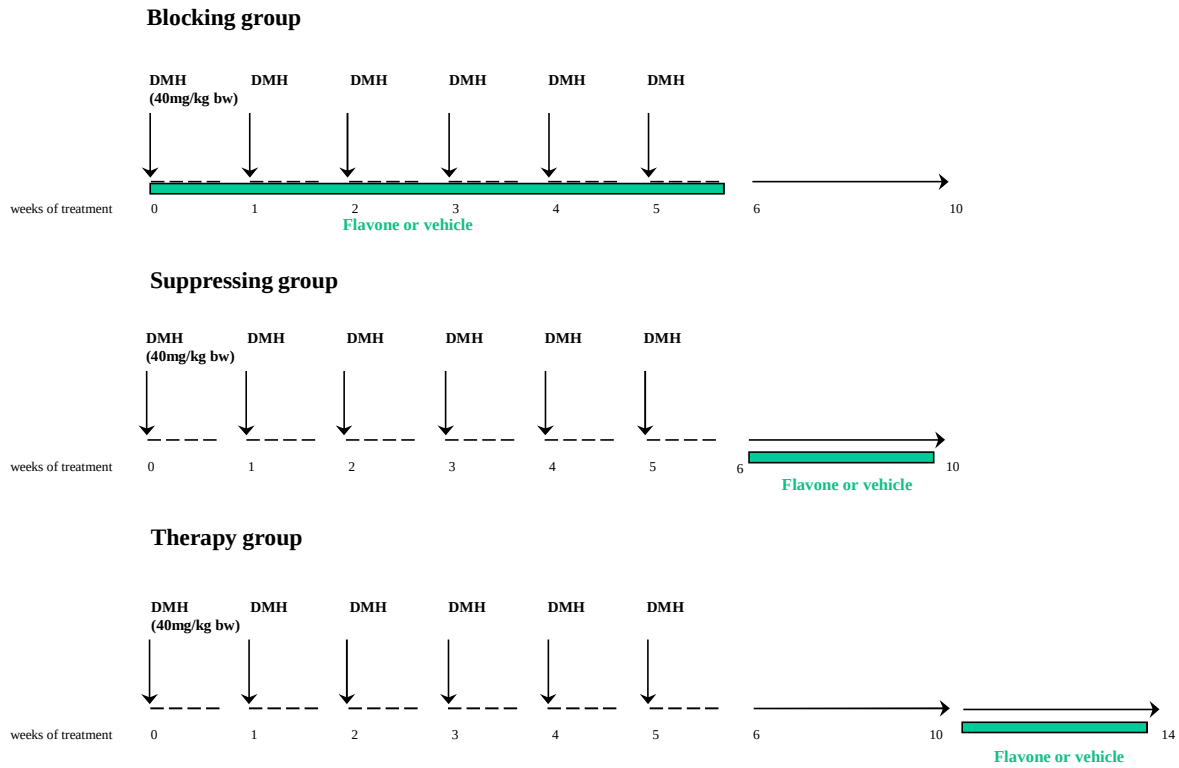

Figure 7: Treatment scheme of the three different treatment groups

3.2.3. ACF preparation and determination

ACF were counted in flat preparations of the colon in seventeen animals from each group. For this purpose, the gut was removed and rinsed with ice cold Tris buffer (pH 7.4). Thereafter the colon was cut in parts matching the length of a slide. Before placing on slides, a stirring rod was inserted and each piece of the colon was dissected along the longitudinal axis. After placing flat on a microscopic slide with the mucosal side up, the colon was covered with a filter paper and fixed in 10% neutral buffered formalin for six hours. The colonic crypts were stained with 2 g/l of methylene blue in PBS for ~10-15 min. The number of ACF and the aberrant crypt multiplicity were determined by light microscopy at 25-fold magnification [188].

3.2.4. Immunohistochemistry

For assessing proliferative activity in colonic tissue, two hours before sacrifice, six mice of each group were injected i.p. with 30 mg/kg body weight of BrdU, which is incorporated into DNA-synthesizing nuclei and can be used for the identification of S-phase cells. Specimens of the colon were routinely formalin-fixed and paraffin-embedded. Serial tissue sections (3-4 µm) were prepared and mounted on glass slides. They were dewaxed,

rehydrated and digested for 2 min with 0.01% trypsin before endogenous peroxidase was quenched with 3% H_2O_2 in Tris-HCl buffer pH 7.8. After blocking non-specific protein-protein interactions with 1% BSA in Tris-HCl buffer for 60 min at room temperature, the slides were incubated with a mouse-anti-BrdU monoclonal antibody (Sigma), diluted 1:10 in blocking buffer, for 90 min at room temperature. Subsequently, a secondary peroxidase-conjugated antibody directed to IgG from mouse (Sigma) was diluted 1:10 in Tris-HCl buffer containing 1% BSA and applied to the slides for 60 min at room temperature. Slides were thoroughly washed with Tris-HCl buffer between the incubation steps. All sections were counterstained with hematoxylin and mounted in entellan (Merck, Darmstadt, Germany). Brown staining of nuclei indicated the cells in the S-phase.

For determination of apoptosis, immunohistochemistry for cleaved caspase-3 was performed in formalin-fixed and paraffin-embedded colonic samples. Sections were dewaxed in xylene, endogenous peroxidase was blocked in all sections with 0.5% H_2O_2 in methanol and epitope retrieval was performed by microwaving for 33 min in citrate buffer (pH 6.0) in a microwave pressure cooker at 750 W. The rabbit polyclonal cleaved caspase-3 (Asp175) antibody (Cell Signalling, Frankfurt, Germany) was diluted 1:200 in blocking buffer (5% gout serum in TBS, pH 7.6) and incubated overnight. Biotinylated anti-rabbit IgG (dilution 1:200) (Vector Laboratories, Wertheim, Germany) served as a secondary antibody. The Avidin Biotin Complex Vectastain Elite Peroxidase-based system (Vector Laboratories) with diaminobenzidine as the substrate (Sigma) served for visualization of cleaved caspase-3. Sections were counterstained as described for the BrdU staining. Staining of brown nuclei indicated cells that underwent apoptosis.

3.3. Sample preparation

3.3.1. Isolation of proteins from HT-29 cells

The most critical step in the two-dimensional electrophoresis affecting its reproducibility remains the isolation of the proteins. Their proteolysis and aggregation has to be minimized while the solubility of preferably all proteins has to be maximized despite their varying physical and chemical properties. Hydrophobic or membrane bound proteins are very hard to lyse while this is much easier for cytosolic proteins, which normally just represent 10% of the total protein in a cell. Therefore the protein spots on a 2D-gel could lead to a misleading impression of the protein abundance in a cell.

3.3.1.1.Preparation of whole cell lysates

The cells exposed to the test compounds (effectors: flavone or camptothecine) were harvested at preconfluent stages. After washing the cells gently two times with ice-cold 0.35 M sucrose solution they were covered with a sucrose solution containing Complete Mini protease inhibitor and scratched from the bottom of the flask by using a cell scraper. The cells were transferred into prechilled Falcon tubes and centrifuged at 4°C and 7000 rpm (Speed vacuum centrifuge RC 10.10, Jouan) for 10 minutes. The pellet was resuspended in 200-400 µl of lysis buffer (depending on the pellet size) and after transfer into Eppendorf tubes homogenized on ice by using a sonicator (20 strokes at amplitude 45). After one hour on ice the samples were centrifuged at 4°C and 14000 rpm (Speed vacuum centrifuge RC 10.10, Jouan) for one hour. The supernatant containing the lysed proteins was transferred into prechilled reaction tubes.

In addition the samples were precipitated by acetone. Therefore the protein lysates were mixed with a fourfold volume of ice-cold acetone and left overnight at –20°C. After centrifuging at 4°C and 8000 rpm (Speed vacuum centrifuge RC 10.10, Jouan) for 10 minutes the supernatant was discarded and the pellet lysed again in lysis buffer, following the above mentioned procedure.

3.3.1.2.Preparation of fractionated cell lysates

After a 24-hour exposure to flavone the cells were harvested at around 90% confluence. For the separation of the whole protein lysate into its cellular compartments the "ProteoExtract – Subcellular Proteome Extraction Kit" from Calbiochem was used. Therefore the cells had to be trypsinized to detach them from the bottom of the culture flasks. The protein fractions represent the proteins of four different cell compartments, i.e. cytosol, membrane/organelles, nucleus and cytoskeleton.

After centrifuging the trypsinized cell suspension at 4°C and 4000 rpm (Speed vacuum centrifuge RC 10.10, Jouan) for 10 minutes, the supernatant was discarded and the pellet homogenized in extraction buffer. According to the manufacturer's instructions the homogenate was separated into the above mentioned four fractions by means of different extraction buffers and centrifugation steps. The resulting fractions were additionally precipitated with acetone as described above.

3.3.2. Isolation of proteins from colons of mice

Colon tissues of six mice of each group served for proteome analysis. Tissue samples were immediately snap-frozen in liquid nitrogen after killing of mice, removal of colons, rinsing them with Tris-buffer and crushing in a mortar in the presence of liquid nitrogen. Samples were stored in aliquots at –80 °C until further use.

For protein extraction, 0.1 g of the colon samples were mixed with 1 ml of lysis buffer, containing protease inhibitor cocktail tablets. The resultant cell lysate was sonicated for 6 x 10 seconds (Hielscher ultrasonic processor, amplitude 45) and centrifuged at 14000 x g for 45 min to collect the supernatant. Lysates were precipitated with acetone overnight and dialyzed in the dark using the Mini Dialysis Kit (Amersham, Freiburg, Germany) at +4 °C according to the manufacturer's instructions.

3.3.3. Photometric determination of the protein concentration

The protein concentrations of the extracted protein lysates were determined according to the method described by Bradford (1976).

Therefore the solubilized proteins were treated with the Bio Rad-Protein-Assay (BioRad, Munich, Germany). The calibration curve was acquired by using standard samples of BSA with predefined concentrations and the Bio Rad Reagent at 595 nm in a photometer. As a reference a similar mixture was prepared with lysis buffer instead of protein solution. Extinction values were subsequently converted into the protein concentration on the basis of the BSA calibration curve. Samples were directly aliquoted and stored at –80°C until further use.

3.4. Two dimensional gel electrophoresis

3.4.1. Pouring of SDS-gels

12.5% SDS polyacrylamide gels were poured in an Ettan Dalt II System gel caster according to the method of Laemmli. Directly after pouring the gel solution every gel was covered with 2 ml of 10% isopropanol to get a flat gelfront. After 8 hours polymerization at room temperature the chamber was kept at 4°C for another two days before the gels were ready to use. The composition for a complete gel caster filled with 14 SDS-PAGE gels is given in table 4.

Table 4: Composition of 12.5% SDS gels

Chemicals	Volume [ml]
acrylamide (30%) / bisacrylamide (0.8%)	375
1.5 M TrisCl, pH 8.8	225
SDS (20%)	4.5
APS (10%)	9
TEMED	0.6

3.4.2. First dimension

In the first dimension proteins are separated by isoelectric focusing [182]. Within an immobilized pH gradient the molecules migrate towards their isoelectric point, which describes the pH value where their net electric charge is zero.

The 18 cm long Immobiline Dry Strips (IPG strips with pH 4-7, 6-11 or 3-10) had to be rehydrated overnight in a reswelling tray. By using the "cup-loading" method the strips were rehydrated in 340 µl rehydration buffer. For the "in-gel rehydration" method the protein lysate was mixed directly with a modified rehydration buffer, allowing to maintain the total rehydration volume and the concentrations of the buffer substances.

Proteins from the HT-29 cells were separated by using pH gradients 4-7 and 6-11 in the first dimension and proteins from murine colonic tissue by the broad range pH gradient 3-10.

Table 5: Different parameters of the first dimensions

	in vitro **whole cell lysate**	***in vitro*** **fractionated into subcellular compartments**	***in vivo*** **total tissue lysate**
material	HT-29 cells	HT-29 cells	colonic tissue
effector/s	flavone or camptothecin	flavone	flavone
used pH gradients	4-7, 6-11	4-7	3-10
cup loading	yes, at pH 4-7	yes	Yes
in-gel rehydration	yes, at pH 6-11	no	No

For the first dimension a total protein amount of 500 µg was applied by cup-loading at the anodic end of an 18-cm-long IPG strip with immobilized broad range pH-gradients (linear IPG strips, pH 3-10, Amersham Biosciences), which were rehydrated overnight in solubilization buffer containing 8 M urea, 2% CHAPS, 2%, pharmalyte and 13 mM DTT. Proteins were focused using the Ettan IPG Phor II from Amersham as described [182] with minor modifications. Focusing was achieved at the following conditions: 1 min at 500 V (gradient), 90 minutes up to 4000 V (gradient), and for a total of 25000 Vh at 8000 V (step-n-

hold). The gel strips with the focused proteins were either frozen at –80°C or directly processed for second dimension.

Table 6: Used IEF programs for the first dimension

Step	Amperage per gel [mA]	Duration [h]	Temperature [°C]
1	4	1	20
2	12	17 minimum	20

3.4.3. Second dimension

In the second dimension proteins are separated through a SDS gel according to their molecular weight.

After equilibration with a buffer containing 6 M urea, 30% glycerol, 0.4% SDS, 50 mM Tris-buffer (pH 8.8) and either DTT or iodacetamide, the IPG strips were transferred onto a 12.5% acrylamide gel for the second dimension. 1 mm-thick 12.5% SDS-polyacrylamide gels were cast according to the method of Laemmli [189] and were run using an Amersham Biosciences Ettan-Dalt II System employing the following conditions: 4 mA per gel for 1 h, then 12 mA per gel.

To visualize the proteins they were stained with a Coomassie solution. Therefore the proteins in the gels had to be fixed in 40% (v/v) ethanol and 10% (v/v) acetic acid for 5 h. Gels were then stained overnight in Coomassie-solution containing 10% (w/v) $(NH_4)_2SO_4$, 2% (v/v) phosphoric acid, 25% (v/v) methanol and 0.625% (w/v) Coomassie brilliant blue G250. Afterwards they were destained in double distilled water until the background was completely clear.

Table 7: Staining procedures and solution composition

Stages	Composition	Duration
fixation	40% ethanol 10% acetic acid	minimum 6 hours
staining	10% $(NH_4)_2SO_4$ 2% H_3PO_4 25% methanol 5% coomassie	over night
destaining	distilled water	until clear background

3.4.4. Analysis of the gels by the software Proteom Weaver

Gels stained with Coomassie were scanned using an Umax scanner Power Look III (software: Magic Scan version V4.5, UMAX) and spots detected by the ProteomWeaver software (Definiens, Munich, Germany). Background subtraction and volume normalization were made automatically by the software. After spot detection, all gels were matched to each other. Six gels of each treatment (HT-29 cells or murine colon tissue) were grouped and compared to six gels of the associated controls.

3.5. Mass spectrometry

3.5.1. Sample preparation and processing

3.5.1.1. In-gel digestion by hand for in vitro experiments

The protein spots were cut out of the gels by using a skin-picker and put into 0.2 ml tubes. Gel pieces had to be washed to remove the Coomassie stain and SDS, which could hamper the identification of the proteins by influencing their spectra. Therefore a washing cycle composed of a 15 minute washing step with 50 µl of 50 mM sodium bicarbonate (NH_4HCO_3) and a 15 minute washing step with a mixture of 50 µl of 50 mM NH_4HCO_3 : acetonitrile (1:1, v/v) was repeated until the spots were clear and transparent before they were shrinked with pure acetonitrile. These gel pieces were dried in a vacuum centrifuge and stored at –20°C until digestion by trypsin.

Dried gel pieces were incubated with excess ice-cold trypsin solution and left in the freezer for two hours for soaking. The excess trypsin was removed and the soaked gel pieces were incubated at 37°C at least for four hours for the digestion of the proteins. The resulting peptides had to be extracted by 10 µl of 1% TFA in an ultrasonic bath. Gel pieces were removed and the peptide solution spotted directly on the target. Remaining peptide solutions were stored at –20°C.

3.5.1.2. Sample spotting on the target by Gobom method

The spotting of the resulting peptide solutions was done by the thin-layer preparation of Gobom [190]. Therefore 1 µl of a saturated α-Cyano-4-hydroxy-cinnamic acid (HCCA) solution in acetone : 0.1% TFA (v/v 97:3) was prespotted on the 400/384 AnchorChip^{TM} target as matrix. Afterwards 3 µl of the samples and 1 µl of the peptide calibration standard was deposed/dropped onto the matrix, respectively. After 3 minutes 2 µl of 0.1% TFA was spotted into the drops and removed quickly for washing out the salts. After a short drying phase the target was brought into the mass spectrometer and the spectra were gained in positive ion mode.

3.5.1.3.Sample spotting for post-source decay analysis

The resulting peptide solutions extracted by 1% TFA were mixed in the ratio 2:1 with the HCCA matrix, dissolved in 30% acetonitrile and 0.1% TFA. 3-5 µl of this solution was spotted onto a stainless steel target and left there for air drying.

3.5.1.4. In-gel digestion and spotting by robotic systems

Matched Coomassie stained spots, differing significantly in their intensities, were excised from the 2-D gels with a PROTEINEER spII spot picker (Bruker Daltonics). Destaining, drying and digestion were performed with the PROTEINEER dp^{TM} workstation using the calibration and digestion kits by following the manufacturer's instructions (Bruker Daltonics). Subsequently, samples were spotted automatically by the workstation either onto an AnchorChip MALDI-target 800/384 by using α-cyano-4-hydroxy-trans-cinnamic acid (HCCA) as matrix, acidified by using an aqueous 0.1% TFA as washing solution and air-dried at room temperature, or onto a prespotted AnchorChip target PAC384 with HCCA matrix for 384 samples and 96 calibration spots.

3.5.2. MALDI-TOF MS

In the late 1980´s, Tanaka, Karas and Hillenkamp were able to identify and define the masses and structures of the first larger biomolecules, by inventing a method that combined matrices with the laser-desorption ionization technique (MALDI) and with time of flight mass analyzers (TOF) leading to the MALDI-TOF technique [180, 181].

The mass spectrometry analysis of tryptic digests was performed with an Autoflex MALDI-TOF mass spectrometer (Bruker Daltonics, Leipzig), operating in reflectron mode with a 20-kV accelerating voltage and a 130-ns delayed extraction. The mass spectrometer itself was calibrated using a calibration standard from Bruker Daltonics.

3.5.3. Computer-aided protein identification

Peptide mass fingerprint (PMF) spectra were acquired in the automatic mode using the AutoXecute module of FlexControl software version 2.4 (Bruker Daltonics). Spectra of identical protein spots from at least four independent gels and from different treatment groups were processed with flexAnalysis 2.4 (Bruker Daltonics), by using the smoothing option and calibrating both external, and internally with the autoproteolysis peptide of trypsin (m/z 2211.10). Background peaks like keratin, Coomassie, etc., were removed and a signal to noise threshold (S/N) of 3 was applied for the samples and 6 for the Peptide Calibration Standard (1000-4000 Da, Bruker Daltonics). Peptides were selected in the mass range of 800-3500 Da. The resulting mass list was evaluated using Bio Tools 3.0 with the search engine Mascot

(version 1.9.00, www.matrixscience.com) and the MSDB database. The criteria for positive identification of proteins were set as follows: ± 50-150 ppm peptide mass tolerance, 0 or 1 missed cleavage, carbamidomethyl modification of cysteine as global and methionine oxidation as variable modification, and charged state as MH+. For further identification of proteins the human sequences were chosen for the experiments with HT-29 and mouse sequences for the animal experiments. A protein was seen as validated when 3 samples satisfactorily showed the same results with a probability based mowse score being significant ($P < 0.05$) and theoretical molecular weight and pI showing at least similar results as in the gels from which they were picked.

In case of two distinct spots in one gel showing the same protein after identification, another procedure was chosen to allow the identification of possible posttranslational modifications of this protein. This method is called post-source decay (PSD) and therefore the obtained PMF spectra of the two spots differing in mass and pI on the Coomassie stained gel were subtracted from each other by using flexAnalysis. Special m/z ratios present in the spot with lower pI which were considered to possess phosphorylation sites and which were absent in the protein spot with higher pI, were used as parent masses in gaining PSD spectra. The spectra were recorded under following conditions: reflector voltage starting at 19 kV for the first segment, being decreased up to 3.45 kV for the tenth segment. There was no realtime smooth chosen for the spectra acquisition. Afterwards the single segments were pasted together by using flexAnalysis with the smoothing and background subtraction option. By means of Bio Tools different PSD spectra of different parent masses were combined together with the PMF spectrum of the corresponding protein and a MS/MS search was done.

3.6. Microarrays

Aliquots of the colonic tissues, described in the sample preparation for 2D-PAGE, served for the genome analysis (chapter 3.3.2.). Total RNA was isolated from all samples by using TRIzol® reagent. The Gene Chip® 3' Expression Arrays (Affymetrix, Santa Clara, CA, USA), customized for NuGO and containing 24,000 genes, were used in this study.

3.6.1. RNA-isolation out of the tissue

A TRIzol®-based RNA extraction was performed with a further cleanup step using RNeasy spin columns (Qiagen, Hilden), as it is recommended in the Affymetrix manual. For total RNA extraction 0.03 g of the snap-frozen, powdered colon samples were mixed with 1 ml of TRIzol® reagent and treated with an ultraturrax at 4°C for 10 s and 1000 rpm. The solution was stored on ice for 15 min and the resulting chloroform phase was removed while the phase beneath contained the RNA. The resulting RNA remaining in the ethanol phase was then subjected to a second cleanup using RNeasy spin columns, and afterwards washed from the columns with DEPC water. Further preparation was performed by using the provided Kits and reagents according to the manufacturer's protocol.

3.6.2. RNA quality-check and quantification

RNA quality was proven by measurements of their absorption ratio (A_{260}/A_{280}) and analysis on a denaturing agarose gel. The ratio had to be lower than 1.8 and the total RNA preparation should show two distinct bands, forming about a 2:1 ratio of intensities for the 28S and 18S rRNA. The RNA quantity was assessed by measurements of their OD at 260 nm.

3.6.2.1. DNA-Arrays

The 16-hour hybridization, washing, staining and scanning of the eucaryotic cartridge arrays was performed according to the manufacturer's protocol (Affymetrix, Santa Clara, CA), by using the GeneChip® hybridization oven 640, the Fluidics Station 450 and the Scanner 3000 with autoloader (GeneChip, Affymetrix, Santa Clara).

3.6.2.2. Processing of total RNA, followed by hybridization and scanning

5 µg of total RNA was used to generate double-stranded cDNA by reverse transcription, followed by a cleanup and synthesis of biotin-labeled cRNA. After cleanup and quantification of the biotynilated cRNA it was subjected to fragmentation and stored at –20°C until hybridization.

An internal standard was applied to demonstrate the hybridization quality of each array. The hybridization was done within an oven at 42°C overnight, while the washing and scanning process was performed at room temperature.

3.6.2.3. Data interpretation by the Genomatix software

Microarrays, passing the quality control, were normalized and probe cell intensity data (.CEL file generation) were summarized by using the GeneChip 4.0 software, which enables sample and array registration, data management, fluidics and scanning instrument control as well as automatic and manual image gridding. The gene expression profile of each tumor tissue was normalized to the median gene expression profile for the entire sample. The ChipInspector software was used for the statistical analysis and the Bibliosphere Pathway software (Genomatix Software, Munich, Germany) for data interpretation (see chapter 3.7.).

The basis of the MeSH filter method used for further data interpretation of the regulated gene targets is represented by the information gained through PubMed articles. In the present study the MeSH term “disease” was applied as a filter on the gene set, consisting of a hierarchy of terms itself. Using the software Bibliosphere for each of these terms a statistical analysis is accomplished based on the number of observed and expected annotations for the terms. The resulting Z-Scores describe whether a special annotation is over- or underrepresented in the analyzed set of genes. Z-Scores are calculated by means of observed minus expected annotations, which are divided by the standard deviation of observed annotations (Z=(observed-expected)/std. deviation(observed)). Another option for filtering the gene sets are the filters according to the Gene Ontology Database (www.geneontology.org), called GOFilter within the Bibliosphere software. The GOFilter “biological process” was chosen for the gene sets allowing the application of several terms, like “TCA” or “apoptosis” for example, to recover putative mechanisms underlying the potential anti-cancer activities of flavone in the murine colons.

3.7. Calculations and statistics

The protein lysates for the cell culture analysis were gained from three independent incubation experiments, while the lysates for the animals were pooled together from the colonic tissues of six individual mice. Concerning the cell culture studies the control gels from three independent runs, coming from three independently done experiments, were compared to those of the corresponding treatment group. Spots differing significantly ($P < 0.05$, Student’s t-test) in their intensities were picked for MALDI-TOF MS analysis. Six gels derived from samples of treated individual mice were grouped and compared to gels derived

from six control mice, resulting in six spot volume values for a special protein spot within one group. Spots differing significantly (at least $P < 0.05$, Mann-Whitney test) in their intensities were picked for MALDI-TOF MS analysis.

Concerning the determination of aberrant crypts in murine colonic tissue and immunohistochemistry analysis the variance analysis between groups was performed by One-way ANOVA and significance of differences between control and treated cells were determined by a Tukey's Multiple Comparison test (GraphPadPrism, San Diego, CA, USA). For each variable at least 3 independent experiments were carried out. Data are given as the mean ± SEM.

The statistical analysis and the comparative study of the array data in the generated .CEL files was done with the ChipInspector software (Genomatix Software, Munich, Germany). FDR range of 0.1% and minimum probe coverage of 4 out of 11 was chosen to get the list with identifiers of gene products and their associated regulation factors. These identifiers could be mapped to genes by using the Bibliosphere Pathway software (Genomatix) for analysis and interpretation of the array data.

4. Results

4.1. Establishment of 2-DE methods

The analyses exploring the impact of flavone on the proteome of colonocytes *in vitro* and *in vivo*, and of camptothecin *in vitro*, were done by two-dimensional gel electrophoresis followed by mass spectrometry via MALDI-TOF.

IPG strips with linear pH gradients of 4-7 and 6-11 were used for separating proteins from HT-29 cells and the broad range pH 3-10 for the proteins from the mice colons, respectively. Three different Coomassie-based staining methods were tested at first for achieving best sensitivity and quantitative analysis.

4.1.1. Staining methods

The most sensitive staining method in proteomics is the silver staining, allowing the detection of 0.1 µg protein per spot. Coomassie staining methods reach sensitivities of 0.1-2 µg protein per spot, are very simple to use, less expensive than silver staining and proteins will not be modified, which is essential for the following MS methods. In earlier studies it was shown that the spots detected by silver staining had not enough protein substance to be identified by MS.

The three different Coomassie staining methods tested here (Figure 8) were Roti®-Blue solution from Roth, Imperial™ Protein Stain from Pierce and the self-mixed Coomassie solution described in chapter 3.4.3. The quality of the gels stained with the Roti®-Blue solution was comparable to the self-mixed solution, with no benefit in detection of low abundant protein spots. The background was better to destain but the disadvantages were a higher consumption of materials and time.

Gels stained with the Imperial™ Protein Stain had to be destained by hand because of sticking of excessive staining on the gels and only 60% of the spots, detectable by the self-mixed staining, were recovered here, which showed low sensitivity.

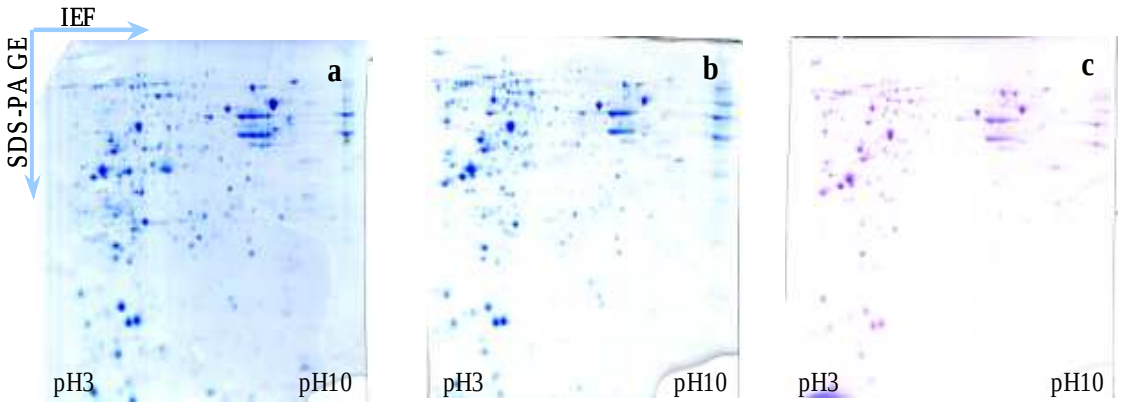

Figure 8: Different staining methods

Proteins from HT-29 cells were separated by pH 3-10 in the first dimension, and after second dimension stained with (a) self-mixed Coomassie solution, (b) Roti®-Blue solution or (c) Imperial™ Protein Stain from Pierce.

4.1.2. Fractionation of the whole cell lysate

Fractionation of a whole cell lysate is an ideal method to visualize the proteins of their associated subcellular organelles or to be able to detect even low abundant proteins, respectively. The methods used for the extraction of the whole cell lysates were already established in our laboratory and only slight modifications were needed for the cell culture studies, when using different pH gradients for the first dimension of 2D-PAGE. However, concerning the fractionation studies, the most effective and reproducible method had to be established.

We used two different fractionation kits, the Proteo Extract® – Subcellular Proteome Extraction Kit from Merck and the Qproteome Soluble Protein Separation Kit from Qiagen. Gels showing the different fractionation steps produced by the latter were not reproducible and showed much too similar protein spot distributions in the different fraction steps. Using the kit from Merck, similar spot distribution in the first two fractions was avoided by minor modifications of the manufacturer's instructions. After the first fractionation step we conducted another washing step and combined the precipitated proteins with the first fraction. Proteins fractionated by that kit showed different protein patterns between the four different fractionation steps and were clearly reproducible. Therefore we chose the fractionation kit from Merck.

4.2. Establishment of automated processes in mass spectrometry

The automation of the technical processes concerning mass spectrometry expectedly permitted a higher throughput after the systems were optimized.

4.2.1. Protein spot handling with robotic systems

After updating the software, installation of new databases and several efforts concerning the network communication of the five involved personal computers, it was possible to transfer the analyzed protein spots to the Spot picker system. These picked spots were transferred to a microtiter plate and placed in the Digester. Several modifications of the system were necessary to change the recovery rate from less than 10% in the beginning to 95% in the end. Adjustments of the spotted solution volumina for trypsinization and of the nitrogen pressure within the system had to be done, as well as the modification of the reaction times.

4.2.2. Acquirement of mass spectra in automatic mode

This modus lead also to a much higher performance since it was possible to gain the spectra overnight and analyze them in an automated process, when the databases referred to, were not frequently used. The acquired mass spectra were automatically processed and analyzed by the flexAnalysis software. After smoothing by using the Savitzky Golay algorithm, the baselines were subtracted and peaks were detected using the SNAP algorithm. The BioTools software from Bruker Daltonics allowed the automatic identification of the proteins by database search on the MASCOT server, using the MSDB database.

4.3. 2-DE analysis of whole cell lysates from flavone- or camptothecin-treated HT-29 cells

HT-29 cells were incubated for 24 h with the effectors flavone (150 µM) or camptothecin (50 µM), respectively. These concentrations, causing comparable apoptosis rates, were determined in earlier experiments [191]. Within the experiments concerning the whole cell lysates of treated HT-29 cells the pH gradients from 4-7 and 6-11 were used for the different treatment substances. The ProteomWeaver software was able to detect around 800 distinct protein spots in a Coomassie stained 2D gel image. For the analysis six gels of non-treated cells, derived from three independent experiments, were compared to six gels of treated cells (flavone or camptothecin). Protein spots, which were found regulated

significantly in their steady state level compared to the associated spot in the control gels, were picked in quadruplicate.

For both treatment substances together we determined forty-six protein spots in the pH range 4-7 and twenty-eight spots in the pH range 6-11 as regulated in their steady state levels. According to the above-mentioned criteria (3.5.3) 72% of those spots in the pH range 4-7 and 89% in the range 6-11 were identified through the Mascot database search.

4.3.1. Effect of flavone exposure on the proteome of HT-29 cells

After the database analysis we were able to identify twenty-two of the twenty-nine differentially expressed protein spots in the pH range 4-7, which were found to be regulated by a 24-hour flavone treatment of the cells. Thirteen proteins showed a higher expression after the treatment, according to the steady state levels of their associated control spots. The proteins delta 3,5-delta 2,4-dienoyl-CoA isomerase, proliferation-associated protein 2G4 and lamin C were identified twice suggesting possible posttranslational modifications of these protein entities (Tab. 8, Fig. 9). Post source decay analysis performed after subtraction of PMF-spectra from the two spots identified as proliferation-associated protein 2G4 not only enabled the definite determination of the protein identity but also revealed the presence of phosphorylation sites within the sequence. The chaperone subunits beta and epsilon of the T-complex protein and the detoxification enzymes glutathione S-transferase P and peroxiredoxin 4 showed higher expression level, and the chaperone T-complex protein subunit zeta was solely detectable in the flavone treated cells. All the identified gene regulating proteins, like elongation factor Tu, proliferation associated protein 2G4 and RuvB-like 1 showed increased steady state levels, as well as most of the metabolism and cytoskeletal proteins, which are listed in Table 8. The only proteins showing decreased expression levels were the detoxification enzyme thioredoxin and the protein stathmin, which is involved in the regulation of the microtubule filament system by destabilizing microtubules and is overexpressed in many human tumors. One of the most interesting proteins, only detectable after flavone incubation is the programmed cell death 6-interacting protein, which is involved in concentrating and sorting of cargo proteins of the multivesicular body for incorporation into intralumenal vesicles.

Table 8: Proteins with pIs 4-7 regulated in steady state levels by flavone in HT-29 cells

The spot numbers are identical to those given in Figure 9. Protein descriptions are according to the Swiss-Prot website (www.expasy.org/sprot/) with their associated primary accession numbers. Proteins altered significantly by 24 h flavone treatment of HT-29 cells, as derived from analysis with the Proteomweaver software, were identified by MALDI-TOF-MS with pI between 4 and 7; Sequence cover. [%], sequence coverage obtained by the identified peptides; Mw/pI theor., mass and pI values taken from the MSDB database; Mw/pI exp., mass values calculated by the Proteomweaver software referring to the low molecular weight standard and calculated pI values; Subcellular location is indicated according to www.expasy.org, www.harvester.embl.de and literature; Reg.-factor F/control, regulation of intensities of protein spots derived from treated cells compared to those derived from the control ($P < 0.05$; Student's t-test); only in F, associated protein spot was only detectable in flavone treated cells; ($n = 6$).

Spot No.	Protein description	Swiss Prot Acc. No.	Sequ. cov. [%]	Mw/pI theor.	Mw/pI exp.	Subcellular location	Reg.-fac. F/C
	Apoptosis						
1	Programmed cell death 6-interacting protein	Q8WUM4	37	97/6.1	90/6.2	cytoplasm	**only in F**
	Chaperones						
2	T-complex protein 1, beta subunit	P78371	53	58/6.0	62/6.4	cytoplasm	**2.19**
3	T-complex protein 1, epsilon subunit	P48643	23	61/5.5	68/5.5	cytoplasm	**2.49**
4	T-complex protein 1, zeta subunit	P40227	52	58/6.3	68/6.6	cytoplasm	**only in F**
	Detoxification enzymes						
5	Glutathione S-transferase P	P09211	52	23/5.4	29/5.6	cytoplasm	**5.57**
6	Peroxiredoxin 4	Q13162	50	31/5.9	32/5.8	cytoplasm	**2.61**
7	Thioredoxin	P10599	66	12/4.8	12/4.7	cytoplasm	**0.51**
	Gene regulating proteins						
8	Elongation factor Tu, mitochondrial [Precursor]	P49411	52	50/7.3	53/6.9	mitochondrion	**6.72**
9	Proliferation-associated protein 2G4	Q9UQ80	26	44/6.1	55/6.5	cytoplasm, nucleus; nucleolus	**2.16**
10	Proliferation-associated protein 2G4	Q9UQ80	50	44/6.1	56/6.3	cytoplasm, nucleus; nucleolus	**2.31**
11	RuvB-like 1	Q9Y265	48	51/6.0	61/6.6	nucleus (mainly), associated with nuclear matrix or in nuclear cytosol; cytoplasm, associated with the cell membranes	**3.18**

	Metabolic enzymes						
12	Delta3,5-delta2,4-dienoyl-CoA isomerase, mitochondrial [Precursor]	Q13011	42	36/8.2	38/6.4	mitochondrion, peroxisome	**2.60**
13	Delta3,5-delta2,4-dienoyl-CoA isomerase, mitochondrial [Precursor]	Q13011	36	36/8.2	37/6.7	mitochondrion, peroxisome	**2.75**
14	Proteasome (Prosome, macropain) subunit, alpha type, 1	Q53YE8	44	30/6.2	37/6.6	cytosol, proteasome core complex (sensu Eukaryota), protein complex	**2.43**
15	Ubiquinol-cytochrome-c reductase complex core protein I, mitochondrial [Precursor]	P31930	51	53/5.9	52/5.3	mitochondrion; mitochondrial inner membrane	**only in F**
16	Septin-11	Q9NVA2	36	55/7.3	59/6.8	localized along stress fibers	**2.70**
17	Stathmin	P16949	41	17/5.8	19/5.8	cytoplasm	**0.47**
	Cytoskeleton proteins						
18	Keratin, type II cytoskeletal 8	P05787	34	56/5.6	60/5.9	intermediate filament associated	**8.20**
19	Keratin, type I cytoskeletal 19	P08727	72	44/5.0	48/5.4	intermediate filament associated	**only in F**
20	Lamin C	P02545	49	65/6.4	66/6.4	nucleus	**only in F**
21	Lamin C	P02545	45	65/6.4	72/6.1	nucleus	**only in F**
	Others						
22	WD repeat protein 61	Q9GZS3	52	34/5.2	39/5.0		**only in F**

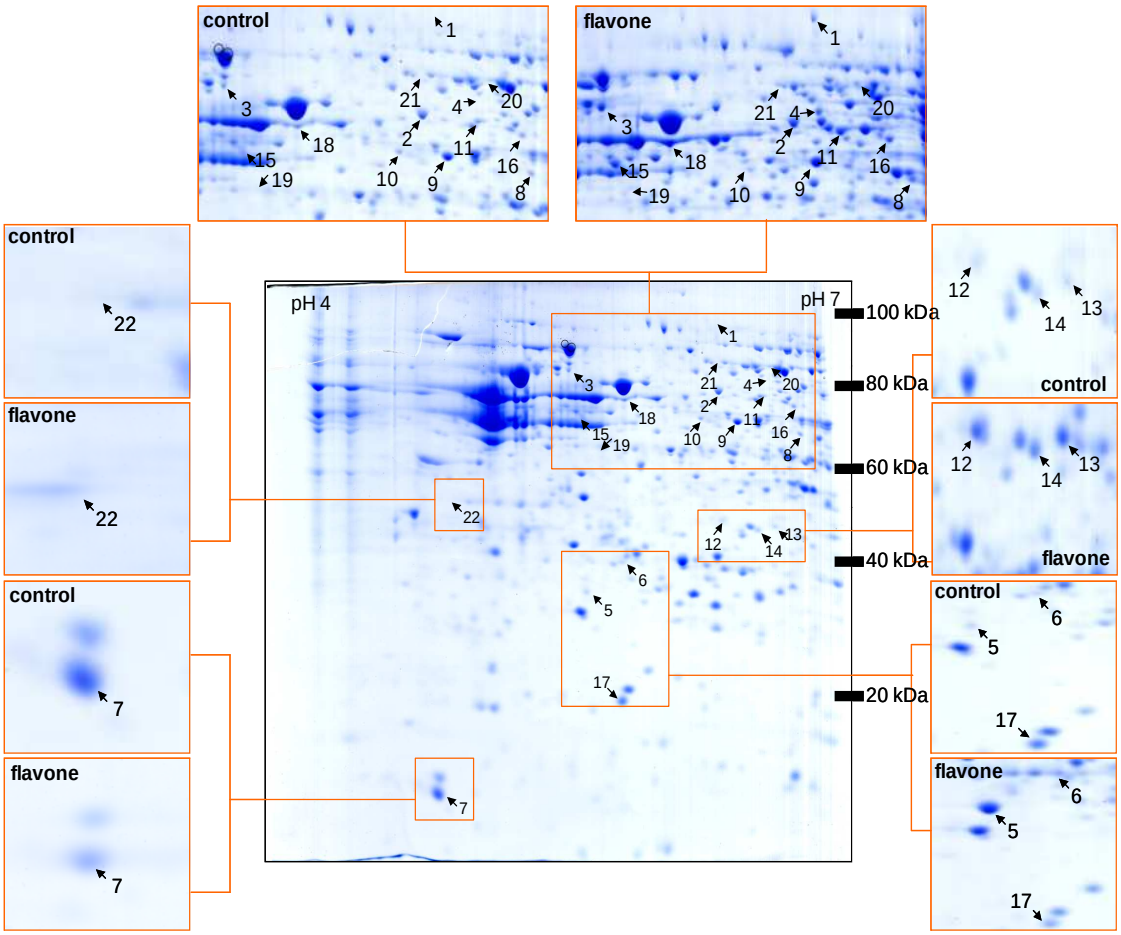

Figure 9: 2D map of proteins with pIs of 4-7 derived from flavone-treated HT-29 cells

Proteins were separated on a linear pH 4-7 IPG-strip in the first dimension and on a 12.5% SDS-polyacrylamide gel in the second dimension. 500 µg of total protein was loaded on a gel and stained with Coomassie subsequent to the separation. Enlargements from identical sections of gels derived from separations of HT-29 proteins from control cells or cells treated with 150 µM flavone are shown around a typical gel derived from control cells. Spot numbers refer to identification in Table 8.

In the pH range 6-11 we identified ten of the fourteen proteins, regulated in their steady state levels after flavone incubation, via database search (Tab. 9, Fig. 10).

Beside the heterogeneous nuclear ribonucleoprotein A2/B1, keratin type I cytoskeletal 18, the metabolism proteins cyclophilin B chain A and glyceraldehyde-3-phosphate dehydrogenase, which was identified twice, were increased in their steady state levels. Coproporphyrinogen III oxidase and glucose-6-phosphate 1-dehydrogenase were exclusively expressed in the flavone treated cells. Alpha enolase, which was identified twice, showed decreased expression levels in one spot and increased levels in a second spot.

Table 9: Proteins with pIs 6-11 regulated in steady state levels by flavone in HT-29 cells

The spot numbers are identical to those given in Figure 10. Abbreviations are explained in the legend to Table 8. Identical proteins that were identified as regulated at both pH-gradients are indicated only once, i.e. in Table 8 and not in addition in Table 9; (n = 6).

Spot No.	Protein description	Swiss Prot Acc. No.	Sequ. cov. [%]	Mw/pI theor.	Mw/pI exp.	Subcellular location	Reg.-fac. F/C
	Gene regulating proteins						
1	Heterogeneous nuclear ribonucleoproteins A2/B1	P22626	42	37/9.0	40/8.6	nuclear; component of ribonucleosomes	**2.18**
2	RNA-binding protein Raly	Q9UKM9	31	33/9.2	44/9.9	nucleus	**0.50**
	Metabolic enzymes						
3	Alpha-Enolase	P06733	51	47/7.0	54/7.7	cytoplasm, cell membrane, nucleus	**2.78**
4	Alpha-Enolase	P06733	53	47/7.0	53/6.7	cytoplasm, cell membrane, nucleus	**0.37**
5	Coproporphyrinogen III oxidase, mitochondrial [Precursor]	P36551	56	41/6.7	44/7.5	mitochondrion; mitochondrial intermembrane space	**only in F**
6	Cyclophilin B, Chain A	P23284	61	20/9.2	20/10.5	endoplasmic reticulum lumen	**11.84**
7	Glucose-6-phosphate 1-dehydrogenase	P11413	60	60/6.4	62/7.1	cytoplasm	**only in F**
8	Glyceraldehyde-3-phosphate dehydrogenase	P04406	46	36/8.3	38/7.7	cytoplasm	**2.00**
9	Glyceraldehyde-3-phosphate dehydrogenase	P04406	49	36/8.6	40/8.4	cytoplasm	**2.33**
	Cytoskeleton proteins						
10	Keratin, type I cytoskeletal 18	P05783	41	48/5.3	30/7.0	intermediate filament associated	**3.45**

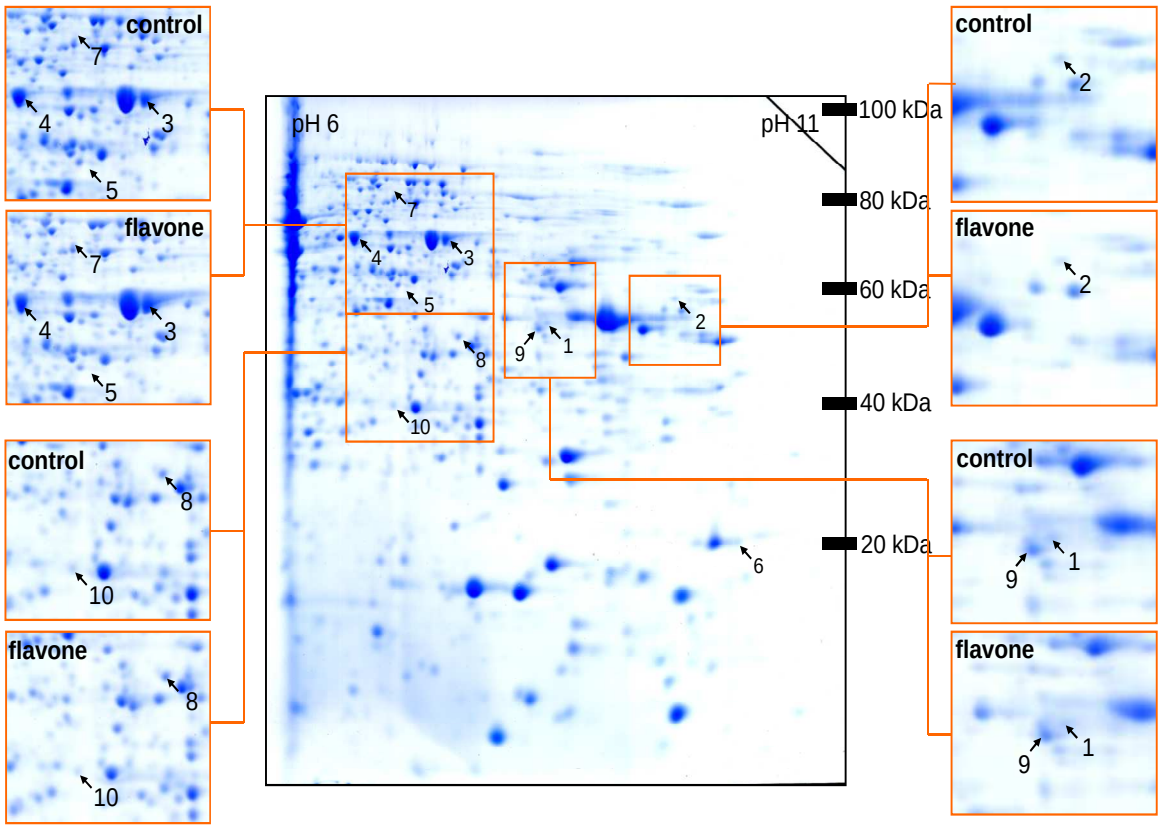

Figure 10: 2D map of proteins with pIs of 6-11 derived from flavone-treated HT-29 cells

Proteins were separated on a linear pH 6-11 IPG-strip in the first dimension and on a 12.5% SDS-polyacrylamide gel in the second dimension. Enlargements from identical sections of gels derived from separations of HT-29 proteins from control cells or cells treated with 150 µM flavone are shown around a typical gel derived from control cells.

Classification of all identified proteins in the whole cell lysates (Tables 8 and 9) that responded to flavone exposure with altered steady state levels according to www.expasy.org and www.harvester.embl.de, revealed that 41% of the responsive proteins play a role in intermediary metabolism and 19% of the regulated proteins are involved in gene regulation. Another 16% represent cytoskeletal proteins that are probably changed as an indicator of ongoing apoptosis, which can be triggered by changes in the levels of proteins with a direct link to programmed cell death (3%). Finally 18% of the responses are observed in proteins that enhance the stress response of cells, such as chaperones (9%) and detoxification proteins (9%), indicating adaptations of the cancer cell to the death-inducing agent (Fig. 11).

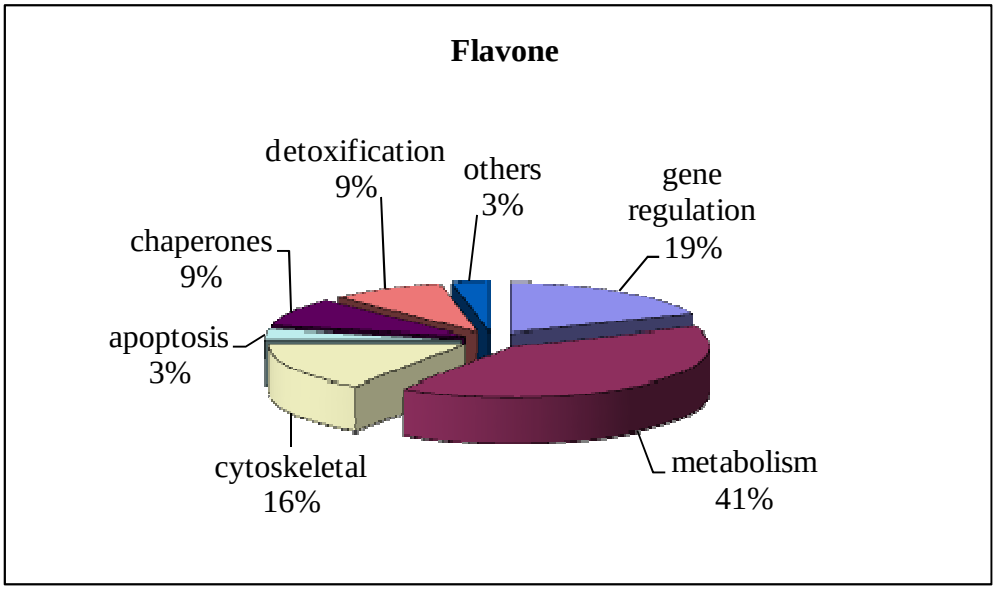

Figure 11: Classification of differentially expressed proteins after flavone incubation

4.3.2. Effect of camptothecin exposure on the proteome of HT-29 cells

Camptothecin was applied to the cells at a concentration of 50 µM since apoptosis induction under these conditions is equal to that observed at 150 µM flavone [191]. 2D-PAGE of the protein extracts from cells treated for 24 h with camptothecin revealed the nature of twenty-five of the thirty-six regulated proteins in the pH range 4-7 through the database analysis (Tab. 10, Fig. 12).

Several proteins identified here showed similar expression changes by camptothecin treatment as those of the cells treated with flavone. For instance the chaperones T-complex protein 1, essential for correct protein folding and the detoxification proteins glutathione S-transferase P and peroxiredoxin 4 showed comparable responses with regard to expression levels. Likewise the gene regulating proteins elongation factor Tu and RuvB-like 1 were affected similarly by flavone and camptothecin, as well as the metabolic proteins delta 3,5-delta 2,4-dienoyl-CoA isomerase, the proteasome subunit alpha type 1, the cell cycle controlling septin-11, and the cytoskeletal protein keratin type II cytoskeletal 8. Additionally the lamines progerin, lamin A and lamin A/C-transcript variant 1 were identified as regulated by camptothecin and showed increased expression levels.

The chaperone endoplasmic reticulum protein ERp29 and the gene regulating heterogeneous nuclear ribonucleoprotein K appeared in decreased steady state levels after camptothecin treatment, as well as stathmin and the premature ovarian failure protein 1B.

Table 10: Proteins with pIs 4-7 regulated in steady state levels by camptothecin in HT-29 cells

The spot numbers are identical to those given in Fig. 12. Proteins altered significantly by 24 h camptothecin treatment of HT-29 cells were identified by MALDI-TOF MS; Reg.-factor C/control, regulation of the spot intensities observed between camptothecin treated cells versus control cells according to Proteomweaver software analysis with $P < 0.05$ (Student's t-test); only in C, associated protein spot was only detectable in the camptothecin exposed cells. Other abbreviations are given in the legend to Table 8; (n = 6).

Spot No.	Protein description	Swiss Prot Acc. No.	Sequ. cov. [%]	Mw/pI theor.	Mw/pI exp.	Subcellular location	Reg.-fac. Campto/C
	Chaperones						
1	Endoplasmic reticulum protein ERp29 [Precursor]	P30040	53	29/6.8	33/6.3	endoplasmic reticulum (ER); ER lumen	**0.55**
2	Protein disulfide-isomerase A3 [Precursor]	P30101	37	57/6.0	54/5.9	endoplasmic reticulum (ER); ER lumen	**only in Campto**
3	T-complex protein 1, beta subunit	P78371	53	58/6.0	62/6.4	cytoplasm	**2.35**
4	T-complex protein 1, epsilon subunit	P48643	23	61/5.5	68/5.5	cytoplasm	**2.96**
5	T-complex protein 1, zeta subunit	P40227	52	58/6.3	68/6.6	cytoplasm	**only in Campto**
	Detoxification enzymes						
6	Glutathione S-transferase P	P09211	52	23/5.4	29/5.6	cytoplasm	**5.51**
7	Peroxiredoxin 4	Q13162	50	31/5.9	32/5.8	cytoplasm	**2.38**
	Gene regulating proteins						
8	Elongation factor Tu, mitochondrial [Precursor]	P49411	52	50/7.3	53/6.9	mitochondrion	**4.61**
9	Heterogeneous nuclear ribonucleoprotein K	P61978	49	51/5.2	68/5.5	cytoplasm; nucleus, nucleoplasm	**0.49**
10	RuvB-like 1	Q9Y265	48	51/6.0	61/6.6	nucleus (mainly), associated with nuclear matrix or in the nuclear cytosol; cytoplasm, associated with the cell membranes	**3.31**

	Metabolic enzymes						
11	Delta3,5-delta2,4-dienoyl-CoA isomerase, mitochondrial [Precursor]	Q13011	36	36/8.2	37/6.7	mitochondrion peroxisome	**2.40**
12	Proteasome (Prosome, macropain) subunit, alpha type, 1	Q53YE8	44	30/6.2	37/6.6	cytosol, proteasome core complex (sensu Eukaryota), protein complex	**2.36**
13	Septin-11	Q9NVA2	36	55/7.3	59/6.8	localized along stress fibers	**2.04**
14	Stathmin	P16949	41	17/5.8	19/5.8	cytoplasm	**0.36**
	Cytoskeleton proteins						
15	Keratin, type II cytoskeletal 8	P05787	34	56/5.6	60/5.9	intermediate filament associated	**6.33**
16	Lamin A	P02545	47	74/6.6	76/6.8	nucleus	**2.43**
17	Lamin A	P02545	47	74/6.6	71/6.0	nucleus	**only in Campto**
18	Lamin C	P02545	49	65/6.4	72/6.0	nucleus	**only in Campto**
19	Lamin C	P02545	45	65/6.4	65/6.3	nucleus	**only in Campto**
20	Lamin A/C transcript variant 1	Q5I6Y4	48	74/6.4	77/6.6	primordial components of the cytoskeleton and the nuclear envelope	**2.88**
21	Lamin A/C transcript variant 1	Q5I6Y4	30	74/6.4	71/6.1	primordial components of the cytoskeleton and the nuclear envelope	**only in Campto**
22	Progerin	Q6UYC3	45	69/6.2	70/6.6	primordial components of the cytoskeleton and the nuclear envelope	**2.99**
23	Progerin	Q6UYC3	42	69/6.2	71/6.8	primordial components of the cytoskeleton and the nuclear envelope	**2.03**
	Others						
24	Premature ovarian failure, 1B	Q5H9E9	45	70/5.9	77/6.2		**0.35**
25	WD repeat protein 61	Q9GZS3	52	34/5.2	39/5.0		**only in Campto**

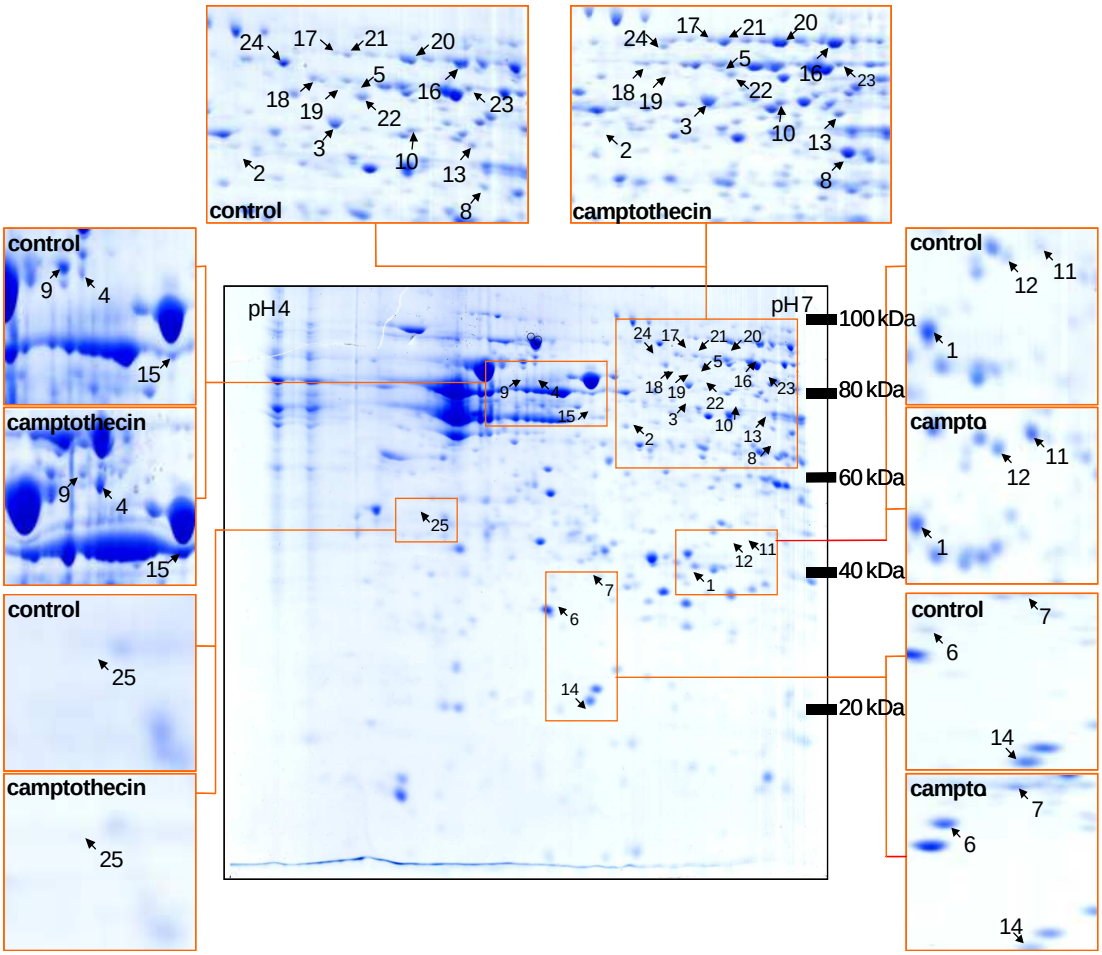

Figure 12: 2D map of proteins with pIs of 4-7 derived from camptothecin-treated HT-29 cells

Proteins were separated on a linear pH 4-7 IPG-strip in the first dimension and on a 12.5% SDS-polyacrylamide gel in the second dimension. Enlargements from identical sections of gels derived from separations of HT-29 proteins from control cells or cells treated with 50 µM camptothecin are shown around a typical gel derived from control cells.

After camptothecin treatment twenty protein spots were found differentially regulated in the pH range 6-11, from which nineteen were identified via database search with the search engine Mascot (Tab. 11, Fig. 13).

The gene regulation enzyme heterogeneous nuclear ribonucleoprotein A2/B1 was identified in two different protein spots, one up and one down regulated compared to the control, probably differing in their phosphorylation stage. The metabolic enzyme alpha enolase, which binds to the c-myc promoter and acts as a transcriptional repressor, was also found twice with differing expression levels. The gene regulating RNA-binding protein Raly and the metabolism proteins GIPC PDZ domain-containing protein 1, inosine-5'-monophosphate dehydrogenase 2 and low molecular weight phosphotyrosine protein phosphatase were found decreased in their expression levels. The metabolic enzymes ATP synthase O subunit, NAD(P)H dehydrogenase [quinone] 1 and glyceraldehyde-3-phosphate dehydrogenase were up-regulated in steady state levels, and the protein cyclophilin B was nearly 10-fold increased in its expression. Keratin type I cytoskeletal 18 was also found increased in its expression level. The mitochondrial aspartate aminotransferase was only detectable under camptothecine treatment.

Table 11: Proteins with pIs 6-11 regulated in steady state levels by camptothecin in HT-29 cells

The spot numbers are identical to those given in Fig. 13. Abbreviations are explained in the legend to Table 10. Identical proteins that were identified as regulated at both pH-gradients are indicated only once, i.e. in Table 10 and not in addition in Table 11; (n = 6).

Spot No.	Protein description	Swiss Prot Acc. No.	Sequ. cov. [%]	Mw/pI theor.	Mw/pI exp.	Subcellular location	Reg.-fac. Campto/C
	Gene regulating proteins						
1	Heterogeneous nuclear ribonucleoproteins A2/B1	P22626	42	37/9.0	40/8.6	nuclear; component of ribonucleosomes	**3.56**
2	Heterogeneous nuclear ribonucleoproteins A2/B1	P22626	44	36/8.7	31/7.9	nuclear; component of ribonucleosomes	**0.49**
3	RNA-binding protein Raly	Q9UKM9	31	33/9.2	44/9.9	nucleus	**0.32**
	Kinases						
4	Phosphoglycerate kinase 1	P00558	24	45/8.3	47/7.2	cytoplasm	**0.42**
	Metabolic enzymes						
5	Alpha-Enolase	P06733	51	47/7.0	54/7.7	cytoplasm, cell membrane, nucleus	**2.76**
6	Alpha-Enolase	P06733	53	47/7.0	53/6.7	cytoplasm, cell membrane, nucleus	**0.37**
7	Aspartate aminotransferase, mitochondrial [Precursor]	P00505	45	48/9.1	48/9.9	mitochondrion; mitochondrial matrix	**only in Campto**
8	ATP synthase O subunit, mitochondrial [Precursor]	P48047	62	23/10.0	26/11.0	mitochondrion; mitochondrial matrix	**2.30**
9	Cyclophilin B, Chain A	P23284	61	20/9.2	20/10.5	endoplasmic reticulum	**9.39**
10	GIPC PDZ domain-containing protein 1	O14908	56	36/5.9	44/6.3	cytoplasm, membrane; peripheral membrane protein	**0.49**
11	Glyceraldehyde-3-phosphate dehydrogenase	P04406	49	36/8.6	40/8.4	cytoplasm	**2.11**

12	Inosine-5'-monophosphate dehydrogenase 2	P12268	31	56/6.4	63/6.9	mitochondrion	**0.49**
13	Low molecular weight phosphotyrosine protein phosphatase	P24666	40	18/7.0	19/7.3	cytoplasm	**0.41**
14	NAD(P)H dehydrogenase [quinone] 1	P15559	38	31/8.9	34/9.9	cytoplasm	**2.07**
	Cytoskeleton proteins						
15	Keratin, type I cytoskeletal 18	P05783	41	48/5.3	30/7.0	intermediate filament associated	**2.32**

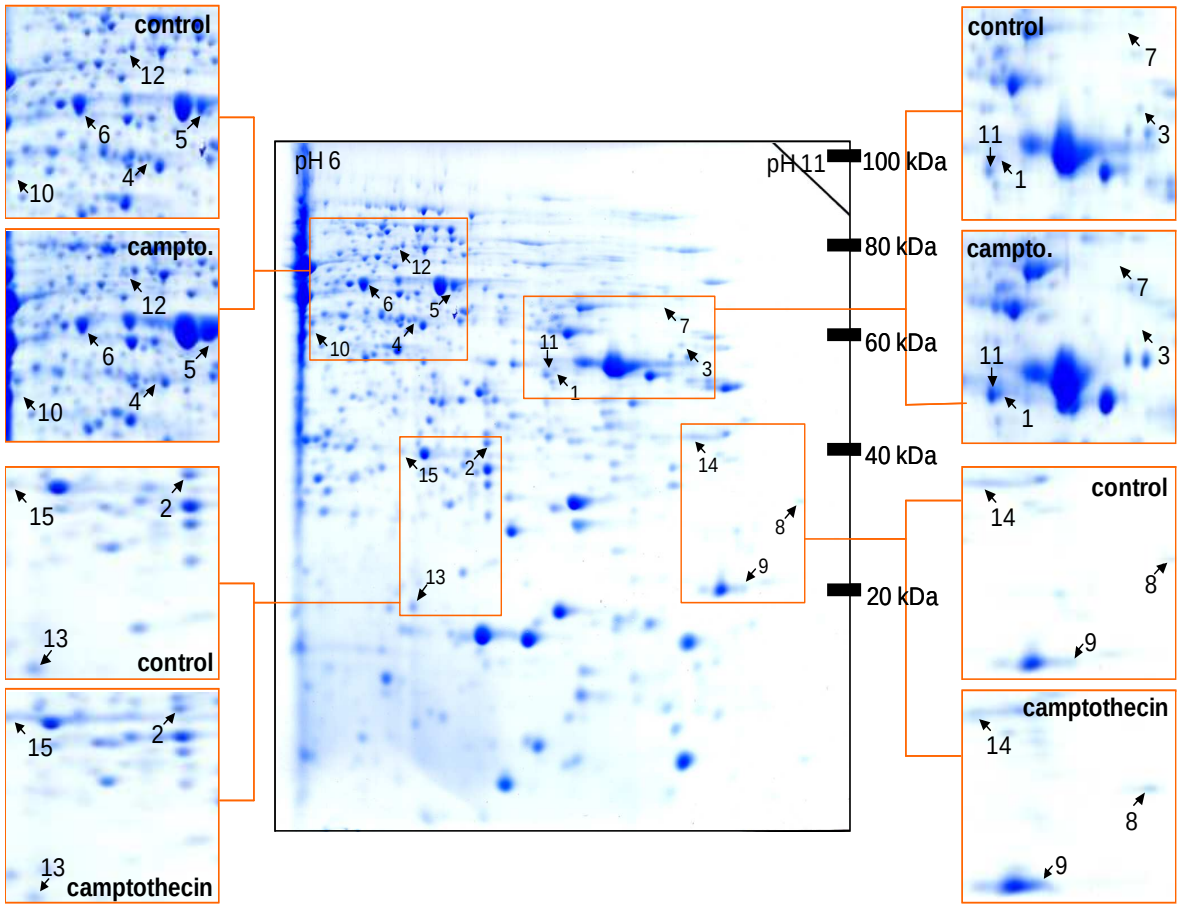

Figure 13: 2D map of proteins with pIs of 6-11 derived from camptothecin-treated HT-29 cells

Proteins were separated on a linear pH 6-11 IPG-strip in the first dimension and on a 12.5% SDS-polyacrylamide gel in the second dimension. Enlargements from identical sections of gels derived from separations of HT-29 proteins from control cells or cells treated with 50 µM camptothecin are shown around a typical gel derived from control cells.

However, a shift in regulated proteins (Tables 10 and 11) could be observed in camptothecin-treated cells versus the flavone-treatment from those playing a role in metabolism (31% versus 41%) to such belonging to the cytoskeleton (32% versus 16%). In camptothecin-exposed cells especially the increase of lamins, which are proteins of the nuclear envelope, appeared as specific markers of the drugs' action (Fig. 14).

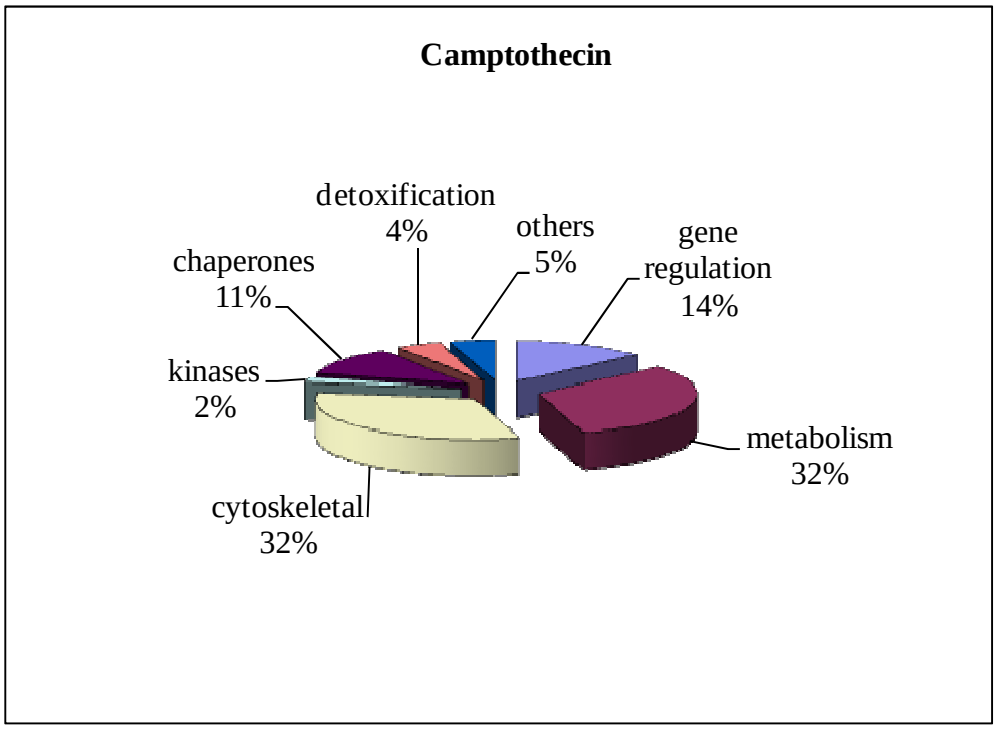

Figure 14: Classification of differentially expressed proteins after camptothecin incubation

4.4. 2-DE analysis of fractionated cell lysates from flavone-treated HT-29 cells

Fractionating the cell lysates according to their cellular compartment is a promising tool to get insights into altered expression levels of the proteins in different subcellular compartments, possibly in their regulatory mechanisms, and to be able to see differences in the expression even of minor abundant proteins, respectively. The fractions I-IV represent the following cellular compartments:

- cytosol
- membrane/organelles
- nucleus
- cytoskeleton

For the fractionation experiments much more cellular material was needed to gain enough protein lysate, so that the number of gels was limited to four per group and additionally to the constraint of the pH range 4-7, which revealed more differentially regulated proteins in the former experiments. Moreover, the analysis was restricted to flavone effects. On a 2D gel image the software detected an average of 500 protein spots in the first three fractions. The statistical analysis of the ProteomWeaver software led to forty-nine spots in fraction I, thirty-seven spots in fraction II, fourteen spots in fraction II and nine spots in fraction IV, which were regulated in their steady state levels compared to the control cells. These spots were picked in quadruplicate, destained, digested enzymatically and spotted by hand onto an 400/384 AnchorChip^{TM} target to gain spectra via MALDI-TOF mass spectrometry. After the software-based analysis of the spectra and the following database search described in 3.5.3 we were able to identify 86% of the 109 regulated protein spots.

4.4.1. Fraction I – cytosolic proteins

Forty-three proteins of the cytosolic fraction were identified via Mascot database search (Tab. 12, Fig. 15). Eighteen of them showed higher expression levels according to their control gels, like the chaperones heat-shock protein beta-1 and protein disulfide-isomerase. Furthermore the detoxification enzyme peroxiredoxin-6 and the gene regulating proteins eucaryotic translation initiation factor 4E-binding protein 1, heterogeneous nuclear ribonucleoprotein H, replication protein 32 kDa subunit, SET protein and the twice identified ribonucleoprotein La. Similar regulation tendencies were found for the metabolic proteins acidic leucine-rich nuclear phosphoprotein 32 family member A, fumarylacetoacetase, lactoylglutathione lyase, stathmin and xaa-pro dipeptidase. Increase in expression levels was

detected for the cell proliferation protein dynactin subunit 2, the signal transducing nuclear autoantigenic sperm protein, keratin type II cytoskeletal 8 and the NSFL1 (P97) cofactor.

Fourteen of the identified proteins showed decreased expression levels compared to the control, like pyridoxal kinase, adenosylhomocysteinase, glycyl-tRNA synthetase, stress-induced-phosphoprotein 1, tryptophanyl-tRNA synthetase and the signal transduction proteins 14-3-3 protein beta/alpha, 14-3-3 protein epsilon isoform transcript variant 1 and calretinin. Furthermore the cell proliferation proteins cofilin-1, destrin and Src substrate cortactin showed similar regulation tendencies, as well as thioredoxin-like protein 2 and the hypothetical protein DKFZp686A0439. The chaperone heat shock cognate 71 kDa protein was identified twice, one protein spot showing a decreased expression, whereas the other one was only detectable in flavone-treated cells. Another five protein spots only showed up in the flavone treatment, like the chaperones 78 kDa glucose-regulated protein and the mitochondrial stress-70 protein, as well as RuvB-like 1, cathepsin Z and the guanine nucleotide-binding protein. Five proteins were not detectable any longer after flavone treatment and therefore only identified in the gels derived from the control cells. These are creatine kinase B-Type, kinesin light chain 4, S-adenosylmethionine synthetase isoform type-2, WD repeat protein 1 and the hypothetical protein AARSD1.

Table 12: Cytosolic proteins with pI between 4-7 regulated in steady state level by flavone in HT-29 cells

Proteins altered significantly by 24 h flavone treatment of HT-29 cells were identified by MALDI-TOF MS; Reg.-fac. F/C, regulation of the spot intensities observed between flavone treated cells versus control cells according to Proteomweaver software analysis with $P < 0.05$ (Student's t-test); only in F, associated protein spot was only detectable in the flavone exposed cells. Other abbreviations are given in the legend to Tab. 8; (n = 6). The spot numbers are identical to those given in Fig. 15.

Spot No.	Protein description	Swiss Prot Acc. No.	Sequ. cov. [%]	Mw/pI theor.	Mw/pI exp.	Subcellular location	Reg.-fac. F/C
	Chaperones						
1	78 kDa glucose-regulated protein [Precursor]	P11021	48	72/4.9	79/5.0	Endoplasmic reticulum; endoplasmic reticulum lumen	**only in F**
2	Heat shock cognate 71 kDa protein	P11142	44	71/5.2	71/5.5	Translocates rapidly from the cytoplasm to the nuclei	**0.40**
3	Heat shock cognate 71 kDa protein	P11142	40	71/5.2	65/5.4	Translocates rapidly from the cytoplasm to the nuclei	**only in F**
4	Heat-shock protein beta-1	P04792	36	23/6.0	29/5.7	Cytoplasm. Nucleus.	**4.44**
5	Protein disulfide-isomerase [Precursor]	P07237	47	57/4.6	61/4.8	Endoplasmic reticulum; endoplasmic reticulum lumen.	**2.92**
6	Stress-70 protein, mitochondrial [Precursor]	P38646	29	74/5.8	72/5.6		**only in F**
	Detoxification enzymes						
7	Peroxiredoxin-6	P30041	65	25/6.0	29/6.0	Cytoplasmic, lysosomal and also found in lung secretory organelles	**2.99**
	Gene regulating proteins						
8	Eukaryotic translation initiation factor 4E-binding protein 1	Q13541	46	25/5.8	29/5.9		**2.17**
9	Heterogeneous nuclear ribonucleoprotein H	P31943	45	49/5.9	54/6.0	Nucleus; nucleoplasm	**2.36**
10	Ribonucleoprotein La	P05455	45	47/6.8	51/6.6	Nucleus	**2.68**

11	Ribonucleoprotein La	P05455	46	47/6.8	52/6.3	Nucleus	**2.26**
12	Replication protein A 32 kDa subunit	P15927	25	30/6.5	33/5.9	Nucleus. Also present in PML nuclear bodies.	**2.01**
13	RuvB-like 1	Q9Y265	40	51/6.0	55/6.4	Nucleus; nuclear matrix. Nucleus; nucleoplasm. Cytoplasm. Membrane.	**only in F**
14	SET protein	Q6FHZ5	30	33/4.1	28/6.0	Cytoplasm, ER, Nucleus	**5.96**
	Kinases						
15	Creatine kinase B-type	P12277	45	43/5.3	47/5.7	Cytoplasm	**only in C**
16	Pyridoxal kinase	O00764	46	35/5.7	38/5.8	Cytoplasm	**0.49**
	Metabolic enzymes						
17	Acidic leucine-rich nuclear phosphoprotein 32 family member A	P39687	31	29/3.4	32/4.0	Nucleus. Cytoplasm. Shuttles between nucleus and cytoplasm	**3.27**
18	Adenosylhomocysteinase	P23526	27	48/5.9	47/6.3	Cytoplasm	**0.50**
19	Cathepsin Z [Precursor]	Q9UBR2	35	33/6.1	40/5.0	Lysosome	**only in F**
20	Fumarylacetoacetase	P16930	51	47/6.5	45/6.7		**2.72**
21	Glycyl-tRNA synthetase	P41250	35	78/5.8	74/6.2		**0.42**
22	Kinesin light chain 4	Q9NSK0	37	70/5.7	67/6.2	nucleus, cytoplasm, mitochondria	**only in C**
23	Lactoylglutathione lyase	Q04760	40	20/5.1	25/5.0		**2.83**
24	S-adenosylmethionine synthetase isoform type-2	P31153	46	44/6.0	53/6.3		**only in C**
25	Stathmin	P54227	49	17/5.7	18/5.5	Cytoplasm	**3.87**
26	Stress-induced-phosphoprotein 1	P31948	42	63/6.4	64/6.4	Cytoplasm, Nucleus	**0.49**
27	Tryptophanyl-tRNA synthetase	P23381	44	53/5.8	56/6.1		**0.35**
28	Xaa-Pro dipeptidase	P12955	41	55/5.6	55/5.9		**3.31**
	Signal transduction						
29	14-3-3 protein beta/alpha	P31946	63	28/4.6	30/4.7	Cytoplasm	**0.36**
30	14-3-3 protein epsilon isoform transcript variant 1	Q4VJB6	57	27/4.8	32/4.6	very abundant in mammalian brain tissues and located preferentially in neurons	**0.36**

31	Calretinin	P22676	50	32/4.9	30/5.0	Brain	**0.49**
32	Guanine nucleotide-binding protein G(I)/G(S)/G(T) beta subunit 2	P62879	35	38/5.6	38/5.6		**only in F**
33	Nuclear autoantigenic sperm protein	P49321	34	49/4.2	68/4.3	Nucleus	**5.52**
	Cell proliferation						
34	Cofilin-1	P23528	62	19/8.2	18/6.4	Nucleus. Cytoplasm.	**0.26**
35	Destrin	P60981	44	19/8.1	18/6.6	Widely distributed in various tissues	**0.30**
36	Dynactin subunit 2	Q13561	39	44/5.0	54/5.2	Cytoplasm. Membrane; peripheral membrane protein	**2.05**
37	Src substrate cortactin	Q14247	43	62/5.1	86/5.4	Cytoplasm, Associated with membrane ruffles and lamellipodia	**0.39**
38	WD-repeat protein 1	O75083	44	67/6.2	65/6.7		**only in C**
	Cytoskeleton proteins						
39	Keratin type II cytoskeletal 8	P05787	39	54/5.4	55/5.6	muscle fibers	**2.21**
	Others						
40	Hypothetical protein AARSD1	Q9BTE6	40	59/5.5	50/6.3	Cytoplasm	**only in C**
41	Hypothetical protein DKFZp686A0439	Q68DG1	42	74/5.2	87/5.4		**0.49**
42	NSFL1 (P97) cofactor	Q5JXA5	55	41/5.0	49/5.0		**2.09**
43	Thioredoxin-like protein 2	O76003	51	33/5.3	43/5.5	Cytoplasmic; under the plasma membrane.	**0.23**

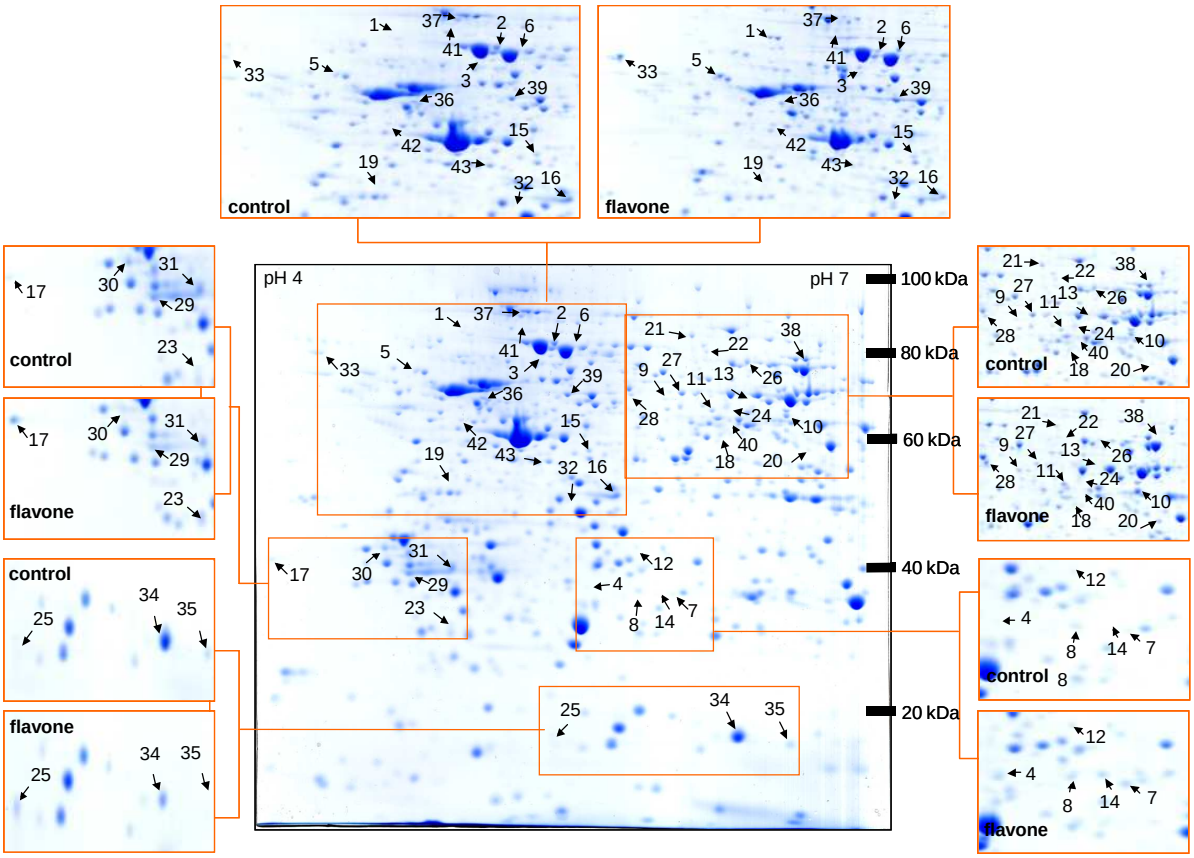

Figure 15: 2D map of cytosolic proteins from flavone-treated HT-29 cells

Proteins were separated on a linear pH 4-7 IPG-strip in the first dimension and on a 12.5% SDS-polyacrylamide gel in the second dimension. Enlargements from identical sections of gels derived from separations of HT-29 proteins from control cells or cells treated with 150 µM flavone are shown around a typical gel derived from control cells.

4.4.2. Fraction II – membrane/organelle proteins

The membrane/organelle fraction led to thirty-three differentially expressed and identified proteins (Tab. 13, Fig. 16). Nine of them showed higher expression levels, like the mitochondrial thioredoxin-dependent peroxide reductase, the gene regulating elongation factor Ts, as well as the metabolic enzymes dihydrolipoamide S-acetyltransferase, inosine-5'-monophosphate dehydrogenase 2 and inorganic pyrophosphatase, while the latter was identified in another protein spot, which was down regulated. The keratins type II cytoskeletal 8 and type I cytoskeletal 18, as well as the lymphocyte antigen 9 and the NS5ATP1 protein were increased in their steady state levels. Eighteen of the differentially expressed proteins showed decreased expression levels after flavone treatment, especially the chaperones and the gene regulating enzymes. The detoxification enzyme glutathione S-transferase P and the metabolism proteins F-actin capping protein alpha-1 subunit, NG,NG-dimethylarginine dimethylaminohydrolase 1, retinal dehydrogenase 1 and the stress-induced-phosphoprotein 1 were also decreased in their steady state levels. In contrast to the other down regulated chaperones in this fraction, the protein disulfide-isomerase A6 was solely detectable in the flavone treated cells. Five proteins belonging to the GO class metabolism were that much decreased in their expression levels through flavone treatment, that they were only detected in the control cells. These proteins are calmodulin, D-3-phosphoglycerate dehydrogenase, glutathione syntethase, G-rich sequence factor 1 and macrophage capping protein.

Table 13: Membrane/organelle proteins with pI between 4-7 regulated in steady state level by flavone in HT-29 cells

Proteins altered significantly by 24 h flavone treatment of HT-29 cells were identified by MALDI-TOF MS; Reg.-fac. F/C, regulation of the spot intensities observed between flavone treated cells versus control cells according to Proteomweaver software analysis with $P < 0.05$ (Student's t-test); only in F, associated protein spot was only detectable in the flavone exposed cells. Other abbreviations are given in the legend to Tab. 8; (n = 6). The spot numbers are identical to those given in Fig. 16.

Spot No.	Protein description	Swiss Prot Acc. No.	Sequ. cov. [%]	Mw/pI theor.	Mw/pI exp.	Subcellular location	Reg.-fac. F/C
	Chaperones						
1	Protein disulfide-isomerase A6 [Precursor]	Q15084	55	47/5.0	58/5.1	Endoplasmic reticulum; endoplasmic reticulum lumen	**only in F**
2	Protein DJ-1	Q99497	83	20/6.3	25/6.3	Nucleus. Cytoplasm. Associated with mitochondria in some cells	**0.44**
3	T-complex protein 1 subunit beta	P78371	61	58/6.0	54/6.4	Cytoplasm	**0.30**
4	T-complex protein 1 subunit epsilon	P48643	50	61/5.5	58/5.6	Cytoplasm	**0.43**
5	T-complex protein 1 subunit zeta	P40227	54	58/6.3	56/6.6	Cytoplasm	**0.32**
	Detoxification enzymes						
6	Glutathione S-transferase P	P09211	57	24/5.4	25/5.6	Cytoplasm	**0.20**
7	Peroxiredoxin 3 Expasy: Thioredoxin-dependent peroxide reductase, mitochondrial [Precursor]	P30048	27	28/7.1	26/6.2	Mitochondrion	**3.42**
	Gene regulating proteins						
8	Elongation factor 1-beta	P24534	32	25/4.5	35/4.4	eukaryotic translation elongation factor 1 complex	**0.41**
9	Elongation factor Ts, mitochondrial [Precursor]	P43897	48	38/7.6	37/6.7	Mitochondrion	**2.04**
10	Eukaryotic translation initiation factor 5A	P63241	75	17/5.1	19/5.1	Cytoplasm, Nucleus	**0.44**
11	Heterogeneous nuclear ribonucleoprotein K	P61978	43	51/5.2	62/5.5	Cytoplasm. Nucleus; nucleoplasm	**0.41**

12	Histone-binding protein RBBP4	Q09028	29	48/4.7	59/4.7	Nucleus	**0.46**
13	Proliferation-associated protein 2G4	Q9UQ80	57	44/6.1	50/6.4	Cytoplasm. Nucleus; nucleolus.	**0.46**
14	SET translocation (Myeloid leukemia-associated)	Q5VXV2	27	31/4.1	25/4.8	Nucleus	**0.22**
15	Transcription intermediary factor 1-beta	Q13263	19	81/5.7	32/4.5	Nucleus	**0.39**
16	Transcription intermediary factor 1-beta	Q13263	19	81/5.7	79/4.6	Nucleus	**0.35**
	Metabolic enzymes						
17	Calmodulin	P62158	53	17/4.1	19/4.0	cytoplasm, plasma membrane	**only in C**
18	D-3-phosphoglycerate dehydrogenase	O43175	42	57/6.3	55/6.7		**only in C**
19	Dihydrolipoamide S-acetyltransferase	Q86YI5	35	69/8.0	74/5.7	pyruvate dehydrogenase complex	**2.39**
20	F-actin capping protein alpha-1 subunit	P52907	72	33/5.5	39/5.5	cytoskeleton	**0.47**
21	Glutathione synthetase	P48637	42	53/5.7	52/5.7		**only in C**
22	G-rich sequence factor 1	Q12849	47	51/5,5	60/5.2	Cytoplasm	**only in C**
23	Inosine-5'-monophosphate dehydrogenase 2	P12268	41	56/6.4	56/6.8		**2.21**
24	Inorganic pyrophosphatase	Q15181	72	36/6.3	40/5.6	Cytoplasm	**0.27**
25	Inorganic pyrophosphatase	Q15181	74	33/5.5	42/5.5	Cytoplasm	**2.52**
26	Macrophage capping protein	P40121	30	39/5.9	43/6.1	Cytoplasm. Nucleus	**only in C**
27	NG,NG-dimethylarginine dimethylaminohydrolase 1	O94760	66	31/5.5	38/5.6		**0.46**
28	Retinal dehydrogenase 1	P00352	42	55/6.3	51/6.6	Cytoplasm	**0.41**
29	Stress-induced-phosphoprotein 1	P31948	53	63/6.4	58/6.7	Cytoplasm, Nucleus	**0.42**
	Cytoskeleton proteins						
30	Keratin type II cytoskeletal 8	P05787	54	54/5.5	53/5.7	muscle fibers	**5.89**
31	Keratin type I cytoskeletal 18	P05783	58	47/5.3	48/5.5	Intermediate filaments	**4.16**
	Others						
32	NS5ATP1	Q546Z2	44	36/8.4	34/5.8		**2.00**
33	Lymphocyte antigen 9	Q5VYH7	22	67/5.3	69/5.9		**3.35**

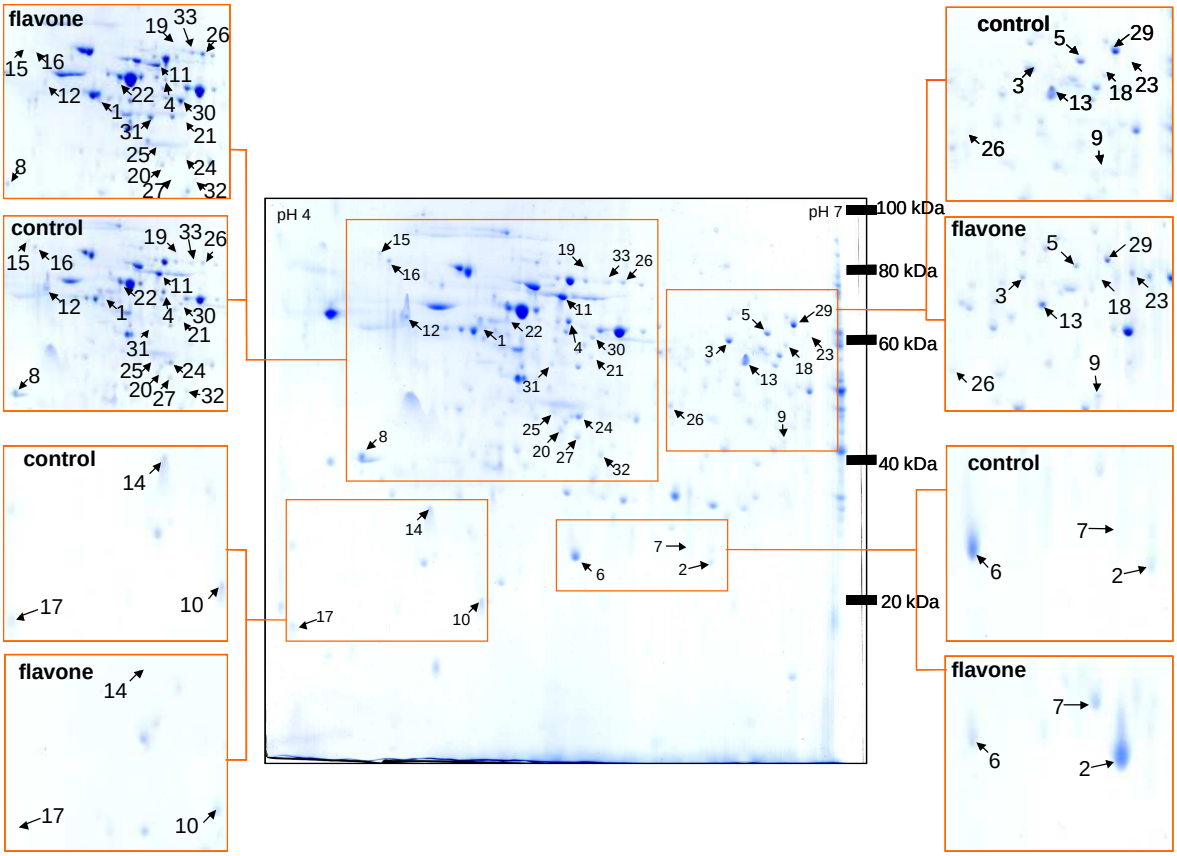

Figure 16: 2D map of membrane/organelle proteins from flavone-treated HT-29 cells

Proteins were separated on a linear pH 4-7 IPG-strip in the first dimension and on a 12.5% SDS-polyacrylamide gel in the second dimension. Enlargements from identical sections of gels derived from separations of HT-29 proteins from control cells or cells treated with 150 µM flavone are shown around a typical gel derived from control cells.

4.4.3. Fraction III – nuclear proteins

After MALDI-TOF mass spectrometry we identified ten protein spots in the nuclear fraction (Tab. 14, Fig. 17). Selenophosphate synthetase 1, the gene regulating proteins heterogenous nuclear ribonucleoprotein H and H3, the chaperone heat shock 70 kDa protein 1, as well as the cytoskeletal proteins lamin A, B2 and C showed decreased steady state levels, while the isoform 1A, the T-complex protein 1 subunit alpha and the calreticulin variant showed increased expression levels.

Table 14: Nuclear proteins with pI between 4-7 regulated in steady state level by flavone in HT-29 cells

Proteins altered significantly by 24 h flavone treatment of HT-29 cells were identified by MALDI-TOF MS; Reg.-fac. F/C, regulation of the spot intensities observed between flavone treated cells versus control cells according to Proteomweaver software analysis with $P < 0.05$ (Student's t-test). Other abbreviations are given in the legend to Tab. 8; (n = 6). The spot numbers are identical to those given in Fig. 17.

Spot No.	Protein description	Swiss Prot Acc. No.	Sequ. cov. [%]	Mw/pI theor.	Mw/pI exp.	Subcellular location	Reg.-fac. F/C
	Chaperones						
1	Heat shock 70 kDa protein 1	P08107	29	70/5.4	71/5.6	endoplasmic reticulum, mitochondrion, nucleus	**0.37**
2	Heat shock 70kDa protein 1	P08107	43	70/5.5	71/5.4	endoplasmic reticulum, mitochondrion, nucleus	**1.65**
3	T-complex protein 1 subunit alpha	P17987	54	61/5.7	62/6.2	Cytoplasm	**1.74**
	Gene regulating proteins						
4	Heterogeneous nuclear ribonucleoprotein H3	P31942	74	35/6.4	41/7.0	Nucleus	**0.34**
5	Heterogeneous nuclear ribonucleoprotein H	P31943	58	49/5.9	55/6.4	Nucleus; nucleoplasm	**0.42**
	Metabolic enzymes						
6	Calreticulin variant [Fragment]	Q53G71	47	47/4.2	67/4.2	located at the periphery of ER and SR membranes	**1.65**
7	Selenophosphate synthetase 1	Q5T5U8	48	43/5.6	46/5.8		**0.36**
	Cytoskeleton proteins						
8	Lamin A Expasy: Lamin-A/C	P02545	52	74/6.6	70/7.1	Nucleus	**0.09**
9	Lamin B2	Q03252	48	68/5.2	69/5.5	Nucleoplasmic side of the inner nuclear membrane	**0.42**
10	Lamin C Expasy: Lamin-A/C	P02545	51	65/6.4	63/6.9	Nucleus	**0.44**

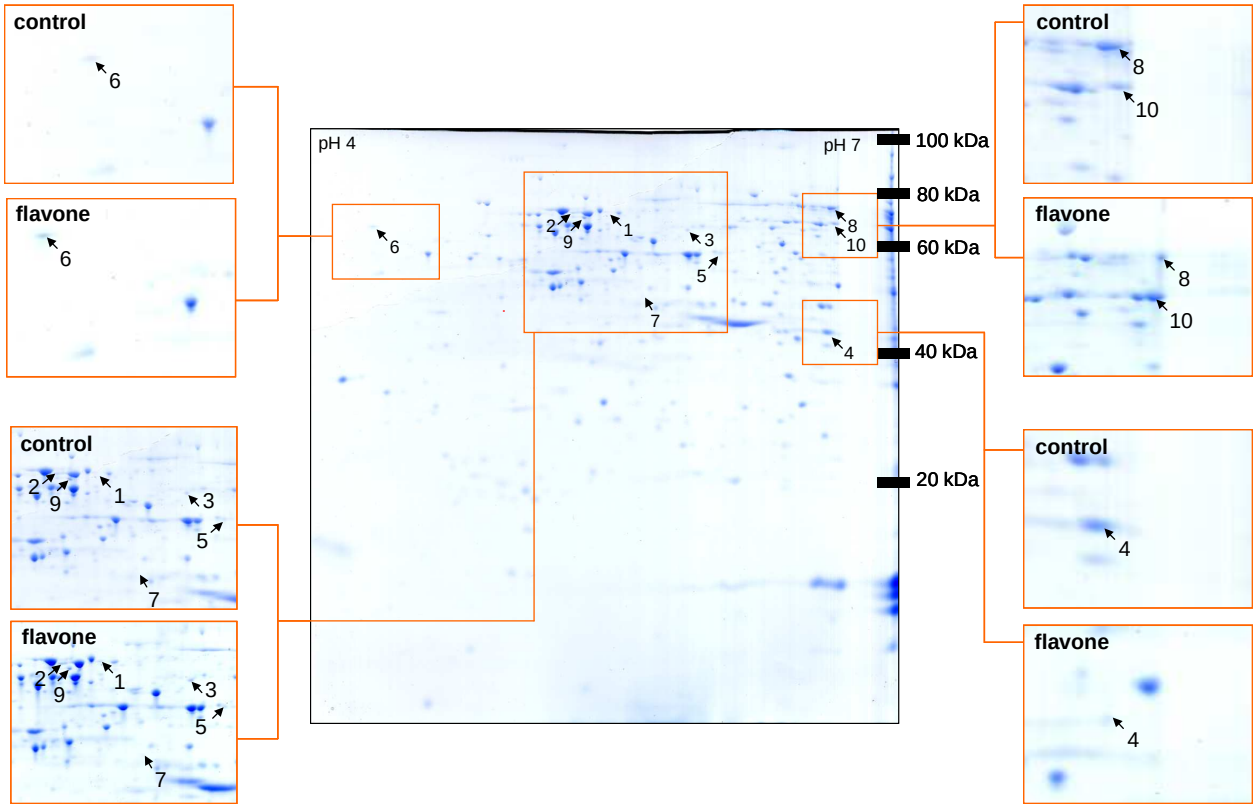

Figure 17: 2D map of nuclear proteins from flavone-treated HT-29 cells

Proteins were separated on a linear pH 4-7 IPG-strip in the first dimension and on a 12.5% SDS-polyacrylamide gel in the second dimension. Enlargements from identical sections of gels derived from separations of HT-29 proteins from control cells or cells treated with 150 µM flavone are shown around a typical gel derived from control cells.

4.4.4. Fraction IV – cytoskeletal proteins

In the cytoskeletal fraction eight proteins were identified through the database analysis as affected in amount by flavone (Tab. 15, Fig. 18). Only the keratin type I cytoskeletal 20 showed higher expression levels in this last fraction after flavone exposure. All others, like the chaperone protein disulfide-isomerase, the premature ovarian failure 1B protein and the cytoskeletal proteins mitofilin and keratin type II cytoskeletal 8, were decreased in their steady state levels. The latter two were each identified twice in different protein spots. The nuclear lamin A/C was that much reduced in its expression after flavone treatment, that it was only detectable in the gels of the control cells.

Table 15: Cytoskeletal proteins with pI between 4-7 regulated in steady state level by flavone in HT-29 cells

Proteins altered significantly by 24 h flavone treatment of HT-29 cells were identified by MALDI-TOF MS; Reg.-fac. F/C, regulation of the spot intensities observed between flavone treated cells versus control cells according to Proteomweaver software analysis with $P < 0.05$ (Student's t-test); only in F, associated protein spot was only detectable in the flavone exposed cells. Other abbreviations are given in the legend to Tab. 8; (n = 6). The spot numbers are identical to those given in Fig. 18.

Spot No.	Protein description	Swiss Prot Acc. No.	Sequ. cov. [%]	Mw/pI theor.	Mw/pI exp.	Subcellular location	Reg.-fac. F/C
	Chaperones						
1	Protein disulfide-isomerase A3 [Precursor]	P30101	44	57/6.0	60/5.9	Endoplasmic reticulum; endoplasmic reticulum lumen	**0.41**
	Cytoskeleton proteins						
2	Keratin type II cytoskeletal 8	P05787	49	54/5.4	57/5.9	Observed in muscle fibers	**0.33**
3	Keratin type II cytoskeletal 8	P05787	37	56/5.5	57/6.0	Observed in muscle fibers	**0.20**
4	Keratin type I cytoskeletal 20	P35900	67	49/5.4	53/5.7	Cytoplasm	**2.10**
5	Lamin-A/C	P02545	46	74/6.6	70/6.5	Nucleus	**only in C**
6	Mitofilin	Q16891	51	83/6.1	84/6.3	Mitochondrion; mitochondrial inner membrane	**0.21**
7	Mitofilin	Q16891	59	80/5.6	86/6.1	Mitochondrion; mitochondrial inner membrane	**0.32**
	Others						
8	Premature ovarian failure, 1B	5H9F0	52	69/5.9	69/6.5		**0.26**

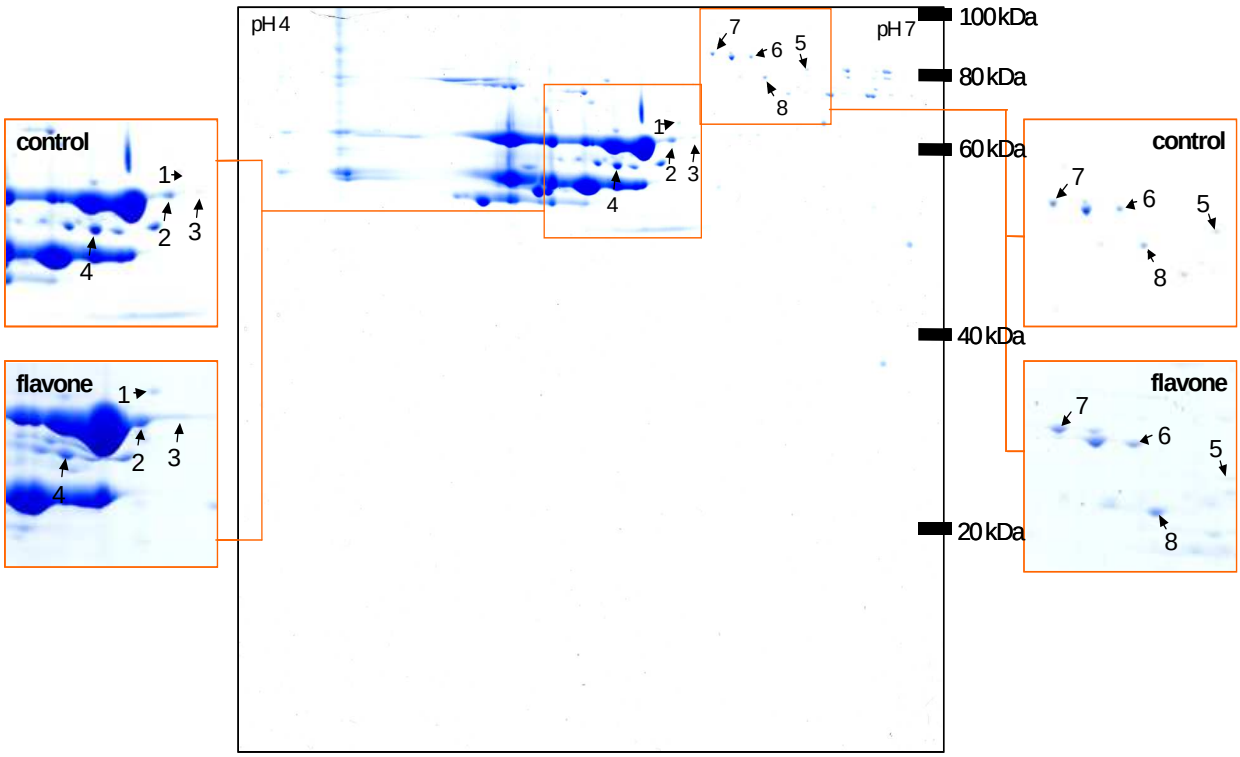

Figure 18: 2D map of cytoskeletal proteins from flavone-treated HT-29 cells

Proteins were separated on a linear pH 4-7 IPG-strip in the first dimension and on a 12.5% SDS-polyacrylamide gel in the second dimension. Enlargements from identical sections of gels derived from separations of HT-29 proteins from control cells or cells treated with 150 µM flavone are shown around a typical gel derived from control cells.

4.5. Histological and histochemical analysis of colonic tissue derived from flavone-treated C57BL/6J mice

4.5.1. Frequency and multiplicity of aberrant crypts in the colonic tissue

C57BL/6J mice were treated with the carcinogen 1,2-dimethylhydrazine (DMH) to induce preneoplastic lesions and divided into three groups (blocking, suppressing and therapy; with n=69 per group) with different modes of flavone treatment, representing the different stages of carcinogenesis. Aberrant crypts are preneoplastic lesions representing the first stages of morphological changes in colonic mucosa during cancer development and crypt multiplicity is usually increasing as carcinogenesis is proceeding. Flavone was applied by gavage either at low dose (15 mg/kg body weight/day) or at high dose (400 mg/kg body weight/day) to investigate its impact on the development of aberrant crypt foci or adenomas. Flavone administration was performed either concomitantly (blocking) or subsequently (suppressing) to DMH treatment, or after a 10-week treatment time with DMH where aberrant crypts had already developed (therapy group). The impact of flavone at low (15 mg/kg body weight) or high dosage (400 mg/kg body weight) on the formation of preneoplastic lesions in the colonic tissue of the DMH-treated animals in the above mentioned groups (blocking, suppressing and therapy) was investigated here. Five weeks after the last i.p. DMH-application the colonic tissue of the animals (n=17 per treatment group) in the blocking and suppressing groups exhibited about forty ACF per animal, as well as in the animals of the therapy group, assessed 4 weeks later. Mice not treated with DMH did not develop any ACF (data not shown). It was clearly demonstrated that flavone is able to reduce significantly the total number of ACF in colonic sections of DMH-treated C57BL/6J mice by acting as a blocking, suppressing or therapy agent, respectively (Fig. 19). Thus it was able to reduce the formation of ACF either during the DMH-induction phase or thereafter, independent of the flavone concentration or its application phase. The most prominent effect of flavone, also shown in Figure 19, was the suppression of the development of microadenomas. These were only detected in the therapy group and flavone was able to suppress the development significantly, with no single animal at the high dose group showing microadenomas.

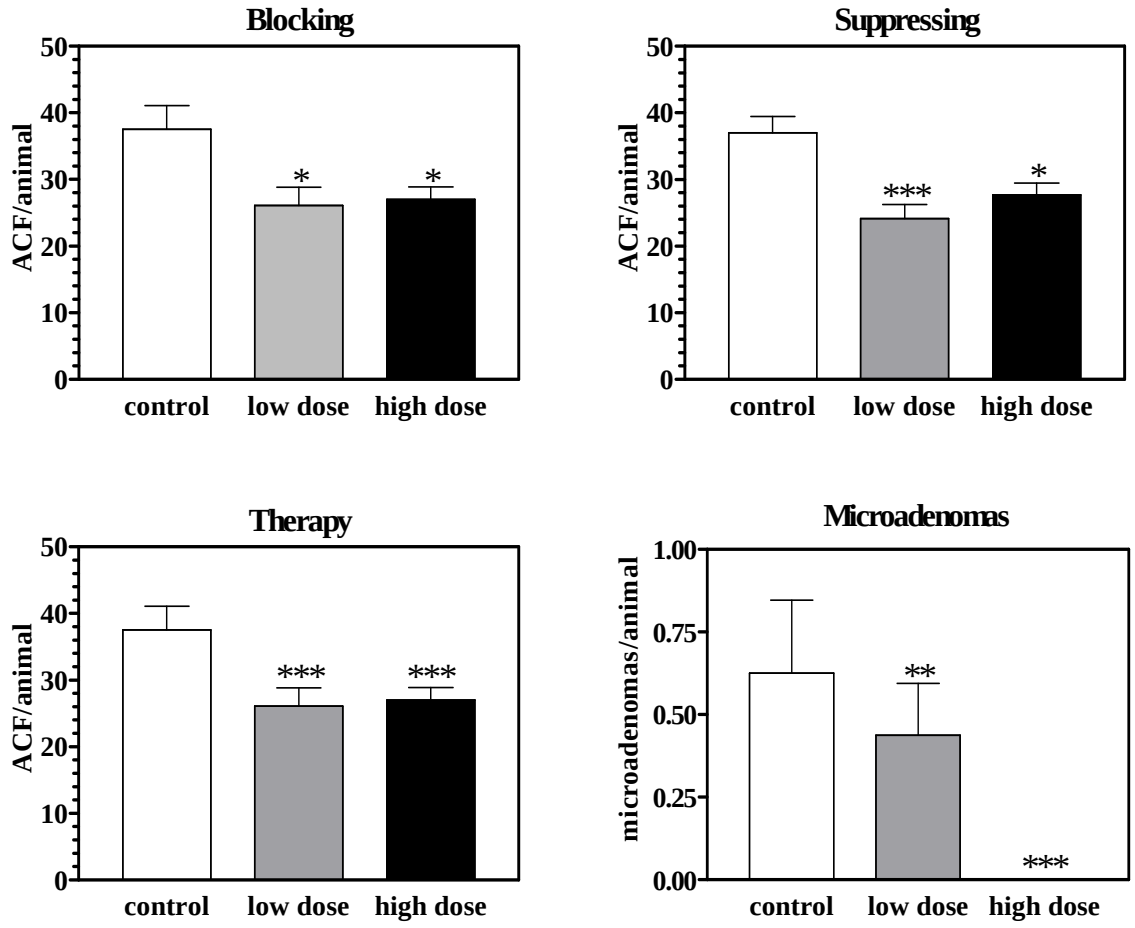

Figure 19: Aberrant crypts and microadenomas in mice from different intervention groups

Flavone at low and high dose reduced the numbers of ACF significantly (*,**,***Student`s t-test: $P<0.05$, $P<0.01$, $P<0.001$) when applied together with DMH (Blocking) or subsequently (Suppressing and Therapy). Microadenomas, solely appearing in the therapy group, were also reduced significantly in the low dose flavone group, and completely under high flavone treatment.

Therefore the impact of flavone on crypt multiplicity was studied in addition to frequency. Figure 20A shows the different crypt multiplicities within the colonic tissue induced by DMH-treatment of C57BL/6J mice. Figure 20B demonstrates that flavone affects crypt multiplicity independent on the dose. The highest impact was assessed in the suppressing and the therapy group concerning cluster of three or more aberrant crypts. The missing effects in the therapy group with more than five AC could be due to the fact that these stages were already developed further into microadenomas, because even the control shows less AC per animal than in the suppressing group.

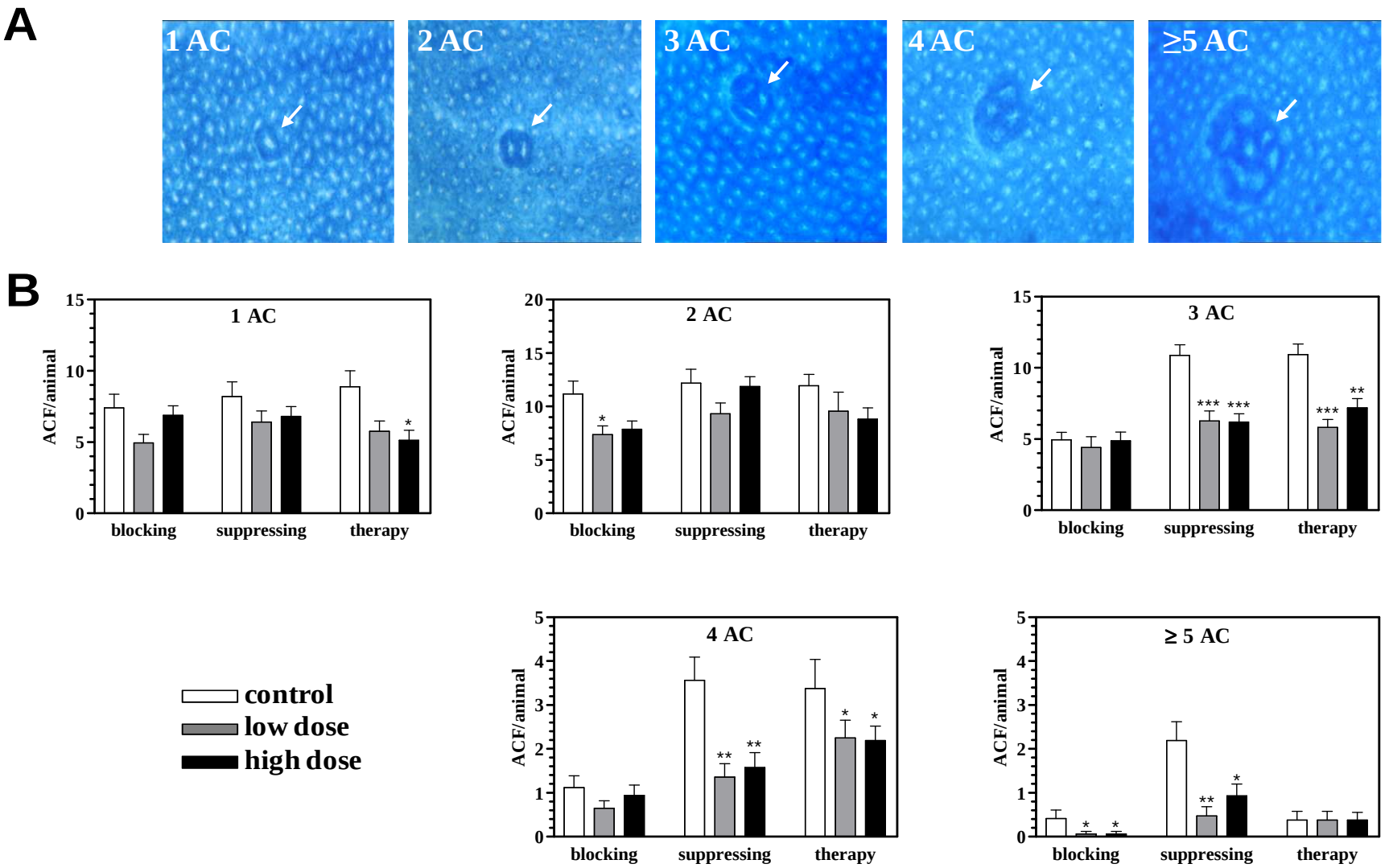

Figure 20: ACF in the tissue and ACF distribution

Flavone suppresses more potently ACF formation with higher crypt multiplicity. **(A)** ACF induced by treatment of mice with DMH with different numbers of aberrant crypts (AC) shown by arrows. **(B)** ACF in mice colonic tissue were counted and grouped by crypt multiplicity in the blocking, suppressing and therapy group after treatment with 15 mg/kg body weight flavone (low dose), 400 mg/kg body weight flavone (high dose) or with vehicle alone (control).

4.5.2. Modification of apoptosis and proliferation rates in the colonocytes of mice *in vivo*

Colonic tissue sections of C57BL/6J mice (n=6 per treatment group), which received BrdU via i.p. injection two hours before sacrifice, served for the analyses, investigating the effects of flavone on the proliferation and apoptosis rates in the murine colonocytes. BrdU is incorporated into DNA-synthesizing nuclei and can therefore be used for the identification of S-phase cells. Staining for BrdU incorporation (proliferation rates) and for caspase-3 (apoptosis rates) did not reveal any significant changes in colonic tissues in the blocking or the suppressing group, neither in the low nor in the high dose flavone groups in DMH-treated mice. Thus flavone had no effect on the apoptosis or proliferation rates in aberrant crypts of the first two groups. Contrary to the therapy group representing higher malignancy stages, where significant changes occurred in both tested rates. Here, the apoptosis rates were increased in the aberrant crypts of mice colons by both flavone doses, while the proliferation rate was significantly reduced by high dose flavone treatment (Fig. 21B).

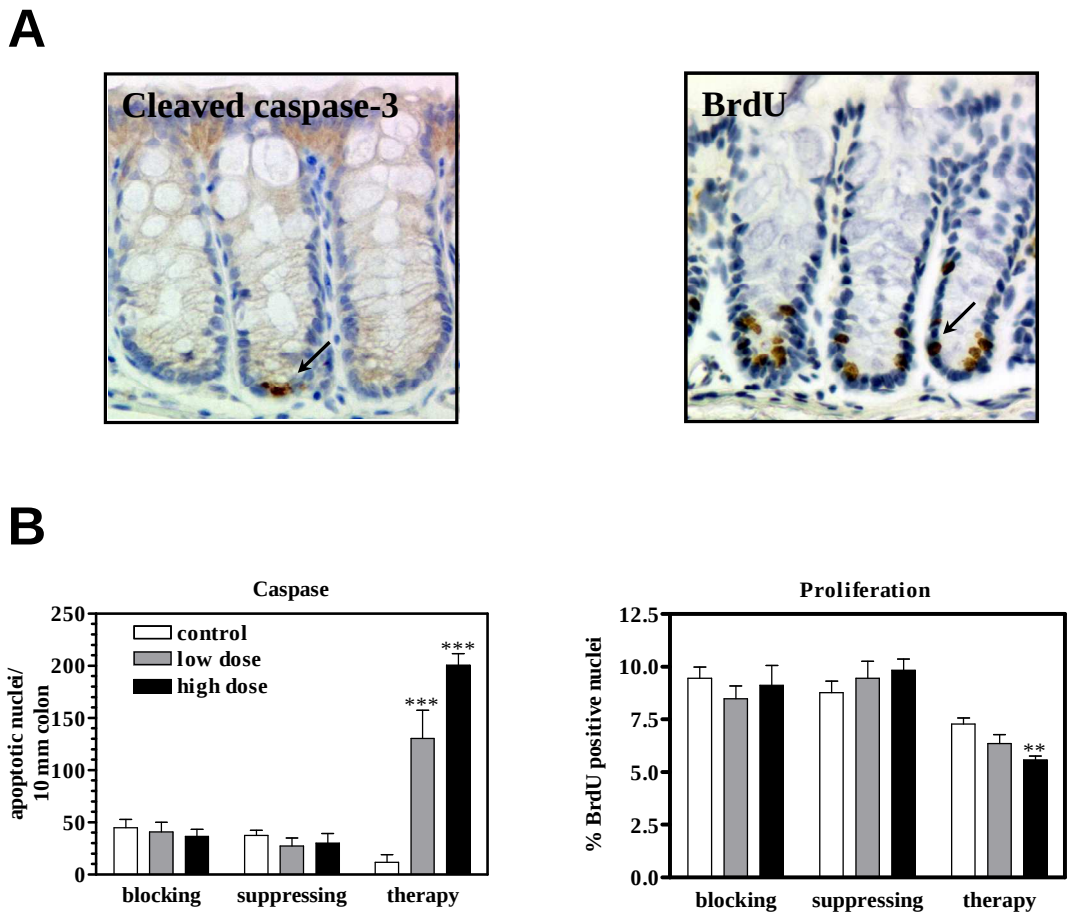

Figure 21: Flavone impact on proliferation and apoptosis rates in aberrant crypts of mice colonic tissues

(A) Cleaved caspase-3 (left panel) and BrdU-incorporation into DNA of S-phase cells (right panel) were detected in tissue sections of mice colon tissues by immunohistochemistry. (B) Nuclei staining positive for cleaved caspase-3 (left panel) or BrdU positive nuclei (right panel) in colonic tissues of mice from the three groups were determined in control animals and those treated either with low (15 mg/kg body weight) or high (400 mg/kg body weight) flavone doses.

4.6. 2-DE analysis of colonic tissue derived from flavone-treated C57BL/6J mice

Gradients between pH 3-10 were used to separate colonic proteins from the mice, treated with low or high dose flavone, or the vehicle alone, in the blocking, suppressing or therapy groups. These different groups concerning flavone treatment were designed to represent different stages of carcinogenesis, with the therapy group representing the highest stage of malignancy, where microadenomas had already developed. The ProteomWeaver software was able to detect around 600 distinct protein spots in a Coomassie stained 2D gel image. For the analysis six gels of the tissue from six different control mice (treated only with vehicle), derived from three independent 2D-PAGE experiments, were compared to six gels of the tissue from treated mice (15 or 400 mg flavone/kg body weight). Protein spots, which were found to be regulated significantly in their steady state level, compared to the associated spot in the control gels, were picked in quadruplicate and identified via MALDI-TOF MS.

4.6.1. Proteome analysis of tissues from the blocking group

Fifteen of the seventeen regulated protein spots were identified via MALDI-TOF in the blocking group treated with 15 mg flavone per kg body weight (low dose). The high dose treatment (400 mg/kg body weight) also changed the levels of seventeen proteins, of which sixteen could be identified (Tab. 16, Fig. 22).

Most of the proteins show the same trend (14) in change in expression levels by both, the low and the high dose flavone treatment. Merely annexin A4 was reduced in its steady state level by the low dose with no effects at the high dose, while the chaperone T-complex protein 1 subunit alpha B and the cytoskeletal protein vinculin were increased in expression levels by the high dose flavone treatment alone. The latter was the only cytoskeletal protein showing an increase in expression level whereas tropomodulin 3 and the keratins were decreased, with the keratin type I cytoskeletal 19 identified in three different protein spots. Except for the mitochondrial glutamate dehydrogenase 1 the other four identified metabolic enzymes were decreased in steady state levels, just as the gene regulating protein nucleoside diphosphate kinase. The nuclear lamin A/C and the fatty acid-binding protein showed increased expression levels.

Table 16: Proteins with pI 3-10 regulated in steady state level by flavone in murine colonic tissue of the blocking group

Protein descriptions are concerning the Swiss-Prot website (www.expasy.org/sprot/) with their associated primary accession numbers The spot numbers are identical to those given in Fig. 4. Proteins altered significantly by treatment of mice with flavone at 15 mg/ kg body weight (low dose; F low) or 400 mg/kg body weight (high dose, F high), as derived from analysis with the ProteomWeaver software, were identified by MALDI-TOF-MS; mowse score, probability based mowse score from Mascot with $P < 0.05$; Sequ. Cov [%], sequence coverage through the identified peptides; Matched peptides, non redundant peptides taken for the identification; measured M/pI, mass values calculated by the Proteome Weaver software referring to the low molecular weight standard and calculated pI values; theoretical M/pI, mass and pI values taken from the MSDB database; Reg.factor K/F low or high, regulation of the intensities of the treatment groups compared to the control group taken from the Proteome Weaver software with $P < 0.05$ (Student´s t-test); n.r., not regulated.

Spot No.	Protein description	Swiss Prot Acc. No.	Sequ. cov. [%]	Mowse Score	Peptides matched	Mw/pI theor.	Mw/pI exp.	Reg.-fac. F low/C	Reg.-fac. F high/C
	Annexins								
9	Annexin A4	P97429	39	153	10	36/5.4	37/5.2	**0.38**	**n.r.**
	Chaperones								
12	Protein disulfide-isomerase A5 [Precursor]	Q921X9	27	146	11	60/7.3	63/7.7	**2.62**	**2.81**
14	T-complex protein 1 subunit alpha B	P11983	35	166	12	61/5.8	63/6.0	**n.r.**	**2.37**
	Cytoskeleton and actin-remodeling proteins								
6	Keratin, type I cytoskeletal 19	P19001	41	160	11	45/5.3	45/4.5	**0.49**	**0.31**
8	Keratin, type I cytoskeletal 19	P19001	37	153	11	45/5.3	44/4.5	**0.51**	**0.46**
11	Keratin, type I cytoskeletal 19	P19001	57	184	17	45/5.3	48/4.6	**0.66**	**0.49**
10	Keratin, type II cytoskeletal 8	P11679	20	90	8	55/5.7	46/4.6	**0.44**	**0.24**
4	Tropomodulin-3	Q9JHJ0	54	163	15	40/5.0	47/4.7	**0.48**	**0.31**
16	Vinculin	Q64727	24	183	16	117/5.8	108/6.1	**n.r.**	**1.91**

	Gene regulating proteins								
17	Lamin-A/C	P48678	33	160	17	74/6.5	79/6.6	**1.86**	**1.54**
2	Nucleoside diphosphate kinase	Q5NC81	46	102	6	17/6.8	17/7.0	**0.34**	**0.38**
	Metabolic enzymes								
5	Creatine kinase B-type	Q04447	32	109	7	43/5.4	49/5.5	**0.31**	**0.47**
15	Glutamate dehydrogenase 1, mitochondrial [Precursor]	P26443	40	190	15	62/8.1	60/7.4	**1.93**	**1.70**
7	Glycerol-3-phosphate dehydrogenase 2	Q8VDT0	28	181	15	81/6.3	80/6.2	**0.27**	**0.40**
3	Propionyl-CoA carboxylase alpha chain, mitochondrial [Precursor]	Q91ZA3	47	217	22	80/6.8	82/6.5	**0.49**	**0.57**
1	similar to Glycerol-3-Phosphate Dehydrogenase	Q8BWM5	43	132	10	35/6.5	43/6.9	**0.49**	**0.45**
	Transport proteins								
13	Fatty acid-binding protein, adipocyte	P04117	54	77	6	15/8.0	14/9.0	**2.25**	**1.85**

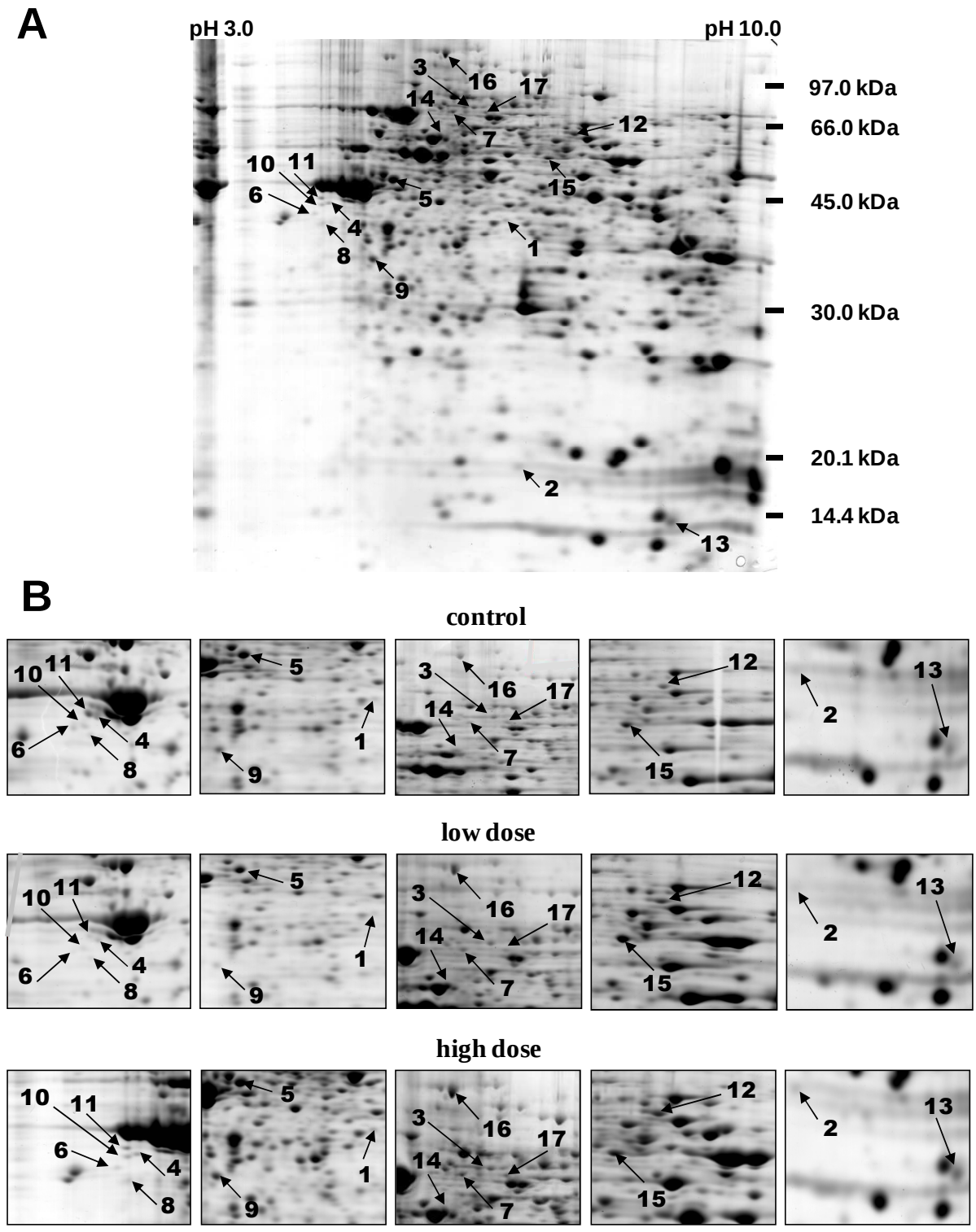

Figure 22: 2D gel of differentially expressed proteins from mice of the blocking group due to flavone treatment

2D-PAGE of proteins from colonic tissue extracts of mice treated with low dose or high dose flavone or with vehicle alone (control) during the phase of DMH-treatment (blocking group). Proteins were separated on a linear pH 3-10 IPG-strip in the first dimension and on a 12.5% SDS-polyacrylamide gel in the second dimension. (A) 2D-gel with separated proteins from the colons of flavone high dose mice. (B) Enlargements from identical sections of gels derived from separations of colon proteins from control mice or mice treated with low or high dose flavone.

4.6.2. Proteome analysis of tissues from the suppressing group

Using flavone as a suppressing agent, i.e. subsequent to DMH-treatment, resulted in the alteration of thirty-six proteins at low dose and thirty-five proteins at high dose treatment of which thirty could be identified in both groups (Tab. 17, Fig. 23). The impact on the protein expression levels was nearly identical at both dosages for proteins affected significantly at low and high doses. Only five proteins were not regulated significantly by both doses applied. The metabolic enzymes aldo-keto reductase and NG,NG-dimethylarginine dimethylamino-hydrolase 1, as well as the detoxification enzyme glutathione synthetase were increased in expression levels by the high dose treatment alone, while the gene regulating heterogeneous nuclear ribonucleoprotein A2/B1 was only up-regulated by low dose flavone. The proteasome subunit beta type 6 was solely detectable in the low dose flavone treatment samples. In contrast to the blocking group, only three of the twelve identified metabolism related proteins showed decreased expression levels, amongst them two were identified as the mitochondrial ornithine aminotransferase. The other metabolic enzymes showed increased expression levels, as well as the transport protein dynactin subunit 3 and the detoxification enzymes glutathione S-transferase Mu 3 and peroxiredoxin 6. The channel proteins, chaperones and cytoskeletal proteins were all decreased in steady state levels by both flavone treatments, likewise the mitochondrial peroxiredoxin 5 and the gene regulating protein eukaryotic translation initiation factor 5A.

The whole protein pattern being differentially expressed by the flavone treatment in the suppressing group differs considerably from those in the blocking group. The sole exception is the metabolism related protein creatine kinase B-type, however showing contrary expression levels with a decrease in the blocking and increase in the suppressing group.

Most interestingly, most of the proteins regulated by flavone-treatment in the suppressing group represent enzymes of the intermediary metabolism and especially of the Krebs-cycle such as citrate synthase, isocitrate dehydrogenase or succinate dehydrogenase, all of which increased in steady state levels.

Table 17: Proteins with pI 3-10 regulated in steady state level by flavone in murine colonic tissue of the suppressing group

Protein descriptions are concerning the Swiss-Prot website (www.expasy.org/sprot/) with their associated primary accession numbers. The spot numbers are identical to those given in Fig. 4. Proteins altered significantly by treatment of mice with flavone at 15 mg/ kg body weight (low dose; F low) or 400 mg/kg body weight (high dose, F high), as derived from analysis with the ProteomWeaver software, were identified by MALDI-TOF-MS; mowse score, probability based mowse score from Mascot with $P < 0.05$; Sequ. Cov [%], sequence coverage through the identified peptides; Matched peptides, non redundant peptides taken for the identification; measured M/pI, mass values calculated by the Proteome Weaver software referring to the low molecular weight standard and calculated pI values; theoretical M/pI, mass and pI values taken from the MSDB database; Reg.factor K/F low or high, regulation of the intensities of the treatment groups compared to the control group taken from the Proteome Weaver software with $P < 0.05$ (Student´s t-test); n.r., not regulated.

Spot No.	Protein description	Swiss Prot Acc. No.	Sequ. cov. [%]	Mowse Score	Peptides matched	Mw/pI theor.	Mw/pI exp.	Reg.-fac. F low/C	Reg.-fac. F high/C
	Channel proteins								
19	Chloride intracellular channel protein 1	Q9Z1Q5	80	364	14	27/5.1	30/5.0	**0.27**	**0.38**
26	Clca3 protein Chloride channel calcium activated 3	Q8R049	38	252	24	101/5.7	74/6.8	**0.30**	**0.28**
	Chaperones								
17	T-complex protein 1 subunit beta	P80314	30	130	10	58/6.0	58/6.5	**0.52**	**0.45**
24	T-complex protein 1 subunit epsilon	P80316	41	163	17	60/5.7	62/6.0	**0.49**	**0.46**
32	Tumor rejection antigen gp96	Q91V38	34	216	19	93/4.7	94/4.5	**0.46**	**0.81**
	Cytoskeleton and actin-remodeling proteins								
25	Moesin	P26041	26	61	11	68/6.2	72/6.9	**0.35**	**0.37**
30	Transgelin 2	Q91VU2	91	276	14	23/8.4	22/9.1	**0.54**	**0.40**
31	Transgelin 2	Q91VU2	84	193	13	23/8.4	23/9.1	**0.41**	**0.45**
33	Tropomyosin beta chain	P58774	44	115	12	33/4.6	45/4.4	**0.18**	**0.17**

	Detoxification enzymes								
11	Glutathione S-transferase Mu 3	P19639	26	99	6	26/8.1	28/8.7	**1.59**	**1.49**
10	Glutathione synthetase	P51855	22	160	10	52/5.6	55/5.6	**n.r.**	**2.34**
23	Peroxiredoxin-5, mitochondrial [Precursor]	P99029	42	117	7	22/9.0	14/8.6	**0.63**	**0.45**
3	Peroxiredoxin-6	O08709	77	230	19	25/5.7	26/6.1	**1.92**	**1.82**
	Gene regulating proteins								
21	Eukaryotic translation initiation factor 5A (Fragment)	Q5NCX0	44	79	7	17/4.9	16/5.0	**0.38**	**0.33**
16	Heterogeneous nuclear ribonucleoprotein A2/B1	Q91ZR9	21	93	6	36/8.7	39/9.6	**1.50**	**n.r.**
	Metabolic enzymes								
14	Adenosine kinase	P55264	14	109	6	40/5.8	51/5.7	**1.65**	**3.16**
5	Aldo-keto reductase AKR1C12	Q9R0M7	12	61	3	38/6.0	40/6.8	**n.r.**	**1.65**
4	Citrate synthase, mitochondrial [Precursor]	Q9CZU6	21	90	11	52/8.7	51/9.0	1.29	**1.57**
2	Creatine kinase B-type	Q04447	40	176	12	43/5.4	50/5.6	**1.42**	**2.45**
22	Fructose-bisphosphate aldolase A	P05064	61	195	14	40/8.4	43/8.7	**0.37**	**0.39**
12	Isocitrate dehydrogenase [NAD] subunit alpha, mitochondrial [Precursor]	Q9D6R2	34	194	14	40/6.3	42/5.8	**1.45**	**1.85**
8	NG,NG-dimethylarginine dimethylaminohydrolase 1	Q9CWS0	64	211	15	32/5.6	39/5.8	**n.r.**	**1.62**
27	Ornithine aminotransferase, mitochondrial [Precursor]	P29758	36	83	10	49/6.2	52/6.3	**0.43**	**0.42**

28	Ornithine aminotransferase, mitochondrial [Precursor]	P29758	48	189	15	49/6.2	51/6.2	**0.44**	**0.54**
7	Pycrl protein - Pyrroline-5-carboxylate reductase-like	Q8R0P9	43	133	14	29/6.8	31/7.7	**1.55**	**1.84**
6	Succinate dehydrogenase [ubiquinone] iron-sulfur protein, mitochondrial [Precursor]	Q9CQA3	44	153	12	33/9.0	32/9.5	**2.39**	**2.28**
9	UDP-glucose 6-dehydrogenase	O70475	47	186	15	55/7.5	59/8.3	**1.56**	**1.73**
	Transport proteins								
1	Dynactin subunit 3	Q9Z0Y1	37	76	6	21/5.8	21/5.8	**1.55**	**2.08**
	Others								
20	Actin-related protein 2/3 complex subunit 5	Q9CPW4	55	84	7	16/5.5	16/5.8	**0.48**	**0.83**
35	Proteasome subunit beta type 6 [Precursor]	Q60692	35	65	5	22/5.0	24/4.9	**only in F low**	**n.r.**

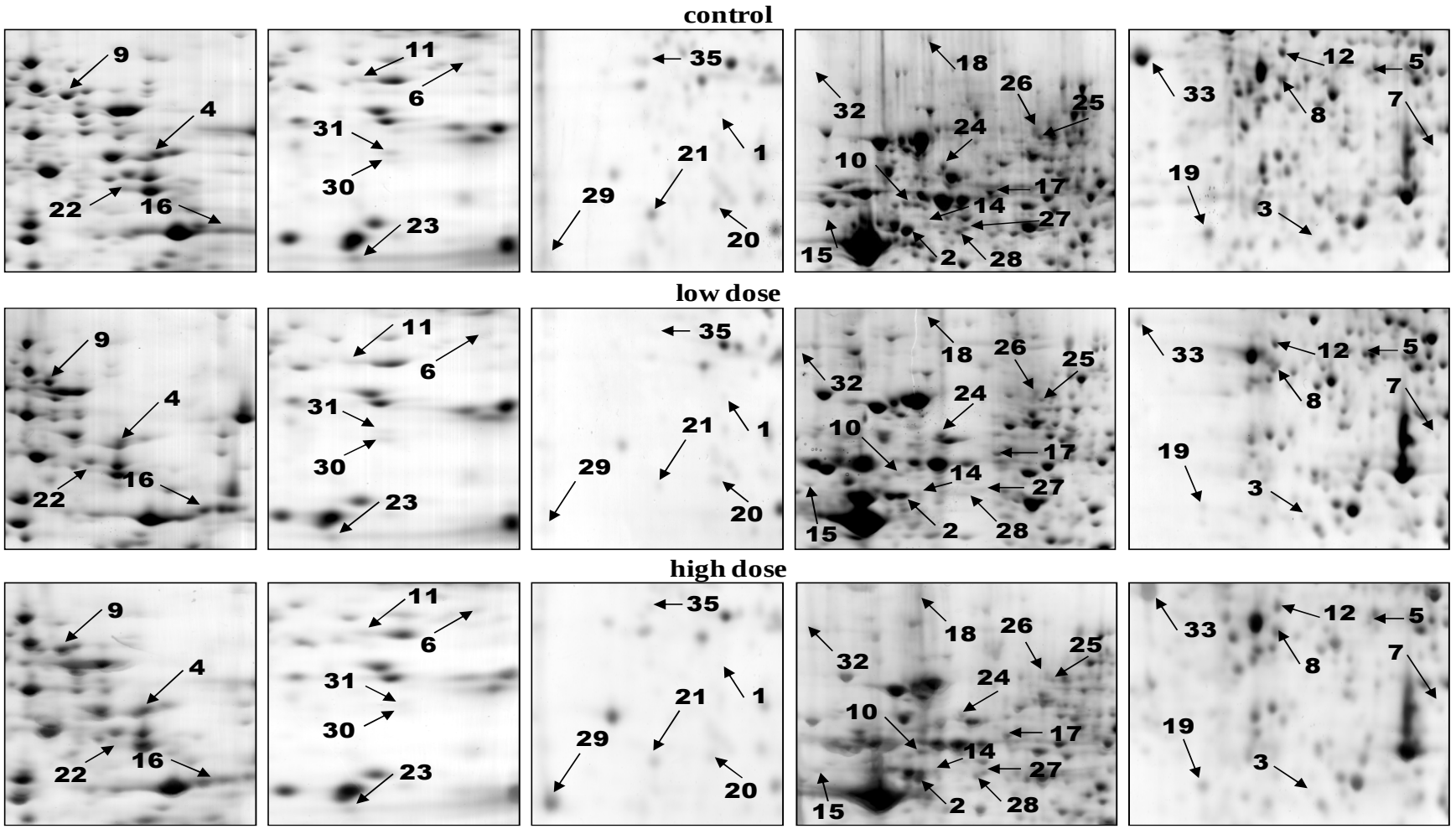

Figure 23: 2D gel of differentially expressed proteins from mice of the suppressing group due to flavone treatment

2D-PAGE of proteins from colonic tissue of mice treated with low dose or high dose flavone or with vehicle alone (control) subsequent to the phase of DMH-treatment (suppressing group). Proteins were separated on a linear pH 3-10 IPG-strip in the first dimension and on a 12.5% SDS-polyacrylamide gel in the second dimension. Identical sections of gels from the control and low or high dose flavone treatment are shown.

4.6.3. Proteome analysis of tissues from the therapy group

Of forty-five proteins regulated in steady state levels by flavone in the therapy group samples, forty could be identified via database search (Tab. 18, Fig. 24). In contrast to the blocking and suppressing groups, there were more proteins identified (15), which were only regulated significantly in steady state levels by one of the two flavone doses.

Of those proteins affected only by the low dose flavone treatment, six proteins were up-regulated, whereas myosin regulatory light chain 2 was diminished in amount. These proteins can be assigned to different functions/classifications, like chaperones, detoxification or gene regulation proteins, and three of them to metabolism. Eight proteins were only regulated significantly by the high dose flavone treatment, five of them showing decreased and the other three proteins increased expression levels. Overall, twenty-two of the differentially expressed proteins can be related to metabolism, while half of them displaying decreased and the other half increased steady state levels. From the latter aspartate aminotransferase and mevalonate (diphospho) decarboxylase are only altered by low dose, while beta enolase and the electron transfer flavoprotein subunit beta are only up regulated by high dose flavone. A number of cytoskeletal and actin-remodeling proteins responded to flavone. As many of them are substrates to caspases their altered status might be due to the initiation of apoptosis processes.

Table 18: Proteins with pI 3-10 regulated in steady state level by flavone in murine colonic tissue of the therapy group

Protein descriptions are concerning the Swiss-Prot website (www.expasy.org/sprot/) with their associated primary accession numbers. The spot numbers are identical to those given in Fig. 4. Proteins altered significantly by treatment of mice with flavone at 15 mg/ kg body weight (low dose; F low) or 400 mg/kg body weight (high dose, F high), as derived from analysis with the ProteomWeaver software, were identified by MALDI-TOF-MS; mowse score, probability based mowse score from Mascot with $P < 0.05$; Sequ. Cov [%], sequence coverage through the identified peptides; Matched peptides, non redundant peptides taken for the identification; measured M/pI, mass values calculated by the Proteome Weaver software referring to the low molecular weight standard and calculated pI values; theoretical M/pI, mass and pI values taken from the MSDB database; Reg.factor K/F low or high, regulation of the intensities of the treatment groups compared to the control group taken from the Proteome Weaver software with $P < 0.05$ (Student´s t-test); n.r., not regulated.

Spot No.	Protein description	Swiss Prot Acc. No.	Sequ. cov. [%]	Mowse Score	Peptides matched	Mw/pI theor.	Mw/pI exp.	Reg.-fac. F low/C	Reg.-fac. F high/C
	Annexins								
1	Annexin A4	P97429	25	63	5	36/5.4	34/5.4	**n.r.**	**0.44**
	Apoptosis								
2	Proteasome subunit alpha type-2	P49722	51	100	7	26/8.4	27/7.3	**0.50**	**0.48**
	Chaperones								
6	DnaJ homolog subfamily A member 2	Q9QYJ0	19	61	7	49/6.1	51/6.2	**2.47**	**n.r.**
3	Protein disulfide-isomerase A6 [Precursor]	Q922R8	37	106	10	49/5.1	54/4.8	**n.r.**	**0.49**
	Cytoskeleton and actin-remodeling proteins								
14	Actin, cytoplasmic 1	P60710	33	70	6	39/5.8	34/5.3	**0.64**	**0.46**
7	Cofilin-2	P45591	48	70	6	19/7.7	20/7.7	**2.19**	**2.55**
4	Keratin, type II cytoskeletal 8	P11679	23	85	9	55/5.7	51/4.7	**0.45**	**0.49**
10	Myosin regulatory light chain 2, smooth muscle isoform	Q9CQ19	40	68	5	20/4.8	20/4.3	**0.50**	**n.r.**
5	Myosin light polypeptide 6	Q60605	35	70	5	17/5.6	17/3.4	**n.r.**	**2.11**
13	Tagln2 protein, Transgelin 2	Q91VU2	47	110	8	26/8.4	24/8.9	**n.r.**	**0.48**
23	Twinfilin-2	Q8BN77	44	88	9	40/6.2	42/6.1	**2.95**	**1.80**
15	Vinculin	Q64727	27	240	20	117/5.8	104/5.5	**n.r.**	**0.49**

	Detoxification enzymes								
17	Glutathione peroxidase 1	P11352	37	90	6	23/6.7	26/6.3	**2.19**	**n.r.**
19	Peroxiredoxin-5, mitochondrial [Precursor]	P99029	32	127	7	17/7.9	18/8.4	**0.49**	**0.41**
	Gene regulating proteins								
8	Elongation factor 2	P58252	17	61	7	96/6.4	97/7.3	**2.17**	**n.r.**
20	Eef1d protein	Q91VK2	43	114	9	31/4.9	39/4.5	**0.70**	**0.44**
	Metabolic enzymes								
24	Adenylate kinase isoenzyme 2, mitochondrial	Q9WTP6	35	90	6	26/7.2	30/7.7	**n.r.**	**0.49**
32	Alpha-enolase	P17182	35	85	10	47/6.4	50/5.8	**0.60**	**0.47**
16	Aminoacylase-1	Q99JW2	37	93	8	46/5.9	46/6.0	**0.47**	**0.61**
12	Aspartate aminotransferase, cytoplasmic	P05201	68	319	20	45/7.6	46/6.8	**2.05**	**n.r.**
9	ATP sulfurylase/APS kinase isoform SK2	Q9QYS0	24	91	7	71/7.3	65/7.7	**1.92**	**2.18**
27	Beta-enolase	P21550	54	209	15	54/7.3	47/6.8	**n.r.**	**2.06**
38	Beta-lactamase-like protein 2	Q99KR3	44	112	8	33/5.9	34/5.6	**0.42**	**0.49**
22	Creatine kinase B-type	Q04447	35	122	9	43/5.4	46/5.6	**2.08**	**2.15**
30	Dihydropteridine reductase	Q8BVI4	45	86	5	26/7.7	30/7.8	**0.49**	**0.46**
18	Electron transfer flavoprotein subunit beta	Q9DCW4	63	206	13	31/9.0	28/8.2	**n.r.**	**2.01**
28	Enoyl-CoA hydratase, mitochondrial [Precursor]	Q8BH95	32	101	8	32/8.8	29/8.4	**0.65**	**0.49**
36	Ester hydrolase C11orf54 homolog	Q91V76	59	246	13	41/6.4	35/5.9	**2.70**	**1.88**
37	Ferritin heavy chain	P09528	44	86	6	19/5.4	21/5.5	**0.51**	**0.28**
29	Isocitrate dehydrogenase [NAD] subunit alpha, mitochondrial [Precursor]	Q9D6R2	31	102	14	40/6.3	42/5.6	**0.49**	**0.49**
11	Isocitrate dehydrogenase [NAD] subunit alpha, mitochondrial [Precursor]	Q9D6R2	40	102	10	40/6.2	45/5.6	**0.50**	**0.49**
26	L-lactate dehydrogenase A chain	P06151	38	136	10	37/7.8	38/7.9	**2.93**	**2.40**
40	Mevalonate (Diphospho) decarboxylase	Q922D7	25	61	5	44/6.0	47/6.1	**4.35**	**n.r.**

31	Peptidyl-prolyl cis-trans isomerase A	P17742	66	153	10	18/7.9	18/8.4	**0.49**	**0.44**
25	Phosphatidylinositol transfer protein alpha isoform	P53810	43	122	7	32/6.0	36/6.5	**2.19**	**3.12**
39	Protein phosphatase 2 (Formerly 2A), alpha isoform	Q7TMX2	30	112	8	64/4.6	67/4.8	**2.54**	**n.r.**
21	Ribosyldihydronicotinamide dehydrogenase [quinone]	Q9JI75	46	83	6	26/6.6	29/7.0	**0.46**	**0.38**
35	Very long-chain specific acyl-CoA dehydrogenase, mitochondrial [Precursor]	P50544	18	110	7	71/8.9	66/8.2	**2.32**	**2.50**
	Others								
33	Serum albumin (Fragment)	Q8CG74	49	81	5	24/5.5	27/4.8	**0.50**	**0.49**
34	Rab GDP dissociation inhibitor beta	Q61598	39	91	11	51/5.9	51/6.0	**2.60**	**2.37**

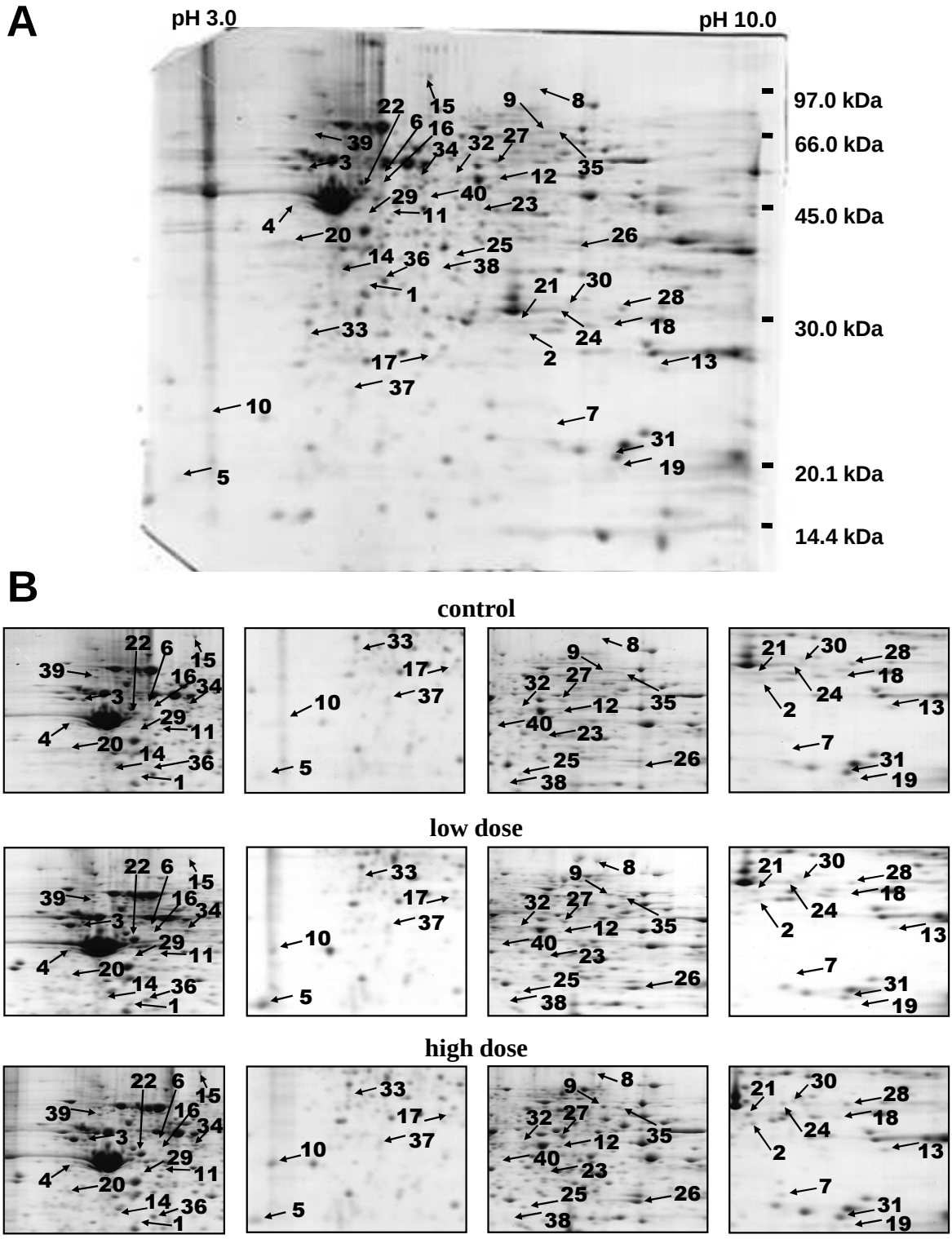

Figure 24: 2D gel of differentially expressed proteins from mice of the therapy group

2D-PAGE of proteins from colonic tissue extracts of mice treated with low dose or high dose flavone or with vehicle alone (control) after incubation phase of DMH-treatment (therapy group). Proteins were separated on a linear pH 3-10 IPG-strip in the first dimension and on a 12.5% SDS-polyacrylamide gel in the second dimension. (A) 2D-gel with separated proteins from the colons of flavone high dose mice. (B) Enlargements from identical sections of gels derived from separations of colon proteins from control mice or mice treated with low or high dose flavone.

4.7. Transcriptome analysis of colonic tissue derived from flavone-treated C57BL/6J mice from the therapy group

The transcriptome analysis of the immediately snap-frozen colonic tissue samples of the flavone-treated mice and their associated controls was done with six individual animals of each treatment (control and two flavone dosages) from the therapy group. Spotted gene sequences on the arrays served to detect the expression of around 24.000 different mouse mRNA species. After statistical analysis with ChipInspector (Genomatix Software GmbH, München, Germany) and further analysis with Bibliosphere, there were 337 genes in the low dose flavone group (15 mg/kg body weight/day) and 3069 genes in the high dose flavone group (400 mg/kg body weight/day) found regulated significantly by using the parameters discussed before (see chapter 9.1. Tables 20/21). Employing the Bibliosphere-software the term “disease” was applied as a MeSH filter on the gene set of the high dose flavone group, which affected both, the proliferation and the apoptosis rates in the histochemical experiments and showed a nearly tenfold higher effect on the gene sets compared to the low dose flavone group. Interstingly, highest Z-Scores were identified for gene sets involved in glucose metabolism preceding those for neoplasms (Tab. 19). Overall, of the nineteen gene sets with Z-Scores ≥ 25 a total of eight were related to glucose metabolism, two to general metabolism, and eight to neoplasms (Tab. 19).

Term	Z-Score
Glucose Metabolism Disorders	61
Diabetes Mellitus	50
Neoplasms	49
Diabetes Mellitus	48
Hypoglycemia	38
Neoplasms by Site	38
Metabolic Diseases	38
Digestive System Neoplasms	34
Nutritional and Metabolic Diseases	34
Diabetes Mellitus, Type 2	34
Pancreatic Neoplasms	33
Adenoma, Islet Cell	33
Cell Transformation, Neoplastic	32
Endocrine System Diseases	32
Neoplasms by Histologic Type	30
Colorectal Neoplasms, Hereditary Nonpolyposis	30
Hyperinsulinism	28
Insulinoma	26
Hyperglycemia	25

Table 19: Z-Scores from MeSH filter disease on the regulated gene set after high dose flavone treatment

Within the Bibliosphere software different filtering processes can be applied by which the regulated transcripts can be grouped according to their biological functions. Starting with the "biological process" GOFilter that encompassed the highest number of regulated transcripts additional filter terms were applied. Based on the finding that 1.399 transcripts with a function in "metabolism" were identified, another filtering for "glucose metabolic process", "fatty acid metabolic process" and "amino acid metabolic process" was performed. Nineteen transcripts were identified by the "glucose metabolic process" filter (chapter 9.1. Tab. 22). Increased levels of aldolase and reduced levels of phosphoenolpyruvate carboxy-kinase mRNAs suggest alterations that favor glycolytic activity with a concomitant decline in the gluconeogenesis pathway. Increased levels of pyruvate dehydrogenase kinase-4, possibly due to increased PPAR-alpha expression, suggest that conversion of pyruvate to lactate may be increased as a result of pyruvate dehydrogenase inhibition. Thirty-three mRNAs were found to be related to fatty acid metabolism (Tab. 23). Very long-chain specific acyl-CoA dehydrogenase was diminished by flavone at the mRNA level. Two members of long chain acyl-CoA synthetase were found up-regulated whereas a medium-chain family member was down regulated. Enoyl-CoA hydratase - mitochondrial isoform - was identified as down regulated. Reduced mRNA-levels of hydroxyacyl-Coenzyme A dehydrogenase and of a trifunctional protein possessing in addition enoyl-Coenzyme A hydratase and 3-ketoacyl-Coenzyme A thiolase activities were identified supporting the notion that ß-oxidation of fatty acids in general may not be enhanced. Twenty-nine regulated transcripts with relevance for amino acid metabolism have been identified (Tab. 24). In particular the down-regulation of glutamate dehydrogenase may suggest a reduced delivery of ketoacids from amino acid degradation to TCA for oxidation.

With the filter "tricarboxylic acid cycle (TCA)" six regulated transcripts coding for TCA proteins were identified with reduced levels under flavone treatment including succinate-CoA ligase, 2 subunits of succinate dehydrogenase, fumarate hydratase, and the dehydrogenases for malate and isocitrate (Tab. 25). In addition, nine transcripts involved in "electron transport chain" (Tab. 26) were found regulated and amongst them the coactivator 1 alpha of peroxisomal proliferator activated receptor gamma (PGC-1 alpha) was found increased. PGC-1 alpha can promote the transcription of enzymes necessary for substrate oxidation and electron transport. However, diminished transcript levels of four subcomplexes, two Fe-S clusters, and the flavoprotein of NADH-dehydrogenase do not support an increased respiratory chain activity.

Amongst the mRNAs coding for nutrient transporters, identified after applying the GOFilter term “transport”, two facilitated glucose transporters, members 5 and 9, the sodium/glucose cotransporter-1, the fatty acid transporter-4 and several amino acid transporters including three transporters belonging to the cationic amino acid transporting y+-system and one for glutamate, were identified as significantly up-regulated (Tab. 27).

Filtering of the transcript data sets for “cell cycle” (152 genes, Tab. 28) and “induction of apoptosis” (47 genes, Tab. 29) identified cell cycle associated transcripts as affected by flavone with most of them altered in a direction that implies an inhibition of cell proliferation. For instance, cyclins A2, B2, D2, D3, G1, and T2 were all down regulated, as were cyclin-dependent kinase 9, a CDC2-related kinase, and cyclin-dependent kinases 2 and 7. Transcripts for inhibitors of cyclin-dependent kinases 1A and 2B were inversly found with increased levels. The growth arrest and DNA-damage-inducible 45 alpha (Gadd45a), which is able to inhibit cell cycle progression but plays also an important role in p53-induced apoptosis, was increased at the mRNA level. Other apoptosis relevant transcripts from a total of forty-seven in this group were those coding for Bcl-2 interacting or related killer proteins, or death associated proteins with increased transcript levels. Most of the caspases, including caspase-3, showed reduced mRNA levels, whereas caspase-8 was the only that displayed an increased mRNA level. Since an increased apoptosis rate was found in the tissues, changes in the transcript levels of the identified genes may just serve as indicators for compensatory mechanims as all of the encoded proteins are known to be activated by proteolytic cleavage.

5. Discussion

Dietary habits are suggested to play a major role in the initiation and progression of colorectal cancer (CRC). If populations living in areas with low risk for getting CRC move to areas, where that type of cancer is of high incidence, they will start to develop the same high risk of CRC, probably by adopting the local dietary habits [89, 192, 193]. Naturally occurring substances in edible plants have recently obtained high interest because of their putative protective effects. In many experimental and epidemiological studies flavonoids have proven to possess a variety of effects including immunomodulatory, antioxidative and anti-carcinogenic activities [87, 135, 170].

Preliminary studies showed that flavone is a potent apoptosis inducer in cancer cell lines without affecting non-transformed colonocytes [191, 194, 195]. To unravel the molecular mechanisms of this capacity to induce apoptosis we exposed the human colon cancer cell line HT-29 for 24 h to flavone or camptothecin, respectively. Proteome analyses, done by 2D-PAGE for separation and subsequent MALDI-TOF mass spectrometry for identification of the proteins, served to identify the molecular targets by which these compounds induce apoptosis in human colorectal cancer cells.

5.1. Proteome analysis of flavone-treated or camptothecin-treated human colon cancer cells

Some of the differentially expressed proteins, which were visualized by 2D-PAGE and subsequently identified by MALDI-TOF MS, could be directly linked to pro-apoptotic or anti-carcinogenic activities. The proteins were classified according to their functional categories (by using www.expasy.org and www.harvester.fzk.de). Both camptothecin and flavone treatments changed very similar proteins. Out of thirty-four identified proteins in the camptothecin-treated cells and twenty-seven in flavone-treated cells, twenty of these proteins were identical and those showed similar changes. The experiment, where flavone-treated cells were fractionated for obtaining their subcellular components revealed another seventy-four differentially expressed proteins, demonstrating the power of subcellular pre-fractionation in increasing the sensitivity with regard to the identification of regulated proteins.

Chaperones

Some variants of heat shock proteins were found influenced in expression level by flavone treatment, as revealed in the fractionated proteome of flavone-treated cells. Heat

shock proteins represent a group of proteins where the expression is increased during exposure to elevated temperature or other stress factors [17]. Their nomenclature is based on their molecular weights and they are responsible for the establishment of correct protein conformation, for prevention of protein aggregation, for the transport of proteins across membranes within the cell and for the stabilization of partially unfolded proteins [196]. Most of the heat shock proteins were found up-regulated in steady state levels by flavone treatment, probably due to the cellular stress response as a compensatory mechanism. Heat shock 70 kDa protein 1 (Hsp70) and Heat shock cognate 71 kDa protein (Hsc71) were both identified in two different spots, one up and one down regulated. Proteins of the Hsp70 family are able to inhibit apoptosis induced by anti-carcinogenic agents [197, 198]. They are also found highly expressed in some tumors and seem to promote tumor cell growth, similar to the T-complex protein subunits beta and epsilon [199, 200], which showed an increased expression level after flavone or camptothecin-treatment. However, the fractionated proteome revealed a decrease in the subunits beta, epsilon and zeta and an increase for the subunit alpha. Interestingly, the stress induced phosphoprotein 1, which mediates the association of the molecular chaperones Hsc70 and Hsp90, was found as down regulated in the cytosol and the membrane/organelle fractions. This suggests that the elevated expression of chaperones will have no effect on apoptosis inhibition, because of the diminished expression of the stress induced phosphoprotein 1, mediating the association of chaperone subunits and therefore preventing their activation.

Detoxification enzymes

Most of the detoxification enzymes were increased in expression levels, probably as a defense mechanism against the apoptosis inducing agents, similar to the chaperones. Glutathione-S-transferase P has been associated with the resistance of tumor cells towards chemotherapeutical agents [201], and was found up-regulated by flavone and camptothecin in the whole cell lysates. Peroxiredoxin 4, and within the fractions peroxiredoxin 3 and 6 were up-regulated in steady state levels by flavone or camptothecin, but thioredoxin was decreased in expression by flavone treatment alone. Thioredoxin is over-expressed in many primary tumors compared to the levels in the equivalent non-transformed tissues, and the inhibition of thioredoxin reductase leads to cell growth inhibition and induction of apoptosis in leukemia cell lines by triggering Bcl-2/Bax and caspase-3 pathways [202, 203]. Therefore the down regulation of thioredoxin by flavone could facilitate apoptosis induction.

Proteins affecting metabolism

The enzyme delta 3,5-delta 2,4-dienoyl-CoA isomerase is facilitating the flux of unsaturated fatty acids through beta-oxidation [204] and showed up-regulated steady state levels in cells treated with both compounds. This mechanism could foster the apoptosis induction of flavone, as it is able to enhance the supply of long chain fatty acids to the mitochondria of HT-29 cells followed by an increased mitochondrial ROS formation [205].

Glyceraldehyde-3-phosphate dehydrogenase catalyzes an important energy-yielding step in carbohydrate metabolism, and alpha enolase not only catalyzes the conversion of 2-phosphoglycerate and phosphoenolpyruvate, but is also involved in negative regulation of cell growth [206]. Both proteins were increased in expression levels by flavone and camptothecin, while alpha enolase was identified in a second protein spot with a decrease. After flavone treatment the glyceraldehyde-3-phosphate dehydrogenase was also identified in a second protein spot with a higher pI and the same expression level. Camptothecin increased expression of NAD(P)H dehydrogenase, which generally protects cells against ROS-damage but is also able to activate chemotherapeutic agents in tumor cells and thereby inducing apoptosis [207]. Camptothecin reduced the expression levels of inosine-5´-monophosphate dehydrogenase 2, while in flavone treated cells two corresponding protein spots, one with increased and one with decreased intensity, were identified. The inhibition of this protein was previously found to induce differentiation of cancer cells [208].

The N(G),N(G)-dimethylarginine dimethylaminohydrolase 1 increases nitric oxide generation and nitric oxide mediated signal transduction [209, 210]. Flavone treatment was able to decrease its expression, which could result in a decrease of NO production favoring apoptosis since higher NO concentrations are able to suppress apoptosis through the scavenging of mitochondrial oxygen radicals [211, 212] in HT-29 cells.

The acidic leucine-rich nuclear phosphoprotein 32 family member A, acting as a tumor suppressor is known to take part in a number of cellular processes, like proliferation, differentiation, caspase-dependent and caspase-independent apoptosis [213, 214] was found up-regulated in the cytosolic fraction of flavone-treated cells. Also up-regulated by flavone was the protein SET, which inhibits protein phosphatase 2A and has been classified as a proto-oncogene [215-217]. Protein phosphatase 2A can be suppressed by the acidic leucine-rich nuclear phosphoprotein 32 family member A.

Flavone was able to increase the expression levels of several proteins playing a role in the ß-oxidation, glycolysis and in the electron transport of the respiratory chain (see figures 25-27). An increased throughput of oxidizable substrates seems to be crucial for the

mechanisms of increased ROS generation triggered by flavone to induce apoptosis. Ubiquinol cytochrome-c reductase is a constituent of complex III of the respiratory chain [218, 219] and coproporphyrinogen III oxidase is involved in porphyrin and thus cytochrome synthesis [220]. Flavone increased the expression level of dihydrolipoamide S-acetyltransferase in the organelle/mitochondria fraction, which is a component of the pyruvate dehydrogenase complex shunting pyruvate into the tricarboxylic acid cycle. The increased expression of these proteins could lead to a higher substrate flux through the respiratory chain and therefore to increased ROS generation, consequential leading to apoptosis in the cancer cells by overcoming the Warburg effect as a common characteristic of most tumors [221].

Another interesting protein with regulation induced by flavone, but not by camptothecin, was the programmed cell death 6-interacting protein, which is involved in mediating the sensitivity for chemotherapeutic agents [222].

Cytoskeletal and actin-remodeling proteins

Most of the cytoskeletal proteins were increased in expression levels by camptothecin or flavone. However, in the proteome of subcellular fractions, keratin type II cytoskeletal 8, lamines and mitofilin were down regulated. Cytoskeletal proteins are normally cleaved after apoptosis induction [223] and it is therefore surprising to find most of them increased in expression levels after apoptosis induction in HT-29 cells by both compounds. This could be due to the method used here for whole lysate protein isolation and the fact, that during apoptosis lamines are released from the nucleus into the cytosol, where they may have been more effectively extracted. This assumption can be supported by the increased expression level of the proliferation-associated protein 2G4 identified in flavone-treated cells despite their reduced proliferation rates [224]. This protein is normally only present in the nucleus during G1 and mid S phase, followed by a low nuclear abundance at the end of S phase, and absence at the S/G2 transition [225]. Mutations in the gene of lamin A lead to a delay in the onset and progression of cytokinesis [226]. Camptothecin induced increased levels of lamin A, lamin A/C transcript variants and lamin A mutant forms (progerins). As all of them are proteins of the nuclear envelope it must be suggested that they are released from their original location into the cytosol following nuclear fragmentation as a consequence of topoisomerase-I inhibition. However, although nuclei from flavone-treated cells fragmented as well [211, 227] increased levels of lamin-type proteins seem a specific marker for agents that initiate apoptosis within the nucleus.

The cytosolic phosphoprotein stathmin regulates the proliferation of cells by promoting the depolymerisation of microtubules, which form the spindle apparatus. Many human tumors show increased expression of this protein, particularly lymphomas and leukemia [228, 229]. Cell cycle progression can be influenced by decreased stathmin levels and it has been shown that an overexpression of this protein correlates with p53 mutations and is associated with tumor progression [230]. Stathmin showed decreased steady state levels by flavone treatment in whole cell lysates, just as after camptothecin treatment. However, the subcellular fractionation revealed increased protein levels in the cytosolic fraction, most likely representing a posttranslationally modified protein, because there are many different species of stathmin observed with specific phosphorylation sites.

Septin 11 showed increased levels upon treatment with both compounds. Septins are conserved GTP-binding proteins but their influence on cancer development is ambiguous. Individual members were shown to either inhibit or promote a variety of cancer relevant processes. For instance, a septin 9 overexpression was observed in diverse tumor types [231] and septin 4 proved to promote apoptosis [232]. Cyclophilin B was found drastically up-regulated by both treatments and has been shown to participate in the induction of chromosomal DNA degradation during cell death execution [233].

Mitofilin, which is a transmembrane protein of the inner mitochondrial membrane, was found down regulated in steady state level by flavone in the cytoskeletal fraction in two distinct protein spots. This protein was identified with a high expression in the human hepatocarcinoma cell line SMMC-7721 [234].

In conclusion, the *in vitro* experiments revealed that although the majority of the protein targets, affected in steady state level by camptothecin or flavone treatment, were essentially the same, agent-specific responses can be observed as well. The apoptosis induction by flavone seems to be mainly achieved through increased substrate oxidation and therefore ROS generation (e.g. increased levels of ubiquinol cytochrome-c reductase and coproporphyrinogen III oxidase), while camptothecin mechanisms mainly involve impairments of the nuclear envelope (increased levels of various lamines), apart from its known topoisomerase-I inhibition capability.

As flavone proved its selectivity within the *in vitro* studies by inducing apoptosis exclusively in cancer cells but not in non-transformed cells such as Ncol-1 cells or mouse primary colonocytes [191], it was investigated whether these auspicious effects could be observed in mice *in vivo* as well. A variety of studies already showed anti-carcinogenic effects

of different other flavonoids *in vivo* [235-237], but some of these substances revealed also negative side effects [238]. Flavone did not induce apoptosis in Ncol-1 cells and during preliminary studies with C57BL/6J mice fed with flavone by gavage no negative side effects were observed (data not shown).

5.2. Histological and histochemical analysis of colonic tissue derived from flavone-treated C57BL/6J mice

DMH-induced ACF and microadenomas in the colonic tissue

Aberrant crypts are preneoplastic lesions representing the first stages of tumorigenesis, and the earliest observable alterations in the colonic mucosa [239-241]. They were assessed in the colon sections of DMH-treated mice (n=17 per group) via light microscopy. In the present study, the carcinogen induced about forty ACF per animal in the colonic tissues and flavone was able to reduce ACF formation at both doses (15 or 400 mg/kg body weight), independent of the time point of intervention during adenoma development. Thus flavone proved to be effective in reducing the generation of ACF either during the DMH-induction phase (blocking group) or thereafter (suppressing or therapy group). Generally the crypt multiplicity (number of crypts per focus) increases while carcinogenesis is proceeding and microadenomas, adenomas and finally carcinomas arise [239, 242, 243]. Flavone reduced the formation of ACF especially in the suppressing and therapy group. In the blocking group we only detected significant effects in ACF with 5 or more aberrant crypts, which could mean that crypts of equal multiplicity in the blocking group differ from those in the other groups. Possibly these aberrant crypts in the blocking group did not cross a certain stage of transformation. Microadenomas, representing a later stage in carcinogenesis, were only detected in the therapy group, where the carcinogen DMH had more time to foster malignancy until flavone was applied. The low dose flavone was able to reduce the occurrence of micradenomas in the murine colon tissue significantly and the high dose of flavone even led to a complete absence of microadenomas in colon tissue. The lack of the flavone effect on crypts with higher multiplicity in the therapy group could be due to the fact that these stages had already been developed into microadenomas, because even the control mice showed less AC per animal than the ones in the suppressing group.

Apoptosis and proliferation in the colonic tissue of BrdU-treated mice

The apoptosis and proliferation rates were assessed via histochemical methods in the colonic sections of BrdU-treated mice. Evasion of apoptosis and increase of proliferation rates

are characteristic for cancer development and progression [18]. As flavone inhibited the development of preneoplastic lesions and microadenomas [244], it was very interesting to investigate whether these effects are due to the increase of apoptosis rates in the aberrant crypts. In the animals of the blocking and suppressing groups, apoptosis and cell proliferation rates remained unaffected by flavone-treatment, probably due to the rather early stage of the transformation process of the tissue. In animals of the therapy group increased apoptosis rates in colonocytes were observed by both flavone treatments, and decreased proliferation rates by the high dose flavone treatment. These findings suggest that flavone apparently targets only cells, which are already in the processes of transformation.

5.3. Proteome analysis of colonic tissue derived from flavone-treated C57BL/6J mice of the blocking and suppressing group

Commonly used strategies to treat colonic tumors target cell proliferation processes e.g. by use of inhibitors of DNA topoisomerase I, an enzyme capable of removing DNA supercoils [245]. Inhibition of cell division, however, affects cell renewal of normal tissues including blood or epithelial cells in the gastrointestinal tract with the known severe side effects. More effective and specific drug interventions may arise from targeting specific attributes of cancer cells with less pronounced effects on normal cells. Therefore the proteomic approach was used to identify potential biomarker altered in murine colon by flavone treatment.

As early as 1924 the Nobel laureate Otto Warburg demonstrated that tumor cells exhibit an altered energy metabolism by providing evidence that they metabolize up to 20 times more glucose than normal cells [246]. However, cancer cells do not use glucose for respiration but show enhanced glycolysis rates with large quantities of lactate produced from pyruvate in the cytosol. Since these processes even proceed in the presence of a high oxygen tension, this distinct metabolic phenotype is called aerobic glycolysis or the Warburg-effect [247]. One might speculate that one reason for this obvious waste of energy in cancer cells with a lack of proper respiratory chain activity prevents mitochondrial ROS production that in turn protects mitochondrial and nuclear DNA from damage with detrimental effects on cell function and a loss of growth advantage [248, 249]. In the *in vitro* studies increased apoptosis was associated with enhanced mitochondrial ROS-production and an increased influx of glycolytic endproducts into mitochondria followed by oxidation (Fig. 25).

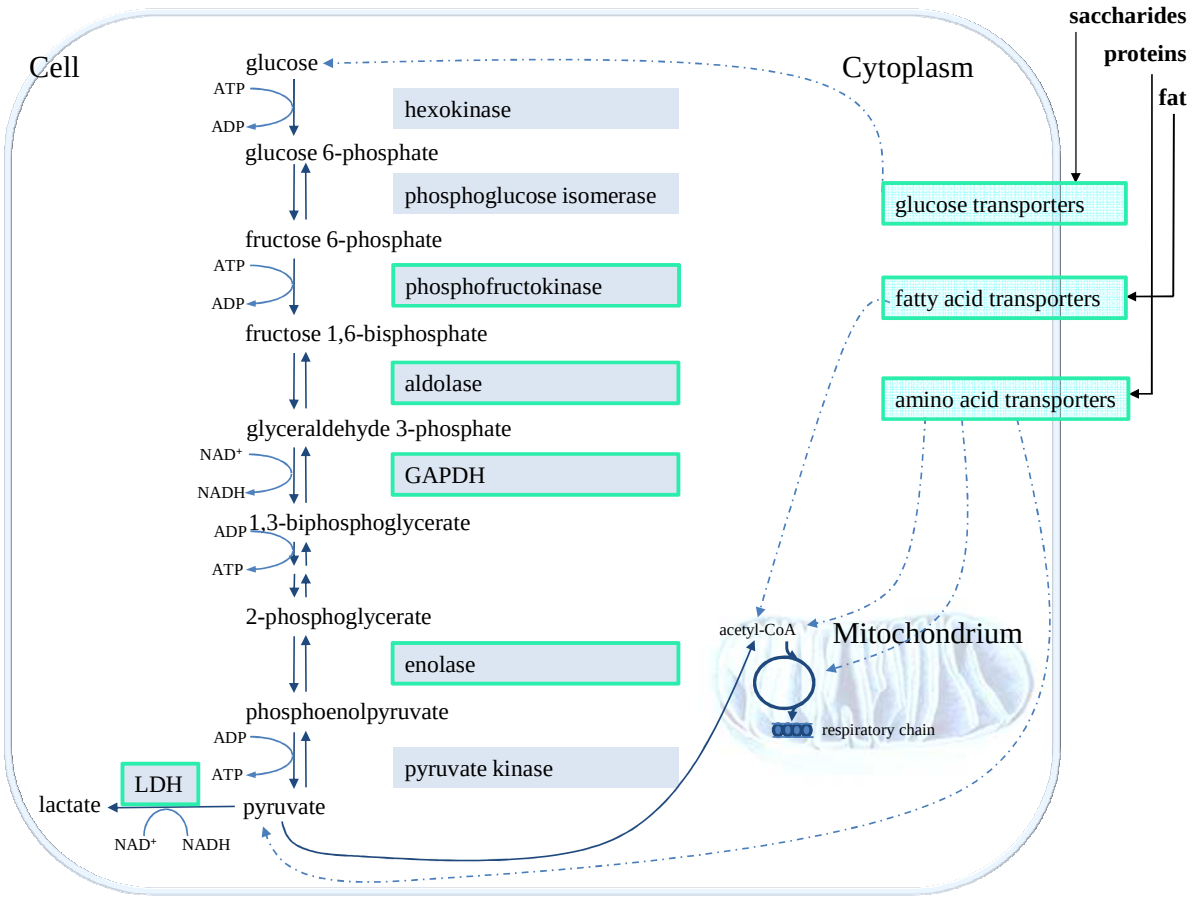

Figure 25: Influence of flavone-treatment on cellular metabolism pathways I - glycolysis

LDH, lactate dehydrogenase; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; cancer cells show an enhanced expression level of several glucose transporter (solute carrier family 2 -facilitated glucose transporter- members 5 and 9), peptide or amino acid transporter (solute carrier family 1 -glutamate transporter- member 7, solute carrier family 15 -H+/peptide transporter- member 2, solute carrier family 15 -oligopeptide transporter- member 1) and fatty acid transporter (solute carrier family 27 -fatty acid transporter- member 4) after flavone treatment, leading to a higher substrate flux into the cells; green framed glycolytic enzymes show enhanced expression on protein or transcript level.

Flavone could similarly induce apoptosis in HT-29 cells when instead of glucose a mixture of palmitoylcarnitine and free carnitine was supplied to cells whereas in the absence of flavone no apoptosis was observed. Additional data obtained in HT-29 cells showed that the cells have reduced carnitine levels and a reduced capacity for mitochondrial fatty acid import most likely caused by an inhibition of acylcarnitine/carnitine antiport [205]. Flavone increased mitochondrial carnitine levels and stimulated the uptake of long-chain fatty acids followed by increased beta-oxidation, ROS-production and induction of apoptosis [250]. These metabolic changes in HT-29 cells caused by flavone were associated with changes in protein expression levels of various enzymes of intermediary metabolism. However, we also observed an adaptation phenomenon. When flavone-induced apoptosis already proceeded

with high rate, cells treated for 24 h with flavone showed thereafter reduced levels of TCA enzymes such as succinate dehydrogenase or isocitrate dehydrogenase [195, 227].

With reference to control mice, which received solely the vehicle by gavage, seventy-four differentially expressed proteins were identified in the low dose group and seventy-seven proteins in the high dose group, using 2D-PAGE and MALDI-TOF. These proteins are involved in the cytoskeleton assembly network, in detoxification and gene regulation mechanisms, and in the intermediary metabolism. The number of proteins of intermediary metabolism altered by flavone in the three different experimental groups is considerably increased with the increasing stage of malignancy in the treatment groups. In the blocking group five metabolic proteins changed in expression level, whereas in the suppressing group twelve and in the therapy group twenty-two were identified. The only protein found regulated in all groups was creatine kinase B-type, showing a decrease in expression level in the blocking group but an increase in the other groups. Glycerol-3-phosphate dehydrogenase and a similar protein were found decreased in expression level by both flavone doses in the blocking group. This could lead to a reduction of the flow of precursors through the gluconeogenetic chain and provide more substrates for glycolysis and mitochondrial oxidation in the examined colonic tissues [19].

The down regulated ornithine aminotransferase in the suppressing group was identified in two distinct protein spots differing slightly in pI and molecular mass suggesting that this protein could be regulated by posttranslational modifications such as phosphorylation. Interestingly, ornithine aminotransferase was shown with increased expression levels in transformed colonic tissues and was defined as a reliable marker to distinguish neoplastic areas from non-transformed mucosa [251]. The flavone-treatment in the suppressing group revealed a number of mitochondrial Krebs-Cycle enzymes, which were increased in protein levels. These differentially regulated proteins, including citrate synthase, isocitrate dehydrogenase and succinate dehydrogenase, suggest that mitochondrial substrate oxidation may have been increased by flavone in colonic cells *in vivo* in the blocking and suppressing group, just as it was observed in HT-29 cells *in vitro* [224] (Fig. 26). Previous experiments with HT-29 cells revealed a decrease in Krebs-Cycle enzymes associated with low ATP-levels and apoptosis of the cells after a 24 hour flavone incubation [195]. However, after only 30 minutes, the cancer cells displayed increased ATP-levels which could lead to reduced rate of Krebs-cycle activity as a compensatory mechanism that also could prevent apoptosis [195]. The higher protein levels of these enzymes observed here in mice tissues of the suppressing group may represent the response of a normal mucosa that at the same time could prevent

cells from being transformed. An increased delivery of energy substrates to mitochondrial citric acid cycle in the presence of flavone may be further indicated by the increased levels of fatty acid-binding protein as observed in the blocking group.

It was previously shown that colon cancer cells are unable to import fatty acids into mitochondria and therefore fatty acids can not be used as energy substrates via ß-oxidation and oxidation of acetyl-CoA in the respiratory chain. However, when colon cancer cells are forced to utilize fatty acids as substrates for energy metabolism, they undergo apoptosis by the increased burden of ROS produced in the respiratory chain [250]. The observed up-regulation of adenosine-kinase by flavone could further promote mitochondrial oxidative metabolism since increased ADP-levels, besides preventing toxic concentrations of adenosine to build up, would allosterically activate isocitrate dehydrogenase as one of the key enzymes of the Krebs-cycle [252].

Previous studies in HT-29 cells revealed that flavone can drastically enhance the uptake of monocarboxylates – mainly of lactate – into mitochondria [227] followed by its oxidation. Most cancer cells obtain their ATP predominantly from converting glucose to lactate even in the presence of abundant oxygen [221, 253, 254]. This “Warburg effect” is overcome by flavone in tumor cells and the increased delivery of energy substrates to the respiratory chain in turn increases the production of $O^{2-\cdot}$ radicals in mitochondria that promotes a very efficient route of apoptosis induction [191, 211, 227, 255, 256]. The increase of substrates leading to enhanced ROS generation seems to be the prime mechanism underling tumor cell apoptosis induction by flavone (Fig. 27). As the alterations in the energy state of transformed cells are obviously linked to apoptosis induction, this also helps to explain why non-transformed cells are not responsive to flavone, which reverses the alterations of tumor cell energy metabolism back to a phenotype reminiscent of normal cells.

In the suppressing group numerous detoxification enzymes, such as glutathione synthetase, glutathione-S-transferase and peroxiredoxin 6 were found up-regulated in steady state levels by flavone treatment, suggesting selective defense mechanisms that rely on GSH are altered in the malignant cells as well. As in the suppressing group no apoptosis within the aberrant crypts was found, these defense mechanisms seem to contribute to the protection of the cells from undergoing apoptosis.

The proteome analysis of the mouse tissues in the blocking and suppressing group suggest that flavone is able to increase the substrate flux to the respiratory chain resulting in an increased $O^{2-\cdot}$ radical generation in mitochondria, consequentially leading to apoptosis in transformed colonocytes and therefore towards reduction of the aberrant crypts.

5.4. Proteome and Transcriptome analysis of colonic tissue derived from flavone-treated C57BL/6J mice of the therapy group

Tissue samples from animals of the therapy group, representing the highest grade of malignancy, were submitted to transcriptome and proteome profiling with subsequent bioinformatic analysis for identifying the molecular targets of flavone. In analogy to the tumor cells in culture, we identified numerous genes and proteins undergoing changes in steady state levels that may indicate similar adaptive changes to flavone treatment in mice *in vivo*. Transcripts of six TCA enzymes including isocitrate and succinate dehydrogenase and fumarate hydratase were found with reduced levels and in addition isocitrate dehydrogenase was also found with reduced protein levels (Fig. 26).

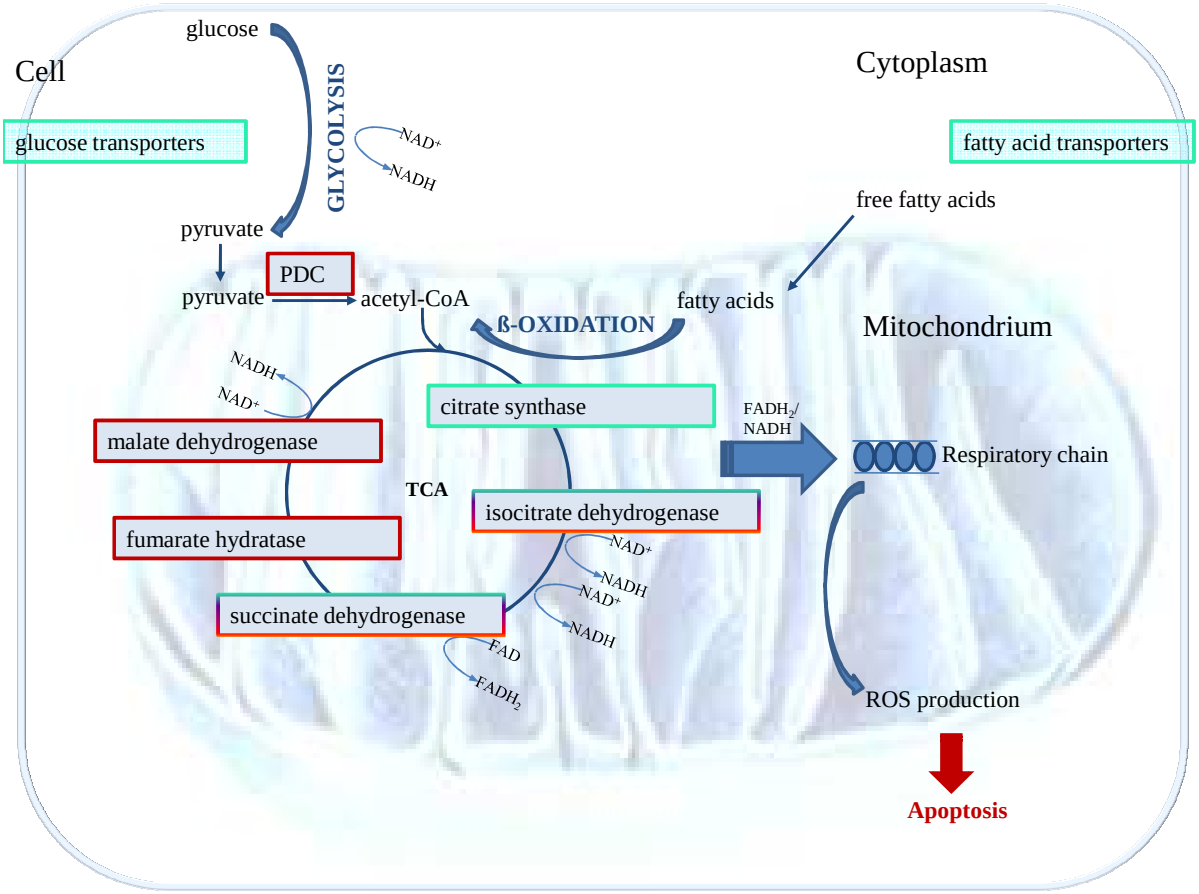

Figure 26: Influence of flavone-treatment on cellular metabolism pathways II – TCA

PDC, Pyruvate dehydrogenase complex; TCA, tricarboxylic acid cycle; green framed TCA enzymes show increased protein levels after flavone-treatment in cells representing non-transformed stages, while red framed TCA enzymes were decreased in expression levels of the transformed cells. Cancer cells try to prevent ROS generation through inhibiting enzymes playing a role in TCA and respiratory chain.

These changes observed *in vivo* after high dose flavone treatment were associated with reduced cell proliferation and increased apoptosis rates in the colonic tissues and thereby mimic similar observations made in HT-29 cells. The low dose flavone treatment failed to influence proliferation rates in the murine colonocytes and showed only 337 gene targets as affected, compared to the 3069 by high dose flavone treatment. A down-regulation of succinate dehydrogenase and fumarate hydratase levels may be interpreted as a direct survival strategy since both proteins have been identified as classic tumor suppressors and mutations in both have been linked to the stabilization of hypoxia-inducible factor-1 which affects gene expression, metabolism, cell survival, tumorigenesis and tumor growth [257-259]. The mechanism by which the regulation of this factor is achieved seems via its prolyl-hydroxylation which promotes proteasomal degradation. The prolyl-hydroxylation requires α-ketoglutarate as a substrate. A deficiency of succinate dehydrogenase or fumarate hydratase could decrease α-ketoglutarate levels [258] and a reduced level of glutamate dehydrogenase as found here as well would in additon reduce α-ketoglutarate availability from amino acids. The observed down-regulation of TCA enzymes and the reduced protein levels of the flavoprotein of NADH-dehydrogenase found *in vitro* as well as here *in vivo* would deprive cells of reduction equivalents for the respiratory chain (Fig. 27). However, we also observed increased protein levels of long-chain fatty acid dehydrogenases in the colonic tissues of flavone-treated mice similar to an up-regulation found in HT-29 cells [195]. Although this may indicate an increased capacity for fatty acid oxidation, the next necessary protein in the ß-oxidation cycle, the enoyl-CoA hydratase, and the final enzyme that releases acetyl-CoA, the 3-ketothiolase, were found with lower expression levels. Yet, the initial step of fatty acid oxidation provides $FADH_2$ for transfer of electrons to complex III of the respiratory chain which may maintain a sufficient electron flow (Fig. 27). Most interestingly, complex III is the major site of ROS formation [260-263], so that ROS-production and ROS-driven apoptosis may be sustained despite an assumed reduced TCA activity (Fig. 26). These adaptations in colonic tumor cells which may originate from the need to meet the energy demand by alternative pathways may also contribute to the differences observed regarding microadenoma formation. When mice were treated under identical conditions as in the present study but with a lower flavone dose (15 mg/kg body weight) similar proteins and similar effects were observed. However, only with the present high dose of flavone the electron transfer protein was found up-regulated and microadenoma formation was prevented.

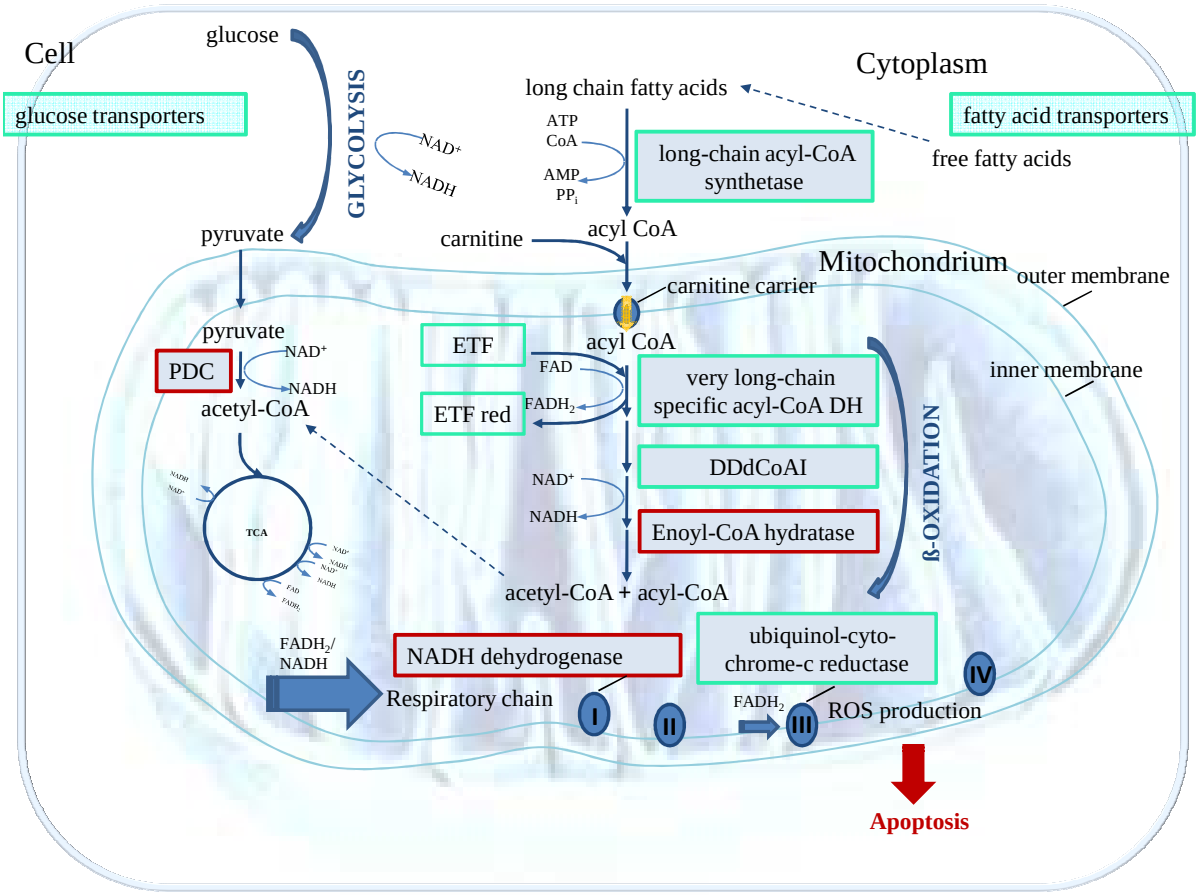

Figure 27: Influence of flavone-treatment on cellular metabolism pathways III – ß-Oxidation and respiratory chain

PDC, Pyruvate dehydrogenase complex; TCA, tricarboxylic acid cycle; DDdCoAI, Delta(3,5)-Delta(2,4)-dienoyl-CoA isomerase; ETF, electron transfer protein; I-IV, Complexes I-IV of the respiratory chain; ß-oxidation is enhanced through higher expression of involved enzymes or fatty acid transporters and enzymes facilitating the substrate flux. The last step in ß-Oxidation is impeded by decreased expression level of enoyl-CoA hydratase, but still many reduction equivalents ($FADH_2$) are produced for the respiratory chain, which leads to increased ROS generation in fast-growing cancer cells, followed by apoptosis.

An indication for a shift in the metabolic phenotype of mouse colon *in vivo* towards a Warburg effect is provided by increased expression of glucose transporters, lactate dehydrogenase, aldolase and enolase (Fig. 25). The enhanced expression of pyruvate dehydrogenase kinase-4 may assist the blockade of TCA by inhibition of the pyruvate dehydrogenase complex (Fig. 26) with a concomitant reduction in the conversion of pyruvate to acetyl-CoA and increased cytosolic lactate production. Cytosolic needs of ATP may be met by this adaptive mechanisms whereas mitochondrial ATP may be derived via the electron transport chain driven by $FADH_2$ derived from a partial break-down of long chain fatty acids provided via increased fatty acid uptake into cells (Fig. 27). This process however would drive ROS-production and promote ROS-mediated apoptosis although the “Warburg

adaptation" of cell metabolism is thought to prevent ROS-generation in the respiratory chain for protection of DNA damage.

In conclusion, our studies show that flavone blocks the development of microadenomas in colonic tissue of DMH-treated mice. An increased supply of energy substrates by a pleiotropic up-regulation of solute carriers in transformed tissue is suggested to provide an initially enhanced substrate flow for ATP production at the expense of increased mitochondrial ROS generation. Transcript as well as protein data strongly suggest that TCA activity in response is reduced leading to a lower supply of $NADH_2$ to the respiratory chain. This may be compensated by an increased use to fatty acids with a partial ß-oxidation that yields $FADH_2$ for maintaining electron flow through the respiratory chain but that also increases ROS production and the rate of ROS-driven apoptosis.

A variety of natural compounds and in particular various flavonoids have been proposed to act as chemopreventive agents that could help to reduce colon cancer incidence. Although there are numerous studies reporting effects in tumor cell cultures and a few animal model studies, human trials that have provided a proof of concept are essentially missing. In addition, these studies require reliable biomarkers for assessing the effectiveness of the intervention and those need to be established. The work documented here based on in vitro and in vivo studies demonstrates that flavone has the potential of an effective chemopreventive agent but even more so as an adjuvant in tumor cell therapy. Numerous biomarkers reflecting its activity in normal and transformed cells have been identified and may guide further studies to demonstrate its effectiveness *in vivo*.

6. Summary

Colorectal cancer is the second leading cause of cancer deaths in Western Europe with diet playing a major role in its initiation and progression. Flavonoids are highly abundant in edible plants and they are suggested to have chemopreventive effects by targeting the molecular pathways which can terminate proliferation, induce apoptosis or inhibit the spread of tumor cells. The flavonoid flavone proved to be a potent and tumor-selective apoptosis inducer in HT-29 human colorectal cancer cells *in vitro*. In the present study a proteomic approach, with 2D-PAGE for protein separation and MALDI-TOF mass spectrometry for identification of regulated protein spots, was used to identify mechanisms of action at the molecular level.

A number of proteins involved in mitochondrial pathways that lead to apoptosis and relate to cell proliferation control were affected in steady state levels in the *in vitro* studies. In comparison to camptothecin, a classical but non-selective anti-tumor agent, flavone specifically influenced enzymes of intermediary metabolism. Interestingly, proteins enabling the substrate flux through tricarboxylic acid cycle (TCA) and respiratory chain, such as dehydrogenases for succinate or NADH were found to be down regulated, suggesting an adaptation of transformed cells to prevent the generation of reactive oxygen species (ROS) as a byproduct of oxidative phosphorylation that in turn induces apoptosis. This assumption was confirmed in C57BL/6J mice, in which microadenomas were induced by the carcinogen 1,2-dimethylhydrazine. Flavone given by gavage at a dose of 400 mg/kg body weight completely prevented the generation of microadenomas and this was associated with diminished expression of several proteins of intermediary metabolism. The resulting energy deprivation appears to be compensated by increased partial ß-oxidation of long-chain fatty acids which results in enhanced generation of ROS and therefore increased apoptosis rates within the malignant cells. Transcriptome analysis using a Gene Chip expression array with 24.000 genes spottet confirmed the proteome data and moreover revealed the increased expression of various solute transporters, suggesting increased substrate supply to colonocytes to be used for TCA-independent energy production.

Strikingly, when mice were treated to develop only preneoplastic lesions, an up-

regulation of proteins from intermediary metabolism was observed stressing the overall suggestion that flavone increases oxidative metabolism of normal and transformed cells. Although transformed cells by adaptive mechanisms try to escape increased ROS-levels the constantly increased ROS-production by fatty acid oxidation seems to force specifically the colon cancer cells to undergo apoptosis.

7. Zusammenfassung

Darmkrebs stellt die zweithäufigste Krebsursache mit Todesfolge in den westlichen Industrieländern dar. Der Ernährung wird hierbei, sowohl bei der Entstehung als auch beim Krankheitsverlauf, eine erhebliche Rolle zugeschrieben. Den in pflanzlichen Nahrungsmitteln enthaltenen Flavonoiden werden chemopräventive Effekte zugeschrieben, die sowohl die Apoptose als auch die Proliferation betreffen sowie die Ausbreitung von Tumorzellen beeinflussen können. In Zellkulturstudien mit der humanen Darmkrebs-Zellinie HT-29 konnte nachgewiesen werden, dass das Flavonoid Flavon *in vitro* hoch wirksam - und gezielt auf Tumorzellen ausgerichtet - Apoptose induzieren kann. In der vorliegenden Studie wurde mittels Proteomanalyse versucht, die Wirkmechanismen auf molekularer Ebene zu ergründen. Hierfür wurden die Proteine von humanen Darmkrebszellen (HT-29) bzw. von Colongewebe der Maus mittels zweidimensionaler Gelelektrophorese (2D-PAGE) aufgetrennt und die in der Expression veränderten Proteinspots per MALDI-TOF Massenspektrometrie identifiziert.

In den *in vitro*-Studien wurden vor allem Proteine im zellularen Spiegel verändert, die an der Mitochondrien vermittelten Apoptose sowie der Zellproliferation beteiligt sind. Verglichen mit Camptothecin, das als klassisches aber nicht selektives Anti-Tumormittel bekannt ist, vermochte Flavon vor allem Enzyme aus dem Intermediärstoffwechsel im Spiegel zu verändern.

Interessanterweise konnte eine verringerte Expression bei Proteinen festgestellt werden, die den Substratfluß durch den Trikarbonsäure-Zyklus (TCA) und die Atmungskette beeinflussen/aufrecht erhalten, wie z.B. Succinat- oder NADH-Dehydrogenasen. Dies könnte auf Anpassungsvorgänge der transformierten Zellen hindeuten, um die Produktion reaktiver Sauerstoffspezies (ROS) zu unterbinden, die als Nebenprodukt der oxidativen Phosphorylierung entstehen können und Apoptose induzieren zu vermögen. In den *in vivo*-Studien mit C57BL/6J-Mäusen, bei denen durch 1,2-Dimethylhydrazin Mikroadenome induziert wurden, konnte nach Flavon-Gabe per Schlundsonde in einer Konzentration von 400 mg/kg Körpergewicht die Bildung von Mikroadenomen völlig verhindert werden. Dies ging einher mit einer verminderten Expression verschiedener Proteine des Intermediärstoffwechsels. Der damit verbundene Energie-/ATP-Mangel wird möglicherweise durch eine partielle erhöhte ß-Oxidation langkettiger Fettsäuren kompensiert, was auch zu einer vermehrten ROS-Produktion führen könnte, und damit die Apoptose in den malignen Zellen induziert. Transkriptom-Analysen mittels Gene Chip Expressions-Arrays (24.000 Gene) konnten die Proteomdaten weitgehend bestätigen. Außerdem konnte eine erhöhte

Expression verschiedener Nährstofftransporter nachgewiesen werden, die eine erhöhte Substrat-Bereitstellung für die Kolonozyten ermöglichen würde und für TCA-unabhängige Prozesse, wie z.B. für die Glykolyse, verwendet werden könnte.

Bemerkenswert ist die Erhöhung der Proteinexpression von Enzymen des Intermediärstoffwechsels bei Mäusen, die lediglich bis zum Stadium der Ausprägung präneoplastischer Läsionen behandelt wurden. Dies läßt vermuten, dass Flavon den oxidativen Metabolismus, sowohl von normalen, als auch von transformierten Zellen erhöhen könnte. Obwohl die transformierten Zellen sich der zunehmenden ROS-Bildung durch Anpassungsmechanismen zu entziehen versuchen, können sie entweder die anfangs verstärkte Überschußproduktion, oder die fortwährende erhöhte ROS-Bildung bei der Fettsäure-Oxidation, nicht verhindern, wodurch sie selektiv in die Apoptose getrieben werden.

8. References

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9. Addendum

9.1. Tables of significantly affected gene targets with or without filter options

Table 20: Significantly regulated gene targets in murine colons of the therapy group by low dose flavone

gene name	gene symbol	identifier	reg factor
3-hydroxy-3-methylglutaryl-Coenzyme A reductase	Hmgcr	15357	**1,29**
6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4	Pfkfb4	270198	**0,80**
A kinase (PRKA) anchor protein 6	Akap6	238161	**1,22**
AHNAK nucleoprotein (desmoyokin)	Ahnak	66395	**1,40**
AHNAK nucleoprotein 2	Ahnak2	382643	**1,25**
ATP-binding cassette, sub-family B (MDR/TAP), member 1A	Abcb1a	18671	**1,56**
ATP-binding cassette, sub-family C (CFTR/MRP), member 9	Abcc9	20928	**1,21**
ATPase, Na+/K+ transporting, alpha 2 polypeptide	Atp1a2	98660	**1,22**
B-cell translocation gene 2, anti-proliferative	Btg2	12227	**0,72**
C1q and tumor necrosis factor related protein 3	C1qtnf3	81799	**1,25**
CAP-GLY domain containing linker protein family, member 4	Clip4	78785	**1,30**
CD38 antigen	Cd38	12494	**0,69**
CDC42 effector protein (Rho GTPase binding) 3	Cdc42ep3	260409	**1,28**
DEAD (Asp-Glu-Ala-Asp) box polypeptide 5	Ddx5	13207	**1,31**
DnaJ (Hsp40) homolog, subfamily C, member 10	Dnajc10	66861	**0,79**
DnaJ (Hsp40) homolog, subfamily C, member 6	Dnajc6	72685	**1,25**
E2F transcription factor 3	E2f3	13557	**1,20**
EGF-like repeats and discoidin I-like domains 3	Edil3	13612	**1,25**
ELAV (embryonic lethal, abnormal vision, Drosophila)-like 4 (Hu antigen D)	Elavl4	15572	**1,34**
EP300 interacting inhibitor of differentiation 2	Eid2	386655	**1,19**
Erbb2 interacting protein	Erbb2ip	59079	**1,34**
FERM, RhoGEF and pleckstrin domain protein 2	Farp2	227377	**0,83**
FK506 binding protein 5	Fkbp5	14229	**0,72**
G protein-coupled receptor 120	Gpr120	107221	**0,75**
GTP cyclohydrolase I feedback regulator	Gchfr	320415	**0,80**
GULP, engulfment adaptor PTB domain containing 1	Gulp1	70676	**1,26**
HtrA serine peptidase 2	Htra2	64704	**0,86**
HtrA serine peptidase 3	Htra3	78558	**1,26**
ISL1 transcription factor, LIM/homeodomain	Isl1	16392	**1,35**
KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	Kdelr3	105785	**0,73**
Kallmann syndrome 1 sequence (human)	Kal1	14038	**0,74**
Kruppel-like factor 10	Klf10	21847	**1,38**
Kv channel interacting protein 4	Kcnip4	80334	**1,17**
LIM domain only 7	Lmo7	380928	**1,35**
N-myc downstream regulated gene 4	Ndrg4	234593	**1,35**
PFTAIRE protein kinase 1	Pftk1	18647	**1,23**
PTEN induced putative kinase 1	Pink1	68943	**1,44**
PYD and CARD domain containing	Pycard	66824	**0,69**
Purkinje cell protein 4	Pcp4	18546	**1,44**
R-spondin 3 homolog (Xenopus laevis)	Rspo3	72780	**1,33**
RAB3D, member RAS oncogene family	Rab3d	19340	**0,80**
RAR-related orphan receptor gamma	Rorc	19885	**0,81**
RAS-like, family 11, member B	Rasl11b	68939	**1,23**
RIKEN cDNA 1100001G20 gene	1100001G20Rik	66107	**1,30**
RIKEN cDNA 1110018M03 gene	1110018M03Rik	67606	**1,30**
RIKEN cDNA 1600029D21 gene	1600029D21Rik	76509	**0,47**
RNA binding motif, single stranded interacting protein 1	Rbms1	56878	**1,27**
RNA binding protein with multiple splicing 2	Rbpms2	71973	**1,53**
Rap1 GTPase-activating protein	Rap1gap	110351	**0,72**
Ras-like without CAAX 2	Rit2	19762	**1,26**
S100 calcium binding protein G	S100g	12309	**0,48**
SAM and SH3 domain containing 1	Sash1	70097	**1,31**
SAM pointed domain containing ets transcription factor	Spdef	30051	**0,57**
SET binding factor 1	Sbf1	77980	**0,82**
SPARC-like 1 (mast9, hevin)	Sparcl1	13602	**1,63**
UDP glucuronosyltransferase 2 family, polypeptide B5	Ugt2b5	22238	**0,75**
UDP-GalNAc:betaGlcNAc beta 1,3-galactosaminyltransferase, polypeptide 1	B3galnt1	26879	**1,41**
UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 10	Galnt10	171212	**0,80**
UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 3	Galnt3	14425	**0,78**
a disintegrin and metallopeptidase domain 23	Adam23	23792	**1,48**
acetyl-Coenzyme A acyltransferase 1B	Acaa1b	235674	**1,47**
adaptor-related protein complex 1, sigma 2 subunit	Ap1s2	108012	**1,27**
adrenergic receptor, alpha 2a	Adra2a	11551	**1,50**
albumin	Alb	11657	**4,51**
aldo-keto reductase family 1, member C6	Akr1c6	83702	**1,53**
alpha 1 microglobulin/bikunin	Ambp	11699	**1,34**
alpha-2-HS-glycoprotein	Ahsg	11625	**1,40**
alpha-2-glycoprotein 1, zinc	Azgp1	12007	**1,20**
amine oxidase, copper containing 3	Aoc3	11754	**1,37**
amyloid beta (A4) precursor protein-binding, family B, member 2	Apbb2	11787	**1,21**
angiotensin II receptor, type 1a	Agtr1a	11607	**1,24**
ankyrin 1, erythroid	Ank1	11733	**1,30**
annexin A13	Anxa13	69787	**0,80**
annexin A7	Anxa7	11750	**1,29**

apolipoprotein A-II	Apoa2	11807	**1,90**
apolipoprotein A-V	Apoa5	66113	**1,27**
apolipoprotein B	Apob	238055	**1,46**
apolipoprotein B editing complex 2	Apobec2	11811	**1,17**
apolipoprotein C-I	Apoc1	11812	**1,39**
apolipoprotein C-IV	Apoc4	11425	**1,25**
apolipoprotein F	Apof	103161	**1,33**
apolipoprotein H	Apoh	11818	**1,57**
arginase type II	Arg2	11847	**0,68**
ash1 (absent, small, or homeotic)-like (Drosophila)	Ash1l	192195	**1,38**
autophagy-related 5 (yeast)	Atg5	11793	**0,81**
basic helix-loop-helix domain containing, class B, 8	Bhlhb8	17341	**0,81**
basic helix-loop-helix domain containing, class B9	Bhlhb9	70237	**1,36**
brain expressed X-linked 2	Bex2	12069	**1,37**
brain expressed gene 1	Bex1	19716	**1,38**
carbamoyl-phosphate synthetase 1	Cps1	227231	**1,27**
carbohydrate sulfotransferase 12	Chst12	59031	**1,19**
carbonic anhydrase 8	Car8	12319	**0,80**
carboxypeptidase E	Cpe	12876	**1,65**
caspase 12	Casp12	12364	**1,22**
cell adhesion molecule with homology to L1CAM	Chl1	12661	**1,29**
cell division cycle 27 homolog (S. cerevisiae)	Cdc27	217232	**1,18**
centaurin, beta 2	Centb2	78618	**1,35**
ceruloplasmin	Cp	12870	**1,24**
chemokine (C-X-C motif) ligand 12	Cxcl12	20315	**1,31**
cholecystokinin A receptor	Cckar	12425	**1,34**
coagulation factor II	F2	14061	**1,40**
coagulation factor II (thrombin) receptor-like 1	F2rl1	14063	**1,34**
coagulation factor XIII, A1 subunit	F13a1	74145	**1,24**
colipase, pancreatic	Clps	109791	**0,57**
collagen, type VIII, alpha 1	Col8a1	12837	**1,40**
collectin sub-family member 12	Colec12	140792	**1,29**
complement component factor h	Cfh	12628	**1,41**
complement component factor i	Cfi	12630	**1,29**
connective tissue growth factor	Ctgf	14219	**1,48**
contactin 1	Cntn1	12805	**1,48**
cordon-bleu	Cobl	12808	**1,41**
cyclin D1	Ccnd1	12443	**1,36**
cyclin I	Ccni	12453	**1,45**
cystathionine beta-synthase	Cbs	12411	**0,82**
cytochrome P450, family 1, subfamily a, polypeptide 2	Cyp1a2	13077	**1,25**
cytochrome P450, family 2, subfamily e, polypeptide 1	Cyp2e1	13106	**2,23**
cytochrome P450, family 3, subfamily a, polypeptide 11	Cyp3a11	13112	**2,50**
degenerative spermatocyte homolog 2 (Drosophila), lipid desaturase	Degs2	70059	**0,74**
delta/notch-like EGF-related receptor	Dner	227325	**1,34**
dermatopontin	Dpt	56429	**1,34**
desmoplakin	Dsp	109620	**1,69**
dickkopf homolog 3 (Xenopus laevis)	Dkk3	50781	**1,17**
dipeptidylpeptidase 10	Dpp10	269109	**1,28**
discoidin domain receptor family, member 2	Ddr2	18214	**1,22**
discoidin, CUB and LCCL domain containing 2	Dcbld2	73379	**1,38**
dual specificity phosphatase 26 (putative)	Dusp26	66959	**1,35**
dystrobrevin alpha	Dtna	13527	**1,37**
dystrophia myotonica-containing WD repeat motif	Dmwd	13401	**1,13**
ectonucleoside triphosphate diphosphohydrolase 6	Entpd6	12497	**0,79**
ectonucleotide pyrophosphatase/phosphodiesterase 2	Enpp2	18606	**1,37**
endonuclease G	Endog	13804	**0,83**
endothelial differentiation, lysophosphatidic acid G-protein-coupled receptor, 2	Edg2	14745	**1,39**
ephrin A1	Efna1	13636	**0,80**
epidermal growth factor-containing fibulin-like extracellular matrix protein 1	Efemp1	216616	**1,36**
erythrocyte protein band 4.1-like 1	Epb4.1l1	13821	**1,47**
esterase 1	Es1	13884	**1,56**
estrogen-related receptor gamma	Esrrg	26381	**1,24**
eukaryotic translation initiation factor 2 alpha kinase 3	Eif2ak3	13666	**0,78**
exocyst complex component 2	Exoc2	66482	**1,31**
expressed sequence AA467197	AA467197	433470	**0,76**
far upstream element (FUSE) binding protein 3	Fubp3	320267	**1,38**
fasciculation and elongation protein zeta 1 (zygin I)	Fez1	235180	**1,22**
fatty acid binding protein 1, liver	Fabp1	14080	**1,74**
fibrinogen, B beta polypeptide	Fgb	110135	**1,38**
fibrinogen, alpha polypeptide	Fga	14161	**1,57**
fibrinogen, gamma polypeptide	Fgg	99571	**1,39**
fibrinogen-like protein 1	Fgl1	234199	**1,22**
fibroblast growth factor 13	Fgf13	14168	**1,39**
fibulin 5	Fbln5	23876	**1,27**
flavin containing monooxygenase 1	Fmo1	14261	**1,23**
flavin containing monooxygenase 2	Fmo2	55990	**1,33**
forkhead box P2	Foxp2	114142	**1,44**
fos-like antigen 2	Fosl2	14284	**1,45**
free fatty acid receptor 2	Ffar2	233079	**0,78**
galanin	Gal	14419	**1,50**
gap junction protein, alpha 1	Gja1	14609	**1,32**
gap junction protein, gamma 1	Gjc1	14615	**1,27**
glucosaminyl (N-acetyl) transferase 1, core 2	Gcnt1	14537	**1,30**
glycine N-methyltransferase	Gnmt	14711	**1,18**
glypican 4	Gpc4	14735	**1,24**

glypican 6	Gpc6	23888	**1,17**
granzyme A	Gzma	14938	**0,76**
gremlin 2 homolog, cysteine knot superfamily (Xenopus laevis)	Grem2	23893	**1,37**
group specific component	Gc	14473	**1,68**
growth arrest specific 1	Gas1	14451	**1,37**
growth associated protein 43	Gap43	14432	**1,27**
growth differentiation factor 10	Gdf10	14560	**1,33**
growth factor receptor bound protein 14	Grb14	50915	**1,30**
guanine nucleotide binding protein (G protein), gamma 2	Gng2	14702	**1,26**
guanylate kinase 1	Guk1	14923	**0,69**
guanylate nucleotide binding protein 3	Gbp3	55932	**1,30**
haptoglobin	Hp	15439	**1,39**
heart and neural crest derivatives expressed transcript 2	Hand2	15111	**1,44**
heat shock protein 1 (chaperonin 10)	Hspe1	15528	**0,61**
heat shock protein 2	Hspa2	15512	**1,28**
heat shock protein 8	Hspb8	80888	**1,32**
hemopexin	Hpx	15458	**1,70**
heparan sulfate (glucosamine) 3-O-sulfotransferase 3B1	Hs3st3b1	54710	**0,86**
hepatoma-derived growth factor, related protein 3	Hdgfrp3	29877	**1,18**
hepcidin antimicrobial peptide	Hamp	84506	**1,51**
heterogeneous nuclear ribonucleoprotein K	Hnrpk	15387	**1,34**
high mobility group nucleosomal binding domain 3	Hmgn3	94353	**1,36**
histidine triad nucleotide binding protein 3	Hint3	66847	**0,71**
histone deacetylase 9	Hdac9	79221	**1,27**
homeo box B9	Hoxb9	15417	**0,82**
homeo box D10	Hoxd10	15430	**1,26**
homeo box D13	Hoxd13	15433	**1,43**
indolethylamine N-methyltransferase	Inmt	21743	**1,48**
inhibitor of DNA binding 4	Id4	15904	**1,51**
insulin-like growth factor binding protein 2	Igfbp2	16008	**1,23**
insulin-like growth factor binding protein 6	Igfbp6	16012	**1,21**
integral membrane protein 2A	Itm2a	16431	**1,28**
integrin alpha 8	Itga8	241226	**1,35**
intelectin 1 (galactofuranose binding)	Itln1	16429	**0,57**
inter alpha-trypsin inhibitor, heavy chain 4	Itih4	16427	**1,34**
interferon-induced protein with tetratricopeptide repeats 1	Ifit1	15957	**1,47**
interferon-induced protein with tetratricopeptide repeats 2	Ifit2	15958	**1,28**
interleukin 33	Il33	77125	**1,26**
killer cell lectin-like receptor, subfamily D, member 1	Klrd1	16643	**0,84**
kinesin family member 5C	Kif5c	16574	**1,24**
kinesin light chain 1	Klc1	16593	**1,36**
leucine rich repeat (in FLII) interacting protein 1	Lrrfip1	16978	**1,46**
lymphatic vessel endothelial hyaluronan receptor 1	Lyve1	114332	**1,37**
mab-21-like 2 (C. elegans)	Mab21l2	23937	**1,26**
mannose binding lectin (C)	Mbl2	17195	**1,27**
matrilin 2	Matn2	17181	**1,32**
membrane protein, palmitoylated 5 (MAGUK p55 subfamily member 5)	Mpp5	56217	**1,29**
methionine adenosyltransferase I, alpha	Mat1a	11720	**1,36**
methionine sulfoxide reductase B3	Msrb3	320183	**1,28**
molybdenum cofactor sulfurase	Mocos	68591	**1,30**
mucin 2	Muc2	17831	**0,67**
myelin and lymphocyte protein, T-cell differentiation protein	Mal	17153	**1,55**
myeloid cell leukemia sequence 1	Mcl1	17210	**1,28**
myosin, light polypeptide 7, regulatory	Myl7	17898	**0,82**
naked cuticle 2 homolog (Drosophila)	Nkd2	72293	**1,16**
necdin	Ndn	17984	**1,57**
nerve growth factor receptor (TNFR superfamily, member 16)	Ngfr	18053	**1,20**
neurofibromatosis 2	Nf2	18016	**0,83**
neurofilament, light polypeptide	Nefl	18039	**1,30**
neuron specific gene family member 1	Nsg1	18196	**1,26**
neurotensin	Nts	67405	**0,61**
non imprinted in Prader-Willi/Angelman syndrome 1 homolog (human)	Nipa1	233280	**1,22**
nuclear fragile X mental retardation protein interacting protein 2	Nufip2	68564	**1,42**
nuclear receptor subfamily 1, group D, member 2	Nr1d2	353187	**1,38**
opsin 3	Opn3	13603	**1,15**
opticin	Optc	269120	**1,27**
paraoxonase 1	Pon1	18979	**1,29**
patched homolog 1	Ptch1	19206	**1,50**
pelota homolog (Drosophila)	Pelo	105083	**1,39**
peptidoglycan recognition protein 1	Pglyrp1	21946	**0,65**
period homolog 3 (Drosophila)	Per3	18628	**1,26**
peripherin	Prph	19132	**1,40**
peroxisome proliferative activated receptor, gamma, coactivator 1 alpha	Ppargc1a	19017	**1,40**
phenylalanine hydroxylase	Pah	18478	**1,40**
phospholipase A2, group IIF	Pla2g2f	26971	**0,87**
phospholipase C, epsilon 1	Plce1	74055	**1,40**
plasma membrane associated protein, S3-12	S3-12	57435	**1,22**
plasminogen	Plg	18815	**1,44**
pleckstrin homology domain containing, family B (evectins) member 1	Plekhb1	27276	**1,18**
pleiotrophin	Ptn	19242	**1,56**
poly (ADP-ribose) polymerase family, member 14	Parp14	547253	**1,29**
poly(rC) binding protein 2	Pcbp2	18521	**1,27**
polybromo 1	Pbrm1	66923	**1,23**
polymerase (DNA directed), beta	Polb	18970	**1,35**
preproenkephalin 1	Penk1	18619	**1,40**
procollagen C-endopeptidase enhancer 2	Pcolce2	76477	**1,28**

profilin 2	Pfn2	18645	**1,36**
proline-rich acidic protein 1	Prap1	22264	**0,63**
proline-rich nuclear receptor coactivator 1	Pnrc1	108767	**1,45**
prostaglandin E receptor 4 (subtype EP4)	Ptger4	19219	**1,39**
protein inhibitor of activated STAT 1	Pias1	56469	**1,22**
protein kinase C, alpha	Prkca	18750	**0,85**
protein kinase, X-linked	Prkx	19108	**1,24**
protein phosphatase 1A, magnesium dependent, alpha isoform	Ppm1a	19042	**1,29**
protein tyrosine phosphatase, receptor type Z, polypeptide 1	Ptprz1	19283	**1,35**
protein tyrosine phosphatase, receptor type, O	Ptpro	19277	**0,82**
protocadherin alpha 4	Pcdha4	12936	**1,43**
purinergic receptor P2Y, G-protein coupled, 14	P2ry14	140795	**1,24**
pyruvate dehydrogenase kinase, isoenzyme 4	Pdk4	27273	**1,54**
radical S-adenosyl methionine domain containing 2	Rsad2	58185	**1,28**
receptor (calcitonin) activity modifying protein 1	Ramp1	51801	**0,76**
receptor tyrosine kinase-like orphan receptor 2	Ror2	26564	**1,45**
recombination signal binding protein for immunoglobulin kappa J region	Rbpj	19664	**1,31**
reelin	Reln	19699	**1,32**
regucalcin	Rgn	19733	**1,35**
regulator of calcineurin 2	Rcan2	53901	**1,34**
resistin like beta	Retnlb	57263	**0,26**
ret proto-oncogene	Ret	19713	**1,44**
reticulon 1	Rtn1	104001	**1,34**
retinol dehydrogenase 7	Rdh7	54150	**1,33**
reversion-inducing-cysteine-rich protein with kazal motifs	Reck	53614	**1,30**
ring finger and FYVE like domain containing protein	Rffl	67338	**1,24**
sarcospan	Sspn	16651	**1,26**
secreted frizzled-related protein 1	Sfrp1	20377	**1,24**
secreted frizzled-related protein 2	Sfrp2	20319	**1,29**
secretin	Sct	20287	**0,74**
secretogranin II	Scg2	20254	**1,51**
secretogranin III	Scg3	20255	**1,33**
sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3A	Sema3a	20346	**1,34**
serine (or cysteine) peptidase inhibitor, clade A, member 1c	Serpina1c	20702	**1,87**
serine (or cysteine) peptidase inhibitor, clade A, member 3K	Serpina3k	20714	**1,72**
serine (or cysteine) peptidase inhibitor, clade C (antithrombin), member 1	Serpinc1	11905	**1,44**
serine (or cysteine) peptidase inhibitor, clade E, member 2	Serpine2	20720	**1,42**
serine/threonine kinase 10	Stk10	20868	**1,36**
serine/threonine/tyrosine kinase 1	Styk1	243659	**1,20**
serum deprivation response	Sdpr	20324	**1,52**
serum/glucocorticoid regulated kinase 2	Sgk2	27219	**1,70**
single-stranded DNA binding protein 2	Ssbp2	66970	**1,25**
solute carrier family 1 (glutamate/neutral amino acid transporter), member 4	Slc1a4	55963	**0,80**
solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	Slc11a2	18174	**0,73**
solute carrier family 39 (zinc transporter), member 4	Slc39a4	72027	**0,64**
sorbin and SH3 domain containing 1	Sorbs1	20411	**1,55**
sortilin-related receptor, LDLR class A repeats-containing	Sorl1	20660	**1,51**
sorting nexin 6	Snx6	72183	**0,84**
spastic paraplegia 3A homolog (human)	Spg3a	73991	**1,24**
special AT-rich sequence binding protein 1	Satb1	20230	**1,32**
stathmin-like 2	Stmn2	20257	**1,41**
stathmin-like 3	Stmn3	20262	**1,26**
stress-induced phosphoprotein 1	Stip1	20867	**0,74**
synaptopodin 2	Synpo2	118449	**1,42**
synaptosomal-associated protein 25	Snap25	20614	**1,43**
synaptotagmin I	Syt1	20979	**1,34**
synaptotagmin-like 4	Sytl4	27359	**0,81**
syntrophin, gamma 2	Sntg2	268534	**1,23**
tachykinin 1	Tac1	21333	**1,52**
tetraspanin 13	Tspan13	66109	**0,61**
tetraspanin 2	Tspan2	70747	**1,32**
tetraspanin 4	Tspan4	64540	**1,18**
thymus cell antigen 1, theta	Thy1	21838	**1,21**
thyrotroph embryonic factor	Tef	21685	**1,34**
tight junction protein 1	Tjp1	21872	**1,37**
transducer of ErbB-2.1	Tob1	22057	**1,62**
transferrin receptor	Tfrc	22042	**0,61**
transforming growth factor beta 1 induced transcript 1	Tgfb1i1	21804	**1,39**
transforming growth factor, beta 2	Tgfb2	21808	**1,30**
transmembrane protein 158	Tmem158	72309	**1,37**
transmembrane protein 16F	Tmem16f	105722	**1,34**
transmembrane protein 184a	Tmem184a	231832	**0,84**
tumor protein D52-like 1	Tpd52l1	21987	**0,75**
ubiquilin 2	Ubqln2	54609	**1,60**
ubiquinol cytochrome c reductase core protein 2	Uqcrc2	67003	**1,23**
ubiquitin specific peptidase 2	Usp2	53376	**1,32**
ubiquitin-conjugating enzyme E2B, RAD6 homology (S. cerevisiae)	Ube2b	22210	**0,76**
ubiquitin-conjugating enzyme E2R 2	Ube2r2	67615	**1,46**
unc-84 homolog B (C. elegans)	Unc84b	223697	**1,36**
uroporphyrinogen III synthase	Uros	22276	**0,83**
vasoactive intestinal polypeptide	Vip	22353	**1,57**
vesicle-associated membrane protein 4	Vamp4	53330	**1,31**
yrdC domain containing (E.coli)	Yrdc	230734	**0,80**
zinc finger E-box binding homeobox 2	Zeb2	24136	**1,33**
zinc finger and BTB domain containing 20	Zbtb20	56490	**1,49**
zinc finger and BTB domain containing 4	Zbtb4	75580	**1,35**

zinc finger and BTB domain containing 7a	Zbtb7a	16969	**1,42**
zinc finger protein 503	Zfp503	218820	**1,51**
zinc finger protein 650	Zfp650	68795	**1,29**
zinc finger protein, multitype 2	Zfpm2	22762	**1,23**
zinc finger, CCCH-type with G patch domain	Zgpat	229007	**0,81**

Table 21: Significantly regulated gene targets in murine colons of the therapy group by high dose flavone

gene name	gene symbol	identifier	**reg factor**
1-acylglycerol-3-phosphate O-acyltransferase 1 (lysophosphatidic acid acyltransferase, alpha)	Agpat1	55979	**1,21**
1-acylglycerol-3-phosphate O-acyltransferase 2 (lysophosphatidic acid acyltransferase, beta)	Agpat2	67512	**0,69**
1-acylglycerol-3-phosphate O-acyltransferase 4 (lysophosphatidic acid acyltransferase, delta)	Agpat4	68262	**1,23**
1-acylglycerol-3-phosphate O-acyltransferase 7 (lysophosphatidic acid acyltransferase, eta)	Agpat7	99010	**1,26**
1-acylglycerol-3-phosphate O-acyltransferase 9	Agpat9	231510	**1,56**
1-aminocyclopropane-1-carboxylate synthase homolog (Arabidopsis)(non-functional)	Accs	329470	**1,29**
2',3'-cyclic nucleotide 3' phosphodiesterase	Cnp	12799	**0,76**
2'-5' oligoadenylate synthetase 1C	Oas1c	114643	**0,84**
2'-5' oligoadenylate synthetase 3	Oas3	246727	**1,26**
2,3-bisphosphoglycerate mutase	Bpgm	12183	**0,71**
2-4-dienoyl-Coenzyme A reductase 2, peroxisomal	Decr2	26378	**0,81**
2-deoxyribose-5-phosphate aldolase homolog (C. elegans)	Dera	232449	**0,72**
3-hydroxy-3-methylglutaryl-Coenzyme A lyase	Hmgcl	15356	**0,59**
3-hydroxy-3-methylglutaryl-Coenzyme A reductase	Hmgcr	15357	**1,34**
3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2	Hmgcs2	15360	**0,65**
3-phosphoinositide dependent protein kinase-1	Pdpk1	18607	**1,36**
4-hydroxyphenylpyruvate dioxygenase-like	Hpdl	242642	**0,85**
4-hydroxyphenylpyruvic acid dioxygenase	Hpd	15445	**0,55**
5'-3' exoribonuclease 2	Xrn2	24128	**0,79**
5'-nucleotidase, cytosolic III	Nt5c3	107569	**0,66**
5-azacytidine induced gene 1	Azi1	12009	**1,16**
5-hydroxytryptamine (serotonin) receptor 3A	Htr3a	15561	**1,27**
5-hydroxytryptamine (serotonin) receptor 7	Htr7	15566	**1,46**
6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2	Pfkfb2	18640	**1,34**
6-pyruvoyl-tetrahydropterin synthase	Pts	19286	**0,72**
A kinase (PRKA) anchor protein 1	Akap1	11640	**1,33**
A kinase (PRKA) anchor protein 11	Akap11	219181	**1,29**
A kinase (PRKA) anchor protein 13	Akap13	75547	**1,51**
A kinase (PRKA) anchor protein 2	Akap2	11641	**1,63**
A kinase (PRKA) anchor protein 6	Akap6	238161	**1,28**
A kinase (PRKA) anchor protein 8	Akap8	56399	**1,52**
ADAM-like, decysin 1	Adamdec1	58860	**0,60**
ADAMTS-like 4	Adamtsl4	229595	**1,19**
ADP-ribosylation factor 2	Arf2	11841	**0,83**
ADP-ribosylation factor guanine nucleotide-exchange factor 2 (brefeldin A-inhibited)	Arfgef2	99371	**1,35**
ADP-ribosylation factor interacting protein 1	Arfip1	99889	**1,25**
ADP-ribosylation factor-like 16	Arl16	70317	**0,79**
ADP-ribosylhydrolase like 2	Adprhl2	100206	**0,86**
ADP-ribosyltransferase 1	Art1	11870	**1,19**
AE binding protein 1	Aebp1	11568	**1,32**
AE binding protein 2	Aebp2	11569	**1,33**
AF4/FMR2 family, member 1	Aff1	17355	**1,51**
AFG3(ATPase family gene 3)-like 1 (yeast)	Afg3l1	114896	**0,81**
AFG3(ATPase family gene 3)-like 2 (yeast)	Afg3l2	69597	**0,85**
AHNAK nucleoprotein (desmoyokin)	Ahnak	66395	**1,52**
AHNAK nucleoprotein 2	Ahnak2	382643	**1,26**
AP2 associated kinase 1	Aak1	269774	**1,89**
ARD1 homolog B (S. cerevisiae)	Ard1b	97243	**1,19**
ARP8 actin-related protein 8 homolog (S. cerevisiae)	Actr8	56249	**0,80**
ASF1 anti-silencing function 1 homolog A (S. cerevisiae)	Asf1a	66403	**0,76**
AT hook containing transcription factor 1	Ahctf1	226747	**1,23**
AT rich interactive domain 1B (Swi1 like)	Arid1b	239985	**1,46**
AT rich interactive domain 4A (Rbp1 like)	Arid4a	238247	**1,43**
AT rich interactive domain 4B (Rbp1 like)	Arid4b	94246	**1,23**
AT rich interactive domain 5B (Mrf1 like)	Arid5b	71371	**1,24**
ATP synthase, H+ transporting mitochondrial F1 complex, beta subunit	Atp5b	11947	**0,57**
ATP synthase, H+ transporting, mitochondrial F1 complex, alpha subunit, isoform 1	Atp5a1	11946	**0,60**
ATP synthase, H+ transporting, mitochondrial F1 complex, delta subunit	Atp5d	66043	**0,54**
ATP-binding cassette, sub-family A (ABC1), member 7	Abca7	27403	**1,53**
ATP-binding cassette, sub-family A (ABC1), member 8a	Abca8a	217258	**1,42**
ATP-binding cassette, sub-family B (MDR/TAP), member 1A	Abcb1a	18671	**1,60**
ATP-binding cassette, sub-family B (MDR/TAP), member 1B	Abcb1b	18669	**1,25**
ATP-binding cassette, sub-family B (MDR/TAP), member 6	Abcb6	74104	**1,50**
ATP-binding cassette, sub-family B (MDR/TAP), member 7	Abcb7	11306	**0,86**
ATP-binding cassette, sub-family B (MDR/TAP), member 8	Abcb8	74610	**0,82**
ATP-binding cassette, sub-family C (CFTR/MRP), member 1	Abcc1	17250	**1,41**
ATP-binding cassette, sub-family C (CFTR/MRP), member 12	Abcc12	244562	**1,33**
ATP-binding cassette, sub-family C (CFTR/MRP), member 3	Abcc3	76408	**1,39**
ATP-binding cassette, sub-family C (CFTR/MRP), member 4	Abcc4	239273	**1,30**
ATP-binding cassette, sub-family C (CFTR/MRP), member 8	Abcc8	20927	**1,50**
ATP-binding cassette, sub-family C (CFTR/MRP), member 9	Abcc9	20928	**1,25**
ATP-binding cassette, sub-family D (ALD), member 2	Abcd2	26874	**0,87**
ATP-binding cassette, sub-family F (GCN20), member 1	Abcf1	224742	**0,82**
ATP-binding cassette, sub-family F (GCN20), member 3	Abcf3	27406	**0,83**
ATP-binding cassette, sub-family G (WHITE), member 2	Abcg2	26357	**0,82**

ATPase family, AAA domain containing 5	Atad5	237877	**1,33**
ATPase type 13A2	Atp13a2	74772	**1,26**
ATPase type 13A3	Atp13a3	224088	**1,24**
ATPase, Ca++ transporting, type 2C, member 2	Atp2c2	69047	**0,69**
ATPase, Cu++ transporting, alpha polypeptide	Atp7a	11977	**1,57**
ATPase, H+ transporting, lysosomal V0 subunit A2	Atp6v0a2	21871	**1,62**
ATPase, H+ transporting, lysosomal V0 subunit B	Atp6v0b	114143	**1,24**
ATPase, H+ transporting, lysosomal V0 subunit E	Atp6v0e	11974	**0,71**
ATPase, H+ transporting, lysosomal V0 subunit E2	Atp6v0e2	76252	**1,39**
ATPase, H+ transporting, lysosomal V1 subunit B2	Atp6v1b2	11966	**1,32**
ATPase, H+ transporting, lysosomal V1 subunit C1	Atp6v1c1	66335	**1,23**
ATPase, H+ transporting, lysosomal V1 subunit H	Atp6v1h	108664	**0,77**
ATPase, H+ transporting, lysosomal accessory protein 1	Atp6ap1	54411	**1,34**
ATPase, H+/K+ transporting, nongastric, alpha polypeptide	Atp12a	192113	**1,57**
ATPase, aminophospholipid transporter (APLT), class I, type 8A, member 1	Atp8a1	11980	**1,37**
ATPase, class VI, type 11A	Atp11a	50770	**1,44**
ATPase, class VI, type 11B	Atp11b	76295	**1,33**
ATX1 (antioxidant protein 1) homolog 1 (yeast)	Atox1	11927	**0,56**
AXIN1 up-regulated 1	Axud1	215418	**1,24**
Atpase, class VI, type 11C	Atp11c	320940	**0,85**
B and T lymphocyte associated	Btla	208154	**1,24**
B double prime 1, subunit of RNA polymerase III transcription initiation factor IIIB	Bdp1	544971	**1,27**
B-box and SPRY domain containing	Bspry	192120	**0,74**
B-cell CLL/lymphoma 7A	Bcl7a	77045	**1,26**
B-cell CLL/lymphoma 9	Bcl9	77578	**1,28**
B-cell CLL/lymphoma 9-like	Bcl9l	80288	**1,30**
B-cell leukemia/lymphoma 6	Bcl6	12053	**1,64**
B-cell linker	Blnk	17060	**1,28**
BAI1-associated protein 2-like 1	Baiap2l1	66898	**0,76**
BCL2-antagonist/killer 1	Bak1	12018	**1,42**
BCL2-associated athanogene 4	Bag4	67384	**1,21**
BCL2-like 13 (apoptosis facilitator)	Bcl2l13	94044	**0,81**
BCL2/adenovirus E1B interacting protein 1, NIP1	Bnip1	224630	**0,80**
BCL2/adenovirus E1B interacting protein 1, NIP2	Bnip2	12175	**1,51**
BCS1-like (yeast)	Bcs1l	66821	**0,83**
BMP and activin membrane-bound inhibitor, homolog (Xenopus laevis)	Bambi	68010	**0,82**
BMP-binding endothelial regulator	Bmper	73230	**1,28**
BMS1 homolog, ribosome assembly protein (yeast)	Bms1	213895	**0,82**
BMX non-receptor tyrosine kinase	Bmx	12169	**0,85**
BR serine/threonine kinase 1	Brsk1	381979	**1,36**
BRCA2 and CDKN1A interacting protein	Bccip	66165	**0,73**
BTAF1 RNA polymerase II, B-TFIID transcription factor-associated, (Mot1 homolog, S. cerevisiae)	Btaf1	107182	**0,80**
BTB and CNC homology 1	Bach1	12013	**1,64**
Bcl-2 binding component 3	Bbc3	170770	**1,30**
Bcl-2-related ovarian killer protein	Bok	51800	**1,23**
Bcl-associated death promoter	Bad	12015	**0,69**
Bcl2-associated athanogene 3	Bag3	29810	**1,24**
Bcl2-interacting killer	Bik	12124	**1,27**
Bcl2-like 1	Bcl2l1	12048	**1,36**
Bcl6 interacting corepressor	Bcor	71458	**1,19**
Braf transforming gene	Braf	109880	**1,25**
Brca1 associated protein 1	Bap1	104416	**1,27**
Bri3 binding protein	Bri3bp	76809	**0,86**
C-terminal binding protein 1	Ctbp1	13016	**1,39**
C-type lectin domain family 4, member a2	Clec4a2	26888	**0,88**
C-type lectin domain family 4, member a3	Clec4a3	73149	**0,85**
C-type lectin domain family 4, member n	Clec4n	56620	**0,82**
C1GALT1-specific chaperone 1	C1galt1c1	59048	**0,83**
C1q and tumor necrosis factor related protein 5	C1qtnf5	235312	**1,41**
CAS1 domain containing 1	Casd1	213819	**1,44**
CASK interacting protein 1	Caskin1	268932	**1,20**
CASP8 and FADD-like apoptosis regulator	Cflar	12633	**0,83**
CCAAT/enhancer binding protein (C/EBP), beta	Cebpb	12608	**1,53**
CCAAT/enhancer binding protein (C/EBP), delta	Cebpd	12609	**0,77**
CCAAT/enhancer binding protein (C/EBP), gamma	Cebpg	12611	**0,82**
CCR4-NOT transcription complex, subunit 3	Cnot3	232791	**1,20**
CCR4-NOT transcription complex, subunit 6	Cnot6	104625	**0,82**
CD14 antigen	Cd14	12475	**0,72**
CD160 antigen	Cd160	54215	**0,85**
CD164 antigen	Cd164	53599	**0,80**
CD177 antigen	Cd177	68891	**0,49**
CD22 antigen	Cd22	12483	**1,40**
CD247 antigen	Cd247	12503	**0,84**
CD3 antigen, delta polypeptide	Cd3d	12500	**0,82**
CD3 antigen, gamma polypeptide	Cd3g	12502	**0,79**
CD300A antigen	Cd300a	217303	**0,80**
CD302 antigen	Cd302	66205	**0,83**
CD320 antigen	Cd320	54219	**1,45**
CD4 antigen	Cd4	12504	**1,30**
CD47 antigen (Rh-related antigen, integrin-associated signal transducer)	Cd47	16423	**1,31**
CD48 antigen	Cd48	12506	**0,81**
CD7 antigen	Cd7	12516	**0,79**
CD79B antigen	Cd79b	15985	**1,20**
CD8 antigen, alpha chain	Cd8a	12525	**0,85**
CD83 antigen	Cd83	12522	**0,88**
CD97 antigen	Cd97	26364	**0,76**

Addendum

CDC14 cell division cycle 14 homolog A (S. cerevisiae)	Cdc14a	229776	**1,41**
CDC16 cell division cycle 16 homolog (S. cerevisiae)	Cdc16	69957	**0,78**
CDC23 (cell division cycle 23, yeast, homolog)	Cdc23	52563	**0,81**
CDC42 effector protein (Rho GTPase binding) 3	Cdc42ep3	260409	**1,29**
CDC42 small effector 2	Cdc42se2	72729	**1,26**
CDK2 (cyclin-dependent kinase 2)-associated protein 1	Cdk2ap1	13445	**0,81**
CDK2-associated protein 2	Cdk2ap2	52004	**0,62**
CDKN2A interacting protein	Cdkn2aip	70925	**0,85**
CDP-diacylglycerol synthase 1	Cds1	74596	**1,88**
CDP-diacylglycerol--inositol 3-phosphatidyltransferase (phosphatidylinositol synthase)	Cdipt	52858	**1,33**
CHK2 checkpoint homolog (S. pombe)	Chek2	50883	**0,84**
CKLF-like MARVEL transmembrane domain containing 8	Cmtm8	70031	**0,84**
CLIP associating protein 1	Clasp1	76707	**1,39**
CLIP associating protein 2	Clasp2	76499	**1,91**
CLP1, cleavage and polyadenylation factor I subunit, homolog (S. cerevisiae)	Clp1	98985	**0,88**
CLPTM1-like	Clptm1l	218335	**0,66**
CNDP dipeptidase 2 (metallopeptidase M20 family)	Cndp2	66054	**1,36**
COMM domain containing 6	Commd6	66200	**0,65**
COMM domain containing 7	Commd7	99311	**0,80**
COMM domain containing 9	Commd9	76501	**0,78**
COP9 (constitutive photomorphogenic) homolog, subunit 2 (Arabidopsis thaliana)	Cops2	12848	**0,69**
COP9 (constitutive photomorphogenic) homolog, subunit 3 (Arabidopsis thaliana)	Cops3	26572	**0,69**
COP9 (constitutive photomorphogenic) homolog, subunit 4 (Arabidopsis thaliana)	Cops4	26891	**0,69**
COP9 (constitutive photomorphogenic) homolog, subunit 5 (Arabidopsis thaliana)	Cops5	26754	**0,68**
COP9 (constitutive photomorphogenic) homolog, subunit 6 (Arabidopsis thaliana)	Cops6	26893	**0,66**
COP9 (constitutive photomorphogenic) homolog, subunit 8 (Arabidopsis thaliana)	Cops8	108679	**1,35**
COX11 homolog, cytochrome c oxidase assembly protein (yeast)	Cox11	69802	**1,28**
COX19 cytochrome c oxidase assembly homolog (S. cerevisiae)	Cox19	68033	**0,65**
CREB binding protein	Crebbp	12914	**1,33**
CREB regulated transcription coactivator 1	Crtc1	382056	**1,18**
CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) phosphatase, subunit 1	Ctdp1	67655	**1,30**
CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase 1	Ctdsp1	227292	**1,42**
CUB domain containing protein 1	Cdcp1	109332	**0,81**
CUG triplet repeat, RNA binding protein 1	Cugbp1	13046	**2,05**
Casitas B-lineage lymphoma b	Cblb	208650	**1,41**
Cd200 antigen	Cd200	17470	**1,60**
Cd200 receptor 2	Cd200r2	271375	**0,82**
Cnksr family member 3	Cnksr3	215748	**1,38**
Crn, crooked neck-like 1 (Drosophila)	Crnkl1	66877	**0,76**
D site albumin promoter binding protein	Dbp	13170	**1,45**
DAZ associated protein 2	Dazap2	23994	**1,26**
DCP1 decapping enzyme homolog A (S. cerevisiae)	Dcp1a	75901	**0,84**
DCUN1D1 DCN1, defective in cullin neddylation 1, domain containing 1 (S. cerevisiae)	Dcun1d1	114893	**1,58**
DEAD (Asp-Glu-Ala-Asp) box polypeptide 21	Ddx21	56200	**0,83**
DEAD (Asp-Glu-Ala-Asp) box polypeptide 27	Ddx27	228889	**0,85**
DEAD (Asp-Glu-Ala-Asp) box polypeptide 39	Ddx39	68278	**0,61**
DEAD (Asp-Glu-Ala-Asp) box polypeptide 4	Ddx4	13206	**0,83**
DEAD (Asp-Glu-Ala-Asp) box polypeptide 41	Ddx41	72935	**0,77**
DEAD (Asp-Glu-Ala-Asp) box polypeptide 5	Ddx5	13207	**1,43**
DEAD (Asp-Glu-Ala-Asp) box polypeptide 54	Ddx54	71990	**0,78**
DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 3, X-linked	Ddx3x	13205	**1,26**
DEAH (Asp-Glu-Ala-His) box polypeptide 32	Dhx32	101437	**0,68**
DEAH (Asp-Glu-Ala-His) box polypeptide 9	Dhx9	13211	**0,85**
DENN/MADD domain containing 1A	Dennd1a	227801	**1,31**
DIP2 disco-interacting protein 2 homolog A (Drosophila)	Dip2a	64451	**1,51**
DIP2 disco-interacting protein 2 homolog B (Drosophila)	Dip2b	239667	**1,35**
DNA methyltransferase 3A	Dnmt3a	13435	**1,49**
DNA segment, Chr 17, human D6S53E	D17H6S53E	114585	**1,26**
DNA segment, Chr 17, human D6S56E 3	D17H6S56E-3	27762	**1,33**
DNA segment, Chr 3, University of California at Los Angeles 1	D3Ucla1	28146	**0,54**
DNA segment, Chr 6, Miriam Meisler 5, expressed	D6Mm5e	110958	**1,21**
DNA segment, Chr 6, Wayne State University 163, expressed	D6Wsu163e	28040	**0,80**
DNA segment, Chr 6, Wayne State University 176, expressed	D6Wsu176e	27999	**1,32**
DOT1-like, histone H3 methyltransferase (S. cerevisiae)	Dot1l	208266	**1,33**
DPH3 homolog (KTI11, S. cerevisiae)	Dph3	105638	**0,79**
DPH4 homolog (JJJ3, S. cerevisiae)	Dph4	99349	**0,83**
Der1-like domain family, member 2	Derl2	116891	**0,69**
DiGeorge syndrome critical region gene 2	Dgcr2	13356	**1,26**
Dmx-like 2	Dmxl2	235380	**1,48**
DnaJ (Hsp40) homolog, subfamily A, member 2	Dnaja2	56445	**0,75**
DnaJ (Hsp40) homolog, subfamily A, member 4	Dnaja4	58233	**0,87**
DnaJ (Hsp40) homolog, subfamily B, member 1	Dnajb1	81489	**0,72**
DnaJ (Hsp40) homolog, subfamily B, member 5	Dnajb5	56323	**1,35**
DnaJ (Hsp40) homolog, subfamily C, member 10	Dnajc10	66861	**1,23**
DnaJ (Hsp40) homolog, subfamily C, member 12	Dnajc12	30045	**0,84**
DnaJ (Hsp40) homolog, subfamily C, member 14	Dnajc14	74330	**1,57**
DnaJ (Hsp40) homolog, subfamily C, member 15	Dnajc15	66148	**0,67**
DnaJ (Hsp40) homolog, subfamily C, member 19	Dnajc19	67713	**1,58**
DnaJ (Hsp40) homolog, subfamily C, member 5	Dnajc5	13002	**1,31**
DnaJ (Hsp40) homolog, subfamily C, member 6	Dnajc6	72685	**1,29**
DnaJ (Hsp40) homolog, subfamily C, member 7	Dnajc7	56354	**1,52**
E26 avian leukemia oncogene 2, 3' domain	Ets2	23872	**0,75**
E2F transcription factor 3	E2f3	13557	**1,54**
E2F-associated phosphoprotein	Eapp	66266	**0,73**
EBNA1 binding protein 2	Ebna1bp2	69072	**0,69**
ECSIT homolog (Drosophila)	Ecsit	26940	**0,74**

EGL nine homolog 3 (C. elegans)	Egln3	112407	**1,39**
EH domain binding protein 1	Ehbp1	216565	**1,18**
ELAV (embryonic lethal, abnormal vision, Drosophila)-like 3 (Hu antigen C)	Elavl3	15571	**1,22**
ELAV (embryonic lethal, abnormal vision, Drosophila)-like 4 (Hu antigen D)	Elavl4	15572	**1,45**
ELK1, member of ETS oncogene family	Elk1	13712	**1,36**
ELKS/RAB6-interacting/CAST family member 1	Erc1	111173	**1,24**
ELOVL family member 6, elongation of long chain fatty acids (yeast)	Elovl6	170439	**1,28**
EMG1 nucleolar protein homolog (S. cerevisiae)	Emg1	14791	**0,55**
EP300 interacting inhibitor of differentiation 1	Eid1	58521	**1,27**
EP300 interacting inhibitor of differentiation 2	Eid2	386655	**1,26**
EPM2A (laforin) interacting protein 1	Epm2aip1	77781	**0,79**
EPS8-like 2	Eps8l2	98845	**1,37**
ER degradation enhancer, mannosidase alpha-like 1	Edem1	192193	**0,67**
ER degradation enhancer, mannosidase alpha-like 2	Edem2	108687	**0,72**
ER degradation enhancer, mannosidase alpha-like 3	Edem3	66967	**0,77**
ER lipid raft associated 2	Erlin2	244373	**1,33**
ERBB receptor feedback inhibitor 1	Errfi1	74155	**1,31**
ERGIC and golgi 2	Ergic2	67456	**0,81**
ESF1, nucleolar pre-rRNA processing protein, homolog (S. cerevisiae)	Esf1	66580	**0,80**
ESP8-like 3	Eps8l3	99662	**1,30**
Ellis van Creveld syndrome 2 homolog (human)	Evc2	68525	**1,27**
Eph receptor A2	Epha2	13836	**1,62**
Eph receptor B4	Ephb4	13846	**1,22**
Erbb2 interacting protein	Erbb2ip	59079	**1,82**
F-box and WD-40 domain protein 11	Fbxw11	103583	**0,86**
F-box and WD-40 domain protein 2	Fbxw2	30050	**0,86**
F-box and WD-40 domain protein 5	Fbxw5	30839	**0,80**
F-box and WD-40 domain protein 7, archipelago homolog (Drosophila)	Fbxw7	50754	**1,31**
F-box and leucine-rich repeat protein 19	Fbxl19	233902	**1,21**
F-box and leucine-rich repeat protein 8	Fbxl8	50788	**0,87**
F-box protein 10	Fbxo10	269529	**1,18**
F-box protein 17	Fbxo17	50760	**0,84**
F-box protein 33	Fbxo33	70611	**1,40**
F-box protein 38	Fbxo38	107035	**1,25**
F11 receptor	F11r	16456	**1,28**
FAT tumor suppressor homolog 1 (Drosophila)	Fat1	14107	**1,53**
FAT tumor suppressor homolog 2 (Drosophila)	Fat2	245827	**0,86**
FAT tumor suppressor homolog 3 (Drosophila)	Fat3	270120	**1,37**
FAT tumor suppressor homolog 4 (Drosophila)	Fat4	329628	**1,34**
FBJ osteosarcoma oncogene	Fos	14281	**1,32**
FCH and double SH3 domains 2	Fchsd2	207278	**1,34**
FERM domain containing 4B	Frmd4b	232288	**0,83**
FERM, RhoGEF and pleckstrin domain protein 2	Farp2	227377	**0,84**
FH2 domain containing 1	Fhdc1	229474	**1,75**
FK506 binding protein 12-rapamycin associated protein 1	Frap1	56717	**1,27**
FK506 binding protein 15	Fkbp15	338355	**1,24**
FK506 binding protein 2	Fkbp2	14227	**0,58**
FK506 binding protein 3	Fkbp3	30795	**0,76**
FK506 binding protein 4	Fkbp4	14228	**1,30**
FMS-like tyrosine kinase 3	Flt3	14255	**1,37**
FUN14 domain containing 2	Fundc2	67391	**1,21**
FXYD domain-containing ion transport regulator 3	Fxyd3	17178	**0,50**
FXYD domain-containing ion transport regulator 6	Fxyd6	59095	**1,32**
FYVE, RhoGEF and PH domain containing 3	Fgd3	30938	**0,82**
FYVE, RhoGEF and PH domain containing 4	Fgd4	224014	**1,34**
Fanconi anemia, complementation group I	Fanci	208836	**1,20**
Fas (TNF receptor superfamily member 6)	Fas	14102	**0,84**
Fas (TNFRSF6) binding factor 1	Fbf1	217335	**1,39**
Fas apoptotic inhibitory molecule 3	Faim3	69169	**1,25**
Fc fragment of IgG binding protein	Fcgbp	215384	**1,35**
Fc receptor, IgE, low affinity II, alpha polypeptide	Fcer2a	14128	**1,27**
Fc receptor, IgG, high affinity I	Fcgr1	14129	**0,82**
Fc receptor, IgG, low affinity IV	Fcgr4	246256	**0,85**
Fc receptor-like 5	Fcrl5	329693	**0,84**
Fgfr1 oncogene partner	Fgfr1op	75296	**1,27**
Fyn proto-oncogene	Fyn	14360	**1,26**
G protein-coupled bile acid receptor 1	Gpbar1	227289	**1,29**
G protein-coupled receptor 116	Gpr116	224792	**1,21**
G protein-coupled receptor 120	Gpr120	107221	**0,67**
G protein-coupled receptor 133	Gpr133	243277	**1,37**
G protein-coupled receptor 175	Gpr175	24100	**1,24**
G protein-coupled receptor 19	Gpr19	14760	**0,86**
G protein-coupled receptor 23	Gpr23	78134	**0,81**
G protein-coupled receptor 34	Gpr34	23890	**0,83**
G protein-coupled receptor 56	Gpr56	14766	**0,85**
G protein-coupled receptor 68	Gpr68	238377	**0,85**
G protein-coupled receptor associated sorting protein 1	Gprasp1	67298	**1,50**
G protein-coupled receptor associated sorting protein 2	Gprasp2	245607	**1,36**
G protein-coupled receptor kinase-interactor 2	Git2	26431	**0,87**
G protein-coupled receptor, family C, group 5, member A	Gprc5a	232431	**1,53**
G-protein coupled receptor 65	Gpr65	14744	**0,81**
GATA binding protein 2	Gata2	14461	**1,26**
GC-rich promoter binding protein 1	Gpbp1	73274	**0,82**
GINS complex subunit 1 (Psf1 homolog)	Gins1	69270	**0,85**
GIPC PDZ domain containing family, member 2	Gipc2	54120	**0,71**
GLI pathogenesis-related 2	Glipr2	384009	**0,83**

Addendum

GLI-Kruppel family member GLI2	Gli2	14633	**0,86**
GPI anchor attachment protein 1	Gpaa1	14731	**0,84**
GPI anchored molecule like protein	Gml	625599	**1,41**
GRB10 interacting GYF protein 2	Gigyf2	227331	**1,36**
GRB2-related adaptor protein 2	Grap2	17444	**0,85**
GRIP1 associated protein 1	Gripap1	54645	**1,42**
GRP1 (general receptor for phosphoinositides 1)-associated scaffold protein	Grasp	56149	**1,26**
GTP binding protein 2	Gtpbp2	56055	**1,35**
GTP cyclohydrolase I feedback regulator	Gchfr	320415	**0,82**
GTPase, IMAP family member 3	Gimap3	83408	**1,18**
H2-K region expressed gene 2	H2-Ke2	14976	**0,62**
H2A histone family, member Z	H2afz	51788	**0,87**
HECT, UBA and WWE domain containing 1	Huwe1	59026	**1,29**
HGF-regulated tyrosine kinase substrate	Hgs	15239	**1,31**
HRAS like suppressor 3	Hrasls3	225845	**0,57**
Hermansky-Pudlak syndrome 1 homolog (human)	Hps1	192236	**0,89**
HtrA serine peptidase 3	Htra3	78558	**1,20**
IK cytokine	Ik	24010	**0,64**
IKAROS family zinc finger 1	Ikzf1	22778	**1,36**
IKAROS family zinc finger 2	Ikzf2	22779	**0,81**
IKAROS family zinc finger 5	Ikzf5	67143	**1,62**
IMP3, U3 small nucleolar ribonucleoprotein, homolog (yeast)	Imp3	102462	**0,69**
IMP4, U3 small nucleolar ribonucleoprotein, homolog (yeast)	Imp4	27993	**0,76**
IQ motif containing GTPase activating protein 1	Iqgap1	29875	**1,29**
IQ motif containing GTPase activating protein 2	Iqgap2	544963	**1,30**
IQ motif containing GTPase activating protein 3	Iqgap3	404710	**1,22**
ISL1 transcription factor, LIM/homeodomain	Isl1	16392	**1,23**
InaD-like (Drosophila)	Inadl	12695	**1,39**
Iroquois related homeobox 1 (Drosophila)	Irx1	16371	**1,33**
Janus kinase 1	Jak1	16451	**0,71**
Jun oncogene	Jun	16476	**1,35**
Jun proto-oncogene related gene d	Jund	16478	**1,43**
K+ voltage-gated channel, subfamily S, 1	Kcns1	16538	**1,25**
KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	Kdelr3	105785	**0,64**
KRI1 homolog (S. cerevisiae)	Kri1	215194	**0,88**
Kallmann syndrome 1 sequence (human)	Kal1	14038	**0,69**
Kruppel-like factor 10	Klf10	21847	**1,27**
Kruppel-like factor 11	Klf11	194655	**1,16**
Kruppel-like factor 16	Klf16	118445	**1,18**
Kruppel-like factor 3 (basic)	Klf3	16599	**1,28**
Kruppel-like factor 6	Klf6	23849	**1,43**
Kruppel-like factor 7 (ubiquitous)	Klf7	93691	**1,42**
Kruppel-like factor 9	Klf9	16601	**1,38**
LAG1 homolog, ceramide synthase 6	Lass6	241447	**1,41**
LEM domain containing 3	Lemd3	380664	**1,51**
LFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase	Lfng	16848	**1,32**
LIM and senescent cell antigen-like domains 1	Lims1	110829	**0,86**
LIM domain binding 3	Ldb3	24131	**1,39**
LIM domain containing preferred translocation partner in lipoma	Lpp	210126	**1,43**
LIM domain only 7	Lmo7	380928	**1,45**
LIM domains containing 1	Limd1	29806	**1,46**
LON peptidase N-terminal domain and ring finger 1	Lonrf1	244421	**1,23**
LPS-responsive beige-like anchor	Lrba	80877	**1,33**
LSM1 homolog, U6 small nuclear RNA associated (S. cerevisiae)	Lsm1	67207	**0,77**
LSM14 homolog A (SCD6, S. cerevisiae)	Lsm14a	67070	**1,28**
LSM2 homolog, U6 small nuclear RNA associated (S. cerevisiae)	Lsm2	27756	**0,74**
LSM3 homolog, U6 small nuclear RNA associated (S. cerevisiae)	Lsm3	67678	**0,70**
LSM4 homolog, U6 small nuclear RNA associated (S. cerevisiae)	Lsm4	50783	**0,72**
LSM6 homolog, U6 small nuclear RNA associated (S. cerevisiae)	Lsm6	78651	**0,86**
M-phase phosphoprotein 10 (U3 small nucleolar ribonucleoprotein)	Mphosph10	67973	**1,25**
M-phase phosphoprotein 9	Mphosph9	269702	**1,26**
MAD homolog 3 (Drosophila)	Smad3	17127	**1,30**
MAD homolog 4 (Drosophila)	Smad4	17128	**1,22**
MAD2L1 binding protein	Mad2l1bp	66591	**1,34**
MAF1 homolog (S. cerevisiae)	Maf1	68877	**0,70**
MAP kinase-activated protein kinase 5	Mapkapk5	17165	**1,36**
MAP/microtubule affinity-regulating kinase 2	Mark2	13728	**1,51**
MARVEL (membrane-associating) domain containing 2	Marveld2	218518	**1,31**
MAS-related GPR, member A3	Mrgpra3	233222	**1,43**
MAS-related GPR, member F	Mrgprf	211577	**1,40**
MAX dimerization protein 1	Mxd1	17119	**1,27**
MKL (megakaryoblastic leukemia)/myocardin-like 1	Mkl1	223701	**0,82**
MKL/myocardin-like 2	Mkl2	239719	**0,80**
MON2 homolog (yeast)	Mon2	67074	**1,28**
MYC-associated zinc finger protein (purine-binding transcription factor)	Maz	17188	**1,29**
MYST histone acetyltransferase (monocytic leukemia) 3	Myst3	244349	**1,25**
MYST histone acetyltransferase 2	Myst2	217127	**1,24**
Max interacting protein 1	Mxi1	17859	**1,24**
Mid1 interacting protein 1 (gastrulation specific G12-like (zebrafish))	Mid1ip1	68041	**1,35**
Mpv17 transgene, kidney disease mutant-like	Mpv17l	93734	**1,27**
Myb protein P42POP	P42pop	232934	**1,26**
MyoD family inhibitor domain containing	Mdfic	16543	**1,43**
N-acetylated alpha-linked acidic dipeptidase-like 1	Naaladl1	381204	**1,36**
N-acetylglucosamine kinase	Nagk	56174	**0,68**
N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidase	Nagpa	27426	**1,20**
N-acetylglutamate synthase	Nags	217214	**0,87**

N-acetylneuraminate pyruvate lyase	Npl	74091	**0,85**
N-acyl phosphatidylethanolamine phospholipase D	Napepld	242864	**0,82**
N-acylsphingosine amidohydrolase (alkaline ceramidase) 3	Asah3	171168	**1,35**
N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 2	Ndst2	17423	**0,85**
N-methylpurine-DNA glycosylase	Mpg	268395	**0,87**
N-myc downstream regulated gene 4	Ndrg4	234593	**1,54**
N-myristoyltransferase 1	Nmt1	18107	**1,33**
NAD kinase	Nadk	192185	**0,72**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 10	Ndufa10	67273	**0,67**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13	Ndufa13	67184	**0,75**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2	Ndufa2	17991	**0,70**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 3	Ndufa3	66091	**0,55**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4	Ndufa4	17992	**0,57**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5	Ndufa5	68202	**0,70**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6 (B14)	Ndufa6	67130	**0,65**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7 (B14.5a)	Ndufa7	66416	**0,47**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8	Ndufa8	68375	**0,61**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9	Ndufa9	66108	**0,55**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 2	Ndufaf2	75597	**0,66**
NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 10	Ndufb10	68342	**0,66**
NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 11	Ndufb11	104130	**0,53**
NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5	Ndufb5	66046	**0,51**
NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6	Ndufb6	230075	**0,56**
NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9	Ndufb9	66218	**0,55**
NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2	Ndufc2	68197	**0,51**
NADH dehydrogenase (ubiquinone) Fe-S protein 4	Ndufs4	17993	**0,58**
NADH dehydrogenase (ubiquinone) Fe-S protein 5	Ndufs5	595136	**0,70**
NADH dehydrogenase (ubiquinone) Fe-S protein 6	Ndufs6	407785	**0,66**
NADH dehydrogenase (ubiquinone) Fe-S protein 7	Ndufs7	75406	**0,60**
NADH dehydrogenase (ubiquinone) Fe-S protein 8	Ndufs8	225887	**0,45**
NADH dehydrogenase (ubiquinone) flavoprotein 1	Ndufv1	17995	**0,64**
NADH dehydrogenase (ubiquinone) flavoprotein 2	Ndufv2	72900	**0,62**
NADPH oxidase activator 1	Noxa1	241275	**0,69**
NADPH oxidase organizer 1	Noxo1	71893	**0,61**
NEDD4 binding protein 2	N4bp2	333789	**1,19**
NFKB inhibitor interacting Ras-like protein 1	Nkiras1	69721	**1,31**
NFU1 iron-sulfur cluster scaffold homolog (S. cerevisiae)	Nfu1	56748	**0,59**
NHS-like 1	Nhsl1	215819	**0,75**
NIMA (never in mitosis gene a)-related expressed kinase 3	Nek3	23954	**1,32**
NIMA (never in mitosis gene a)-related expressed kinase 4	Nek4	23955	**0,86**
NIMA (never in mitosis gene a)-related expressed kinase 6	Nek6	59126	**0,76**
NLR family, pyrin domain containing 6	Nlrp6	101613	**1,42**
NMD3 homolog (S. cerevisiae)	Nmd3	97112	**0,73**
NUAK family, SNF1-like kinase, 2	Nuak2	74137	**1,37**
NUF2, NDC80 kinetochore complex component, homolog (S. cerevisiae)	Nuf2	66977	**0,80**
Niemann Pick type C2	Npc2	67963	**0,69**
OCIA domain containing 1	Ociad1	68095	**0,85**
OCIA domain containing 2	Ociad2	433904	**0,60**
ORAI calcium release-activated calcium modulator 2	Orai2	269717	**0,86**
ORAI calcium release-activated calcium modulator 3	Orai3	269999	**0,83**
OTU domain containing 7B	Otud7b	229603	**1,24**
OTU domain, ubiquitin aldehyde binding 1	Otub1	107260	**1,26**
OVO homolog-like 1 (Drosophila)	Ovol1	18426	**1,28**
P140 gene	RP23-157O10.7	56013	**1,36**
P450 (cytochrome) oxidoreductase	Por	18984	**0,66**
PAK1 interacting protein 1	Pak1ip1	68083	**1,29**
PAX interacting (with transcription-activation domain) protein 1	Paxip1	55982	**0,84**
PCTAIRE-motif protein kinase 3	Pctk3	18557	**1,22**
PDLIM1 interacting kinase 1 like	Pdik1l	230809	**1,49**
PDS5, regulator of cohesion maintenance, homolog A (S. cerevisiae)	Pds5a	71521	**1,55**
PDZ and LIM domain 2	Pdlim2	213019	**1,26**
PDZ and LIM domain 4	Pdlim4	30794	**1,35**
PDZ and LIM domain 5	Pdlim5	56376	**0,82**
PDZ and LIM domain 7	Pdlim7	67399	**1,20**
PDZ binding kinase	Pbk	52033	**0,72**
PDZ domain containing 11	Pdzd11	72621	**0,73**
PDZ domain containing 2	Pdzd2	68070	**1,27**
PDZ domain containing 3	Pdzd3	170761	**1,36**
PDZ domain containing 8	Pdzd8	107368	**0,85**
PDZK1 interacting protein 1	Pdzk1ip1	67182	**0,62**
PERP, TP53 apoptosis effector	Perp	64058	**1,48**
PHD finger protein 1	Phf1	21652	**1,55**
PHD finger protein 12	Phf12	268448	**0,87**
PHD finger protein 14	Phf14	75725	**1,35**
PHD finger protein 6	Phf6	70998	**0,83**
PIF1 5'-to-3' DNA helicase homolog (S. cerevisiae)	Pif1	208084	**1,32**
PR domain containing 15	Prdm15	114604	**1,19**
PR domain containing 2, with ZNF domain	Prdm2	110593	**1,29**
PRELI domain containing 1	Prelid1	66494	**1,24**
PRP31 pre-mRNA processing factor 31 homolog (yeast)	Prpf31	68988	**0,82**
PRP4 pre-mRNA processing factor 4 homolog B (yeast)	Prpf4b	19134	**0,86**
PTEN induced putative kinase 1	Pink1	68943	**1,45**
PTK2 protein tyrosine kinase 2 beta	Ptk2b	19229	**1,36**
PYD and CARD domain containing	Pycard	66824	**0,47**
Pbx/knotted 1 homeobox	Pknox1	18771	**0,81**
Prkr interacting protein 1 (IL11 inducible)	Prkrip1	66801	**0,80**

Purkinje cell protein 4	Pcp4	18546	**1,46**
R-spondin 3 homolog (Xenopus laevis)	Rspo3	72780	**1,29**
RAB GTPase activating protein 1-like	Rabgap1l	29809	**1,20**
RAB guanine nucleotide exchange factor (GEF) 1	Rabgef1	56715	**0,85**
RAB1, member RAS oncogene family	Rab1	19324	**0,67**
RAB11 family interacting protein 1 (class I)	Rab11fip1	75767	**1,21**
RAB11 family interacting protein 4 (class II)	Rab11fip4	268451	**1,26**
RAB11 family interacting protein 5 (class I)	Rab11fip5	52055	**1,38**
RAB15, member RAS oncogene family	Rab15	104886	**0,64**
RAB17, member RAS oncogene family	Rab17	19329	**1,47**
RAB18, member RAS oncogene family	Rab18	19330	**1,30**
RAB20, member RAS oncogene family	Rab20	19332	**0,76**
RAB21, member RAS oncogene family	Rab21	216344	**1,23**
RAB25, member RAS oncogene family	Rab25	53868	**0,49**
RAB27A, member RAS oncogene family	Rab27a	11891	**0,85**
RAB27b, member RAS oncogene family	Rab27b	80718	**0,72**
RAB33B, member of RAS oncogene family	Rab33b	19338	**1,37**
RAB37, member of RAS oncogene family	Rab37	58222	**0,84**
RAB3A, member RAS oncogene family	Rab3a	19339	**1,23**
RAB3D, member RAS oncogene family	Rab3d	19340	**0,76**
RAB4A, member RAS oncogene family	Rab4a	19341	**0,81**
RAB6B, member RAS oncogene family	Rab6b	270192	**1,56**
RAB7, member RAS oncogene family-like 1	Rab7l1	226422	**0,73**
RAB9, member RAS oncogene family	Rab9	56382	**1,30**
RAD1 homolog (S. pombe)	Rad1	19355	**0,84**
RAD18 homolog (S. cerevisiae)	Rad18	58186	**1,22**
RAD23a homolog (S. cerevisiae)	Rad23a	19358	**1,28**
RAD50 homolog (S. cerevisiae)	Rad50	19360	**0,81**
RAD51 associated protein 1	Rad51ap1	19362	**0,83**
RAD51 homolog (S. cerevisiae)	Rad51	19361	**0,76**
RAD51-like 3 (S. cerevisiae)	Rad51l3	19364	**0,87**
RAD52 homolog (S. cerevisiae)	Rad52	19365	**0,81**
RAD54 like (S. cerevisiae)	Rad54l	19366	**0,84**
RAN binding protein 1	Ranbp1	19385	**0,54**
RAN binding protein 3	Ranbp3	71810	**1,29**
RAN binding protein 5	Ranbp5	70572	**1,20**
RAN binding protein 9	Ranbp9	56705	**0,79**
RAP1, GTP-GDP dissociation stimulator 1	Rap1gds1	229877	**0,82**
RAP2B, member of RAS oncogene family	Rap2b	74012	**1,28**
RAP2C, member of RAS oncogene family	Rap2c	72065	**1,29**
RAR-related orphan receptor gamma	Rorc	19885	**0,81**
RAS p21 protein activator 4	Rasa4	54153	**0,83**
RAS, guanyl releasing protein 2	Rasgrp2	19395	**1,29**
RAS-like, family 11, member B	Rasl11b	68939	**1,23**
RAS-related C3 botulinum substrate 2	Rac2	19354	**1,30**
RB-associated KRAB repressor	Rbak	57782	**1,33**
RELT-like 1	Rell1	100532	**1,96**
RELT-like 2	Rell2	225392	**1,16**
REST corepressor 2	Rcor2	104383	**1,36**
REV1 homolog (S. cerevisiae)	Rev1	56210	**1,29**
REV3-like, catalytic subunit of DNA polymerase zeta RAD54 like (S. cerevisiae)	Rev3l	19714	**1,35**
RFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase	Rfng	19719	**1,35**
RIKEN cDNA 1110001D15 gene	1110001D15Rik	68553	**0,84**
RIKEN cDNA 1110002N22 gene	1110002N22Rik	68550	**0,77**
RIKEN cDNA 1110008L16 gene	1110008L16Rik	66132	**0,79**
RIKEN cDNA 1110018M03 gene	1110018M03Rik	67606	**1,30**
RIKEN cDNA 1110032A04 gene	1110032A04Rik	66183	**0,67**
RIKEN cDNA 1110049F12 gene	1110049F12Rik	66193	**0,76**
RIKEN cDNA 1190002H23 gene	1190002H23Rik	66214	**0,77**
RIKEN cDNA 1190017O12 gene	1190017O12Rik	68936	**0,71**
RIKEN cDNA 1200002N14 gene	1200002N14Rik	71712	**1,40**
RIKEN cDNA 1200009F10 gene	1200009F10Rik	67454	**0,83**
RIKEN cDNA 1300018J18 gene	1300018J18Rik	223776	**0,70**
RIKEN cDNA 1600027N09 gene	1600027N09Rik	73247	**1,30**
RIKEN cDNA 1600029D21 gene	1600029D21Rik	76509	**0,41**
RIKEN cDNA 1700041G16 gene	1700041G16Rik	73299	**0,85**
RIKEN cDNA 1700081L11 gene	1700081L11Rik	76719	**1,32**
RIKEN cDNA 1810010M01 gene	1810010M01Rik	69036	**0,48**
RIKEN cDNA 1810046J19 gene	1810046J19Rik	103742	**0,61**
RIKEN cDNA 1810047C23 gene	1810047C23Rik	192169	**0,67**
RIKEN cDNA 2010002N04 gene	2010002N04Rik	106878	**0,88**
RIKEN cDNA 2010106G01 gene	2010106G01Rik	66552	**1,48**
RIKEN cDNA 2010107E04 gene	2010107E04Rik	70257	**0,68**
RIKEN cDNA 2210407C18 gene	2210407C18Rik	78354	**0,65**
RIKEN cDNA 2310008H09 gene	2310008H09Rik	66356	**0,87**
RIKEN cDNA 2410015N17 gene	2410015N17Rik	66422	**0,62**
RIKEN cDNA 2410127E18 gene	2410127E18Rik	76788	**1,35**
RIKEN cDNA 2510003E04 gene	2510003E04Rik	72320	**1,18**
RIKEN cDNA 2610207I05 gene	2610207I05Rik	233789	**0,82**
RIKEN cDNA 2700094K13 gene	2700094K13Rik	72657	**0,69**
RIKEN cDNA 2810002O09 gene	2810002O09Rik	72345	**1,16**
RIKEN cDNA 3110003A22 gene	3110003A22Rik	68053	**0,86**
RIKEN cDNA 4121402D02 gene	4121402D02Rik	74026	**1,43**
RIKEN cDNA 4631426J05 gene	4631426J05Rik	77590	**1,24**
RIKEN cDNA 4921505C17 gene	4921505C17Rik	78757	**1,34**
RIKEN cDNA 4921513D23 gene	4921513D23Rik	223989	**1,28**

RIKEN cDNA 4921533L14 gene	4921533L14Rik	68187	**1,46**
RIKEN cDNA 4930504E06 gene	4930504E06Rik	75007	**0,80**
RIKEN cDNA 4930583H14 gene	4930583H14Rik	67749	**1,53**
RIKEN cDNA 5730403B10 gene	5730403B10Rik	66626	**1,18**
RIKEN cDNA 5730410E15 gene	5730410E15Rik	319613	**0,80**
RIKEN cDNA 5830443L24 gene	5830443L24Rik	76074	**0,84**
RIKEN cDNA 5830467P10 gene	5830467P10Rik	241639	**0,79**
RIKEN cDNA 6620401K05 gene	6620401K05Rik	235610	**0,84**
RIKEN cDNA 9030409G11 gene	9030409G11Rik	71529	**1,16**
RIKEN cDNA 9030425E11 gene	9030425E11Rik	71566	**1,34**
RIKEN cDNA A230067G21 gene	A230067G21Rik	241694	**0,81**
RIKEN cDNA D230014K01 gene	D230014K01Rik	217364	**1,26**
RIKEN cDNA D930001I22 gene	D930001I22Rik	228859	**1,18**
RIKEN cDNA E130016E03 gene	E130016E03Rik	623474	**0,83**
RIO kinase 3 (yeast)	Riok3	66878	**1,43**
RNA binding motif protein 15	Rbm15	229700	**1,35**
RNA binding motif protein 25	Rbm25	67039	**1,38**
RNA binding motif protein 38	Rbm38	56190	**1,24**
RNA binding motif protein 45	Rbm45	241490	**1,31**
RNA binding motif protein 5	Rbm5	83486	**1,41**
RNA binding motif protein 6	Rbm6	19654	**1,83**
RNA binding motif, single stranded interacting protein	Rbms3	207181	**1,70**
RNA binding motif, single stranded interacting protein 1	Rbms1	56878	**1,44**
RNA binding motif, single stranded interacting protein 2	Rbms2	56516	**1,38**
RNA binding protein with multiple splicing 2	Rbpms2	71973	**1,74**
RNA polymerase 1-1	Rpo1-1	20016	**0,67**
RNA polymerase 1-2	Rpo1-2	20017	**0,84**
RNA polymerase 1-3	Rpo1-3	20018	**0,62**
RNA terminal phosphate cyclase-like 1	Rcl1	59028	**0,82**
ROD1 regulator of differentiation 1 (S. pombe)	Rod1	230257	**0,75**
RPA interacting protein	Rpain	69723	**0,84**
RUN domain containing 1	Rundc1	217201	**1,21**
Rab interacting lysosomal protein	Rilp	280408	**1,19**
Rab40c, member RAS oncogene family	Rab40c	224624	**0,87**
Rab9 effector protein with kelch motifs	Rabepk	227746	**0,77**
Rac GTPase-activating protein 1	Racgap1	26934	**0,79**
Rac/Cdc42 guanine nucleotide exchange factor (GEF) 6	Arhgef6	73341	**1,30**
Rad51 homolog c (S. cerevisiae)	Rad51c	114714	**0,83**
Ral GEF with PH domain and SH3 binding motif 2	Ralgps2	78255	**1,53**
Rap guanine nucleotide exchange factor (GEF) 6	Rapgef6	192786	**1,70**
Rap1 GTPase-activating protein	Rap1gap	110351	**0,71**
Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	Raph1	77300	**1,78**
Ras association (RalGDS/AF-6) domain family (N-terminal) member 9	Rassf9	237504	**0,86**
Ras association (RalGDS/AF-6) domain family member 4	Rassf4	213391	**0,86**
Ras association (RalGDS/AF-6) domain family member 5	Rassf5	54354	**0,82**
Ras association (RalGDS/AF-6) domain family member 6	Rassf6	73246	**0,67**
Ras-like without CAAX 2	Rit2	19762	**1,32**
Rho GTPase activating protein 17	Arhgap17	70497	**1,27**
Rho GTPase activating protein 18	Arhgap18	73910	**1,18**
Rho GTPase activating protein 21	Arhgap21	71435	**1,31**
Rho GTPase activating protein 24	Arhgap24	231532	**0,84**
Rho GTPase activating protein 29	Arhgap29	214137	**1,32**
Rho GTPase activating protein 8	Arhgap8	109270	**0,86**
Rho GTPase-activating protein	Grit	330914	**0,77**
Rho guanine nucleotide exchange factor (GEF) 5	Arhgef5	54324	**1,27**
Rho-associated coiled-coil containing protein kinase 1	Rock1	19877	**1,39**
Rho-guanine nucleotide exchange factor	Rgnef	110596	**0,78**
Rho-related BTB domain containing 2	Rhobtb2	246710	**0,83**
Rtf1, Paf1/RNA polymerase II complex component, homolog (S. cerevisiae)	Rtf1	76246	**1,47**
S100 calcium binding protein A1	S100a1	20193	**0,52**
S100 calcium binding protein A10 (calpactin)	S100a10	20194	**0,59**
S100 calcium binding protein A4	S100a4	20198	**1,37**
S100 calcium binding protein A6 (calcyclin)	S100a6	20200	**0,66**
S100 calcium binding protein A8 (calgranulin A)	S100a8	20201	**0,78**
S100 calcium binding protein G	S100g	12309	**0,60**
SAC3 domain containing 1	Sac3d1	66406	**0,80**
SAM and SH3 domain containing 1	Sash1	70097	**1,58**
SAM pointed domain containing ets transcription factor	Spdef	30051	**0,52**
SAP30-like	Sap30l	50724	**1,39**
SAR1 gene homolog A (S. cerevisiae)	Sar1a	20224	**0,80**
SAR1 gene homolog B (S. cerevisiae)	Sar1b	66397	**0,58**
SCAN domain-containing 1	Scand1	19018	**0,71**
SEBOX homeobox	Sebox	18292	**1,51**
SEC13 homolog (S. cerevisiae)	Sec13	110379	**0,72**
SEC22 vesicle trafficking protein-like A (S. cerevisiae)	Sec22a	317717	**0,83**
SEC23A (S. cerevisiae)	Sec23a	20334	**1,23**
SECIS binding protein 2	Secisbp2	75420	**1,24**
SERTA domain containing 1	Sertad1	55942	**1,39**
SERTA domain containing 2	Sertad2	58172	**1,29**
SERTA domain containing 4	Sertad4	214791	**1,29**
SET domain containing (lysine methyltransferase) 7	Setd7	73251	**1,64**
SET domain containing 1A	Setd1a	233904	**1,22**
SFFV proviral integration 1	Sfpi1	20375	**1,27**
SFT2 domain containing 2	Sft2d2	108735	**1,19**
SGT1, suppressor of G2 allele of SKP1 (S. cerevisiae)	Sugt1	67955	**0,63**
SH3 domain containing ring finger 2	Sh3rf2	269016	**1,55**

SH3 domain protein D19	Sh3d19	27059	**1,43**
SH3-domain GRB2-like 2	Sh3gl2	20404	**0,86**
SH3-domain GRB2-like B1 (endophilin)	Sh3glb1	54673	**1,28**
SID1 transmembrane family, member 1	Sidt1	320007	**0,81**
SIVA1, apoptosis-inducing factor	Siva1	30954	**0,72**
SLIT and NTRK-like family, member 5	Slitrk5	75409	**1,22**
SLIT and NTRK-like family, member 6	Slitrk6	239250	**0,82**
SLIT-ROBO Rho GTPase activating protein 2	Srgap2	14270	**1,24**
SLIT-ROBO Rho GTPase activating protein 3	Srgap3	259302	**1,34**
SPARC-like 1 (mast9, hevin)	Sparcl1	13602	**1,56**
SRY-box containing gene 12	Sox12	20667	**1,38**
SRY-box containing gene 18	Sox18	20672	**1,38**
SRY-box containing gene 4	Sox4	20677	**1,29**
SRY-box containing gene 6	Sox6	20679	**0,90**
SRY-box containing gene 8	Sox8	20681	**0,81**
ST3 beta-galactoside alpha-2,3-sialyltransferase 3	St3gal3	20441	**0,73**
ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 2	St6galnac2	20446	**0,76**
STARD3 N-terminal like	Stard3nl	76205	**0,73**
START domain containing 10	Stard10	56018	**0,61**
START domain containing 3	Stard3	59045	**0,74**
STIP1 homology and U-Box containing protein 1	Stub1	56424	**0,84**
STT3, subunit of the oligosaccharyltransferase complex, homolog B (S. cerevisiae)	Stt3b	68292	**0,87**
SUMO/sentrin specific peptidase 2	Senp2	75826	**1,30**
SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1	Smarcd1	83797	**1,58**
SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 2	Smarcd2	83796	**1,28**
Scl/Tal1 interrupting locus	Stil	20460	**0,85**
Sec61 alpha 1 subunit (S. cerevisiae)	Sec61a1	53421	**0,69**
Sec61, alpha subunit 2 (S. cerevisiae)	Sec61a2	57743	**0,85**
Sjogren syndrome antigen B	Ssb	20823	**1,24**
Sjogren's syndrome nuclear autoantigen 1	Ssna1	68475	**0,63**
Smg-5 homolog, nonsense mediated mRNA decay factor (C. elegans)	Smg5	229512	**1,19**
Smg-7 homolog, nonsense mediated mRNA decay factor (C. elegans)	Smg7	226517	**1,30**
Snf2-related CREBBP activator protein	Srcap	546001	**1,33**
Son of sevenless homolog 2 (Drosophila)	Sos2	20663	**1,49**
Sp2 transcription factor	Sp2	78912	**1,25**
Spi-B transcription factor (Spi-1/PU.1 related)	Spib	272382	**1,38**
Src homology 2 domain containing F	Shf	435684	**1,16**
Suppression of tumorigenicity 7	St7	64213	**0,75**
Swi/SNF related matrix associated, actin dependent regulator of chromatin, subfamily a-like 1	Smarcal1	54380	**0,83**
T-box 15	Tbx15	21384	**1,17**
T-box 3	Tbx3	21386	**1,35**
T-cell leukemia translocation altered gene	Tcta	102791	**0,82**
T-cell leukemia, homeobox 2	Tlx2	21909	**1,26**
T-cell, immune regulator 1, ATPase, H+ transporting, lysosomal V0 protein A3	Tcirg1	27060	**1,32**
TAF11 RNA polymerase II, TATA box binding protein (TBP)-associated factor	Taf11	68776	**0,86**
TAF13 RNA polymerase II, TATA box binding protein (TBP)-associated factor	Taf13	99730	**1,38**
TAF15 RNA polymerase II, TATA box binding protein (TBP)-associated factor	Taf15	70439	**1,31**
TAF4B RNA polymerase II, TATA box binding protein (TBP)-associated factor	Taf4b	72504	**1,39**
TAF5-like RNA polymerase II, p300/CBP-associated factor (PCAF)-associated factor	Taf5l	102162	**0,84**
TAF7 RNA polymerase II, TATA box binding protein (TBP)-associated factor	Taf7	24074	**0,85**
TAF8 RNA polymerase II, TATA box binding protein (TBP)-associated factorq	Taf8	63856	**1,34**
TAO kinase 1	Taok1	216965	**1,27**
TAR DNA binding protein	Tardbp	230908	**0,79**
TATA box binding protein	Tbp	21374	**0,82**
TBC1 domain family, member 8	Tbc1d8	54610	**0,83**
TBK1 binding protein 1	Tbkbp1	73174	**1,31**
TCF3 (E2A) fusion partner	Tfpt	69714	**0,85**
TEA domain family member 3	Tead3	21678	**1,27**
THO complex 1	Thoc1	225160	**0,82**
THO complex 7 homolog (Drosophila)	Thoc7	66231	**0,82**
TIP41, TOR signalling pathway regulator-like (S. cerevisiae)	Tiprl	226591	**1,45**
TM2 domain containing 3	Tm2d3	68634	**0,85**
TNF receptor-associated protein 1	Trap1	68015	**0,73**
TNFRSF1A-associated via death domain	Tradd	71609	**0,73**
TOX high mobility group box family member 3	Tox3	244579	**1,43**
TOX high mobility group box family member 4	Tox4	268741	**0,83**
TP53 regulated inhibitor of apoptosis 1	Triap1	69076	**0,80**
TRH-degrading enzyme	Trhde	237553	**0,84**
TSC22 domain family 2	Tsc22d2	72033	**1,31**
TSC22 domain family 4	Tsc22d4	78829	**1,41**
TSPY-like 4	Tspyl4	72480	**1,43**
TSR2, 20S rRNA accumulation, homolog (S. cerevisiae)	Tsr2	69499	**0,83**
TYRO protein tyrosine kinase binding protein	Tyrobp	22177	**0,75**
Tia1 cytotoxic granule-associated RNA binding protein-like 1	Tial1	21843	**0,82**
Tnf receptor-associated factor 6	Traf6	22034	**1,30**
Traf and Tnf receptor associated protein	Ttrap	56196	**0,85**
Traf3 interacting protein 2	Traf3ip2	103213	**0,78**
Trk-fused gene	Tfg	21787	**0,67**
TruB pseudouridine (psi) synthase homolog 1 (E. coli)	Trub1	72133	**0,84**
TruB pseudouridine (psi) synthase homolog 2 (E. coli)	Trub2	227682	**1,36**
U7 snRNP-specific Sm-like protein LSM10	Lsm10	116748	**0,75**
UDP glucuronosyltransferase 2 family, polypeptide B36	Ugt2b36	231396	**0,83**
UDP glucuronosyltransferase 2 family, polypeptide B5	Ugt2b5	22238	**0,76**
UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 1	B3galt1	26877	**0,82**
UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 4	B4galt4	56375	**0,71**
UDP-GalNAc:betaGlcNAc beta 1,3-galactosaminyltransferase, polypeptide 1	B3galnt1	26879	**1,39**

Addendum

UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 1	B3gnt1	108902	**1,28**
UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5	B3gnt5	108105	**0,72**
UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 10	Galnt10	171212	**0,82**
UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 11	Galnt11	231050	**0,84**
UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 3	Galnt3	14425	**0,85**
UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 6	Galnt6	207839	**0,78**
UDP-glucose ceramide glucosyltransferase	Ugcg	22234	**1,36**
UDP-glucose dehydrogenase	Ugdh	22235	**1,32**
UDP-glucose pyrophosphorylase 2	Ugp2	216558	**1,30**
UPF2 regulator of nonsense transcripts homolog (yeast)	Upf2	326622	**1,27**
UPF3 regulator of nonsense transcripts homolog A (yeast)	Upf3a	67031	**1,29**
USP6 N-terminal like	Usp6nl	98910	**1,48**
UbiA prenyltransferase domain containing 1	Ubiad1	71707	**0,83**
Von Willebrand factor homolog	Vwf	22371	**0,83**
WAP four-disulfide core domain 1	Wfdc1	67866	**1,20**
WAP four-disulfide core domain 15B	Wfdc15b	192201	**0,85**
WASP family 1	Wasf1	83767	**1,31**
WBP2 N-terminal like	Wbp2nl	74716	**1,33**
WD repeat and SOCS box-containing 1	Wsb1	78889	**1,49**
WD repeat domain 13	Wdr13	73447	**1,27**
WD repeat domain 18	Wdr18	216156	**0,80**
WD repeat domain 26	Wdr26	226757	**1,28**
WD repeat domain 44	Wdr44	72404	**1,43**
WD repeat domain 61	Wdr61	66317	**0,66**
WNK lysine deficient protein kinase 2	Wnk2	75607	**1,23**
WT1-interacting protein	Wtip	101543	**0,79**
WW domain binding protein 11	Wbp11	60321	**1,47**
WW domain binding protein 2	Wbp2	22378	**1,34**
WW domain binding protein 7	Wbp7	75410	**1,42**
WW domain containing adaptor with coiled-coil	Wac	225131	**1,73**
Werner helicase interacting protein 1	Wrnip1	78903	**0,80**
Williams-Beuren syndrome chromosome region 16 homolog (human)	Wbscr16	94254	**0,82**
Wolf-Hirschhorn syndrome candidate 1 (human)	Whsc1	107823	**0,85**
Wolf-Hirschhorn syndrome candidate 1-like 1 (human)	Whsc1l1	234135	**1,26**
Wolf-Hirschhorn syndrome candidate 2 (human)	Whsc2	24116	**0,76**
Wolfram syndrome 1 homolog (human)	Wfs1	22393	**1,41**
X-linked myotubular myopathy gene 1	Mtm1	17772	**1,34**
X-ray repair complementing defective repair in Chinese hamster cells 2	Xrcc2	57434	**1,19**
X-ray repair complementing defective repair in Chinese hamster cells 3	Xrcc3	74335	**1,20**
X-ray repair complementing defective repair in Chinese hamster cells 6	Xrcc6	14375	**0,84**
XPA binding protein 2	Xab2	67439	**0,81**
YEATS domain containing 4	Yeats4	64050	**1,26**
Yip1 interacting factor homolog A (S. cerevisiae)	Yif1a	68090	**0,61**
Z-DNA binding protein 1	Zbp1	58203	**1,24**
a disintegrin and metallopeptidase domain 23	Adam23	23792	**1,49**
a disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 1	Adamts1	11504	**1,24**
a disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 3	Adamts3	330119	**0,84**
a disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 5 (aggrecanase-2)	Adamts5	23794	**1,32**
a disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 8	Adamts8	30806	**1,35**
abhydrolase domain containing 11	Abhd11	68758	**0,69**
abhydrolase domain containing 5	Abhd5	67469	**1,31**
abhydrolase domain containing 6	Abhd6	66082	**1,67**
abl-interactor 2	Abi2	329165	**1,36**
acetoacetyl-CoA synthetase	Aacs	78894	**0,76**
acetyl-Coenzyme A acetyltransferase 1	Acat1	110446	**0,76**
acetyl-Coenzyme A acyltransferase 1B	Acaa1b	235674	**2,10**
acetyl-Coenzyme A carboxylase beta	Acacb	100705	**1,28**
acid phosphatase 5, tartrate resistant	Acp5	11433	**0,59**
acid phosphatase, prostate	Acpp	56318	**0,81**
acidic (leucine-rich) nuclear phosphoprotein 32 family, member E	Anp32e	66471	**1,29**
acireductone dioxygenase 1	Adi1	104923	**0,73**
actin filament associated protein 1	Afap1	70292	**1,29**
actin related protein 2/3 complex, subunit 2	Arpc2	76709	**1,39**
actin-binding LIM protein 1	Ablim1	226251	**1,33**
actin-like 6A	Actl6a	56456	**1,40**
actin-like 7b	Actl7b	11471	**1,28**
actinin, alpha 1	Actn1	109711	**1,31**
activating signal cointegrator 1 complex subunit 3	Ascc3	77987	**0,86**
activating transcription factor 6	Atf6	226641	**1,15**
activin A receptor, type 1B	Acvr1b	11479	**1,50**
activin A receptor, type IC	Acvr1c	269275	**0,82**
activin receptor IIA	Acvr2a	11480	**1,39**
acyl-CoA synthetase long-chain family member 3	Acsl3	74205	**1,75**
acyl-CoA synthetase long-chain family member 4	Acsl4	50790	**1,33**
acyl-CoA synthetase medium-chain family member 3	Acsm3	20216	**0,62**
acyl-CoA synthetase short-chain family member 1	Acss1	68738	**1,29**
acyl-CoA thioesterase 11	Acot11	329910	**1,63**
acyl-CoA thioesterase 4	Acot4	171282	**1,36**
acyl-CoA thioesterase 6	Acot6	217700	**1,40**
acyl-CoA thioesterase 8	Acot8	170789	**0,82**
acyl-Coenzyme A dehydrogenase family, member 9	Acad9	229211	**1,25**
acyl-Coenzyme A dehydrogenase, short/branched chain	Acadsb	66885	**1,37**
acyl-Coenzyme A dehydrogenase, very long chain	Acadvl	11370	**0,77**
acyl-Coenzyme A oxidase 2, branched chain	Acox2	93732	**1,23**
acylpeptide hydrolase	Apeh	235606	**0,67**
adaptor protein complex AP-1, sigma 1	Ap1s1	11769	**1,19**

adaptor protein complex AP-2, alpha 2 subunit	Ap2a2	11772	**0,83**
adaptor-related protein complex 1, sigma 2 subunit	Ap1s2	108012	**1,26**
adaptor-related protein complex 3, beta 1 subunit	Ap3b1	11774	**0,85**
adaptor-related protein complex 3, beta 2 subunit	Ap3b2	11775	**1,16**
adducin 2 (beta)	Add2	11519	**1,16**
adenosine deaminase, RNA-specific, B1	Adarb1	110532	**1,24**
adenylate cyclase 5	Adcy5	224129	**1,47**
adenylate cyclase 9	Adcy9	11515	**1,20**
adenylate cyclase activating polypeptide 1 receptor 1	Adcyap1r1	11517	**1,26**
adenylate kinase 3 alpha-like 1	Ak3l1	11639	**1,36**
adipose differentiation related protein	Adfp	11520	**1,33**
adrenergic receptor, alpha 2a	Adra2a	11551	**1,65**
advanced glycosylation end product-specific receptor	Ager	11596	**1,29**
aftiphilin	Aftph	216549	**1,40**
agrin	Agrn	11603	**1,37**
alcohol dehydrogenase 5 (class III), chi polypeptide	Adh5	11532	**0,72**
aldehyde dehydrogenase 9, subfamily A1	Aldh9a1	56752	**1,28**
aldehyde dehydrogenase family 1, subfamily A1	Aldh1a1	11668	**1,38**
aldehyde dehydrogenase family 1, subfamily A2	Aldh1a2	19378	**1,48**
aldehyde dehydrogenase family 6, subfamily A1	Aldh6a1	104776	**1,45**
aldo-keto reductase family 1, member A4 (aldehyde reductase)	Akr1a4	58810	**0,75**
aldo-keto reductase family 1, member B7	Akr1b7	11997	**1,38**
aldo-keto reductase family 1, member C12	Akr1c12	622402	**0,62**
aldo-keto reductase family 1, member C13	Akr1c13	27384	**1,34**
aldolase 3, C isoform	Aldoc	11676	**1,27**
alkB, alkylation repair homolog 1 (E. coli)	Alkbh1	211064	**0,83**
alkB, alkylation repair homolog 2 (E. coli)	Alkbh2	231642	**0,84**
alkB, alkylation repair homolog 7 (E. coli)	Alkbh7	66400	**0,72**
alkaline phosphatase, intestinal	Alpi	76768	**1,40**
alkaline phosphatase, liver/bone/kidney	Alpl	11647	**1,23**
allantoicase	Allc	94041	**1,19**
alpha glucosidase 2 alpha neutral subunit	Ganab	14376	**0,78**
alpha-N-acetylglucosaminidase (Sanfilippo disease IIIB)	Naglu	27419	**0,85**
amiloride-sensitive cation channel 2, neuronal	Accn2	11419	**1,23**
amine oxidase (flavin containing) domain 2	Aof2	99982	**0,81**
amine oxidase, copper containing 3	Aoc3	11754	**1,41**
amine oxidase, flavin containing 1	Aof1	218214	**1,42**
amphiphysin	Amph	218038	**1,24**
amphiregulin	Areg	11839	**0,76**
amplified in osteosarcoma	Os9	216440	**1,32**
amyloid beta (A4) precursor protein-binding, family B, member 2	Apbb2	11787	**1,28**
amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 2 (human)	Als2cr2	227154	**1,44**
anaphase promoting complex subunit 4	Anapc4	52206	**0,83**
ancient ubiquitous protein	Aup1	11993	**0,77**
androgen binding protein alpha	Abpa	11354	**1,46**
androgen binding protein beta	Abpb	233099	**0,84**
androgen binding protein gamma	Abpg	110187	**0,81**
angiogenin, ribonuclease A family, member 4	Ang4	219033	**0,29**
angiogenin, ribonuclease, RNase A family, 5	Ang	11727	**0,63**
angiomotin like 2	Amotl2	56332	**1,38**
angiomotin-like 1	Amotl1	75723	**0,83**
angiopoietin-like 7	Angptl7	654812	**1,37**
angiotensin I converting enzyme (peptidyl-dipeptidase A) 1	Ace	11421	**0,83**
angiotensin II receptor, type 1a	Agtr1a	11607	**1,26**
angiotensin receptor-like 1	Agtrl1	23796	**1,16**
angiotensinogen (serpin peptidase inhibitor, clade A, member 8)	Agt	11606	**0,78**
ankyrin 1, erythroid	Ank1	11733	**1,34**
ankyrin 3, epithelial	Ank3	11735	**1,30**
ankyrin repeat and SOCS box-containing protein 1	Asb1	65247	**1,27**
ankyrin repeat and SOCs box-containing protein 5	Asb5	76294	**0,84**
ankyrin repeat domain 12	Ankrd12	106585	**1,77**
ankyrin repeat domain 23	Ankrd23	78321	**1,17**
ankyrin repeat domain 27 (VPS9 domain)	Ankrd27	245886	**1,28**
ankyrin repeat domain 54	Ankrd54	223690	**0,84**
annexin A13	Anxa13	69787	**0,71**
annexin A2	Anxa2	12306	**0,71**
annexin A3	Anxa3	11745	**0,66**
annexin A7	Anxa7	11750	**1,28**
anterior gradient 2 (Xenopus laevis)	Agr2	23795	**0,31**
anterior gradient homolog 3 (Xenopus laevis)	Agr3	403205	**0,83**
anthrax toxin receptor 1	Antxr1	69538	**1,36**
apelin	Apln	30878	**1,24**
apolipoprotein A-I binding protein	Apoa1bp	246703	**0,64**
apolipoprotein B	Apob	238055	**1,57**
apolipoprotein B editing complex 3	Apobec3	80287	**0,84**
apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 4 (putative)	Apobec4	71281	**1,36**
apolipoprotein L 7a	Apol7a	75761	**1,29**
apoptosis inhibitor 5	Api5	11800	**0,76**
apurinic/apyrimidinic endonuclease 2	Apex2	77622	**0,85**
aquaporin 1	Aqp1	11826	**0,62**
aquaporin 4	Aqp4	11829	**1,33**
arachidonate lipoxygenase 3	Aloxe3	23801	**1,23**
archain 1	Arcn1	213827	**0,80**
arginase type II	Arg2	11847	**0,74**
arginine glutamic acid dipeptide (RE) repeats	Rere	68703	**1,61**
arginine vasopressin receptor 1B	Avpr1b	26361	**1,56**

arginine-rich, mutated in early stage tumors	Armet	74840	**0,54**
arginine-tRNA-protein transferase 1	Ate1	11907	**1,48**
arginyl aminopeptidase (aminopeptidase B)	Rnpep	215615	**0,71**
arginyl-tRNA synthetase	Rars	104458	**0,73**
arginyl-tRNA synthetase 2, mitochondrial (putative)	Rars2	109093	**0,71**
armadillo repeat containing 8	Armc8	74125	**1,30**
aryl hydrocarbon receptor nuclear translocator	Arnt	11863	**1,70**
aryl-hydrocarbon receptor repressor	Ahrr	11624	**0,84**
arylacetamide deacetylase (esterase)	Aadac	67758	**0,59**
arylalkylamine N-acetyltransferase	Aanat	11298	**1,21**
ash1 (absent, small, or homeotic)-like (Drosophila)	Ash1l	192195	**1,47**
asparagine synthetase	Asns	27053	**0,69**
asparagine-linked glycosylation 5 homolog (yeast, dolichyl-phosphate beta-glucosyltransferase)	Alg5	66248	**0,58**
asparagine-linked glycosylation 6 homolog (yeast, alpha-1,3,-glucosyltransferase)	Alg6	320438	**0,78**
aspartyl-tRNA synthetase	Dars	226414	**0,69**
aspartyl-tRNA synthetase 2 (mitochondrial)	Dars2	226539	**0,87**
aspartylglucosaminidase	Aga	11593	**0,80**
astrotactin 1	Astn1	11899	**1,27**
atonal homolog 1 (Drosophila)	Atoh1	11921	**0,62**
atrophin 1	Atn1	13498	**0,66**
aurora kinase A	Aurka	20878	**0,76**
aurora kinase A interacting protein 1	Aurkaip1	66077	**0,61**
aurora kinase B	Aurkb	20877	**0,78**
autophagy-related 10 (yeast)	Atg10	66795	**1,55**
autophagy-related 12 (yeast)	Atg12	67526	**0,87**
autophagy-related 4B (yeast)	Atg4b	66615	**1,24**
autophagy-related 5 (yeast)	Atg5	11793	**0,79**
autophagy-related 9A (yeast)	Atg9a	245860	**1,23**
avian musculoaponeurotic fibrosarcoma (v-maf) AS42 oncogene homolog	Maf	17132	**1,52**
axin 1	Axin1	12005	**0,84**
baculoviral IAP repeat-containing 2	Birc2	11797	**1,51**
baculoviral IAP repeat-containing 5	Birc5	11799	**0,70**
baculoviral IAP repeat-containing 6	Birc6	12211	**1,79**
basic helix-loop-helix domain containing, class B, 8	Bhlhb8	17341	**0,79**
basic helix-loop-helix domain containing, class B2	Bhlhb2	20893	**1,44**
beaded filament structural protein 2, phakinin	Bfsp2	107993	**1,21**
beaded filament structural protein in lens-CP94	Bfsp1	12075	**0,84**
beta-1,4-N-acetyl-galactosaminyl transferase 1	B4galnt1	14421	**0,76**
beta-carotene 9', 10'-dioxygenase 2	Bcdo2	170752	**0,83**
beta-site APP-cleaving enzyme 2	Bace2	56175	**0,65**
bicaudal D homolog 2 (Drosophila)	Bicd2	76895	**1,27**
biliverdin reductase A	Blvra	109778	**0,77**
bladder cancer associated protein homolog (human)	Blcap	53619	**1,78**
bleomycin hydrolase	Blmh	104184	**0,77**
blocked early in transport 1 homolog (S. cerevisiae)-like	Bet1l	54399	**0,84**
bone morphogenetic protein 2	Bmp2	12156	**2,00**
bone morphogenetic protein 5	Bmp5	12160	**0,83**
bone morphogenetic protein 7	Bmp7	12162	**0,85**
bone morphogenic protein receptor, type II (serine/threonine kinase)	Bmpr2	12168	**1,47**
brain abundant, membrane attached signal protein 1	Basp1	70350	**1,37**
brain expressed X-linked 2	Bex2	12069	**1,57**
brain expressed gene 1	Bex1	19716	**1,45**
breakpoint cluster region homolog	Bcr	110279	**0,83**
breast cancer anti-estrogen resistance 1	Bcar1	12927	**1,13**
breast carcinoma amplified sequence 1	Bcas1	76960	**1,37**
breast carcinoma amplified sequence 3	Bcas3	192197	**1,40**
bromodomain PHD finger transcription factor	Bptf	207165	**1,34**
bromodomain adjacent to zinc finger domain, 1B	Baz1b	22385	**0,82**
bromodomain adjacent to zinc finger domain, 2B	Baz2b	407823	**1,42**
bromodomain and PHD finger containing, 1	Brpf1	78783	**1,39**
bromodomain containing 2	Brd2	14312	**1,36**
bruno-like 4, RNA binding protein (Drosophila)	Brunol4	108013	**1,20**
budding uninhibited by benzimidazoles 3 homolog (S. cerevisiae)	Bub3	12237	**1,28**
butyrylcholinesterase	Bche	12038	**0,86**
c-abl oncogene 1, receptor tyrosine kinase	Abl1	11350	**1,45**
c-fos induced growth factor	Figf	14205	**1,25**
c-mer proto-oncogene tyrosine kinase	Mertk	17289	**1,69**
c-myc binding protein	Mycbp	56309	**1,35**
cAMP responsive element binding protein 1	Creb1	12912	**0,87**
cAMP responsive element binding protein 3-like 1	Creb3l1	26427	**0,63**
cAMP responsive element binding protein 3-like 3	Creb3l3	208677	**1,38**
cAMP responsive element binding protein 3-like 4	Creb3l4	78284	**0,69**
cAMP responsive element modulator	Crem	12916	**0,84**
cDNA sequence BC023882	BC023882	231123	**0,85**
cDNA sequence BC067047	BC067047	277360	**1,34**
cadherin 13	Cdh13	12554	**1,23**
cadherin 15	Cdh15	12555	**1,24**
cadherin 17	Cdh17	12557	**1,31**
cadherin 3	Cdh3	12560	**1,29**
cadherin, EGF LAG seven-pass G-type receptor 2 (flamingo homolog, Drosophila)	Celsr2	53883	**1,24**
calbindin-28K	Calb1	12307	**0,82**
calcitonin-related polypeptide, beta	Calcb	116903	**1,37**
calcium and integrin binding family member 3	Cib3	234421	**0,83**
calcium binding and coiled coil domain 1	Calcoco1	67488	**1,29**
calcium channel, voltage-dependent, alpha2/delta subunit 1	Cacna2d1	12293	**1,39**
calcium channel, voltage-dependent, beta 4 subunit	Cacnb4	12298	**0,85**

calcium homeostasis endoplasmic reticulum protein	Cherp	27967	**1,32**
calcium modulating ligand	Caml	12328	**0,79**
calcium regulated heat stable protein 1	Carhsp1	52502	**0,76**
calcium/calmodulin-dependent protein kinase ID	Camk1d	227541	**0,84**
calcium/calmodulin-dependent protein kinase II gamma	Camk2g	12325	**1,30**
calcyclin binding protein	Cacybp	12301	**0,83**
calmegin	Clgn	12745	**1,20**
calmodulin 3	Calm3	12315	**0,47**
calmodulin-like 4	Calml4	75600	**0,73**
calnexin	Canx	12330	**1,44**
calpain 8	Capn8	170725	**0,89**
calpain 9 (nCL-4)	Capn9	73647	**0,72**
calpastatin	Cast	12380	**1,28**
calponin 1	Cnn1	12797	**1,45**
calponin 2	Cnn2	12798	**1,24**
calsequestrin 1	Casq1	12372	**1,38**
calsyntenin 1	Clstn1	65945	**0,70**
canopy 3 homolog (zebrafish)	Cnpy3	72029	**0,81**
cappuccino	Cno	117197	**0,85**
carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 14	Chst14	72136	**1,22**
carbohydrate (chondroitin 6/keratan) sulfotransferase 3	Chst3	53374	**1,20**
carbohydrate sulfotransferase 11	Chst11	58250	**1,20**
carbohydrate sulfotransferase 12	Chst12	59031	**1,38**
carbonic anhydrase 1	Car1	12346	**0,75**
carbonic anhydrase 8	Car8	12319	**0,83**
carbonic anyhydrase 12	Car12	76459	**1,30**
carbonyl reductase 3	Cbr3	109857	**0,64**
carboxylesterase 1	Ces1	12623	**0,80**
carboxylesterase 3	Ces3	104158	**0,86**
carboxylesterase 7	Ces7	67935	**1,23**
carboxypeptidase E	Cpe	12876	**1,75**
carboxypeptidase M	Cpm	70574	**0,73**
cardiomyopathy associated 5	Cmya5	76469	**1,35**
cardiotrophin-like cytokine factor 1	Clcf1	56708	**1,16**
carnitine deficiency-associated gene expressed in ventricle 3	Cdv3	321022	**1,37**
cartilage intermediate layer protein 2	Cilp2	68709	**1,36**
cartilage intermediate layer protein, nucleotide pyrophosphohydrolase	Cilp	214425	**1,31**
casein kinase 1, epsilon	Csnk1e	27373	**1,53**
casein kinase 1, gamma 2	Csnk1g2	103236	**0,81**
caseinolytic peptidase X (E.coli)	Clpx	270166	**1,30**
caseinolytic peptidase, ATP-dependent, proteolytic subunit homolog (E. coli)	Clpp	53895	**0,63**
caspase 1	Casp1	12362	**0,64**
caspase 3	Casp3	12367	**0,70**
caspase 4, apoptosis-related cysteine peptidase	Casp4	12363	**0,79**
caspase 6	Casp6	12368	**0,67**
caspase 8 associated protein 2	Casp8ap2	26885	**1,42**
caspase recruitment domain family, member 14	Card14	170720	**1,20**
castor homolog 1, zinc finger (Drosophila)	Casz1	69743	**1,33**
catalase	Cat	12359	**1,29**
catenin (cadherin associated protein), alpha 1	Ctnna1	12385	**1,41**
catenin (cadherin associated protein), alpha-like 1	Ctnnal1	54366	**0,85**
catenin (cadherin associated protein), beta 1	Ctnnb1	12387	**0,65**
catenin beta interacting protein 1	Ctnnbip1	67087	**0,77**
catenin, beta like 1	Ctnnbl1	66642	**0,77**
cathepsin H	Ctsh	13036	**0,65**
cathepsin J	Ctsj	26898	**0,84**
cathepsin K	Ctsk	13038	**1,24**
cathepsin O	Ctso	229445	**0,80**
caudal type homeo box 2	Cdx2	12591	**1,49**
caveolin, caveolae protein 1	Cav1	12389	**1,41**
cell adhesion molecule 4	Cadm4	260299	**1,21**
cell adhesion molecule with homology to L1CAM	Chl1	12661	**1,30**
cell adhesion molecule-related/down-regulated by oncogenes	Cdon	57810	**1,39**
cell division cycle 123 homolog (S. cerevisiae)	Cdc123	98828	**0,73**
cell division cycle 2 homolog A (S. pombe)	Cdc2a	12534	**0,64**
cell division cycle 25 homolog A (S. pombe)	Cdc25a	12530	**1,56**
cell division cycle 25 homolog B (S. pombe)	Cdc25b	12531	**0,87**
cell division cycle 27 homolog (S. cerevisiae)	Cdc27	217232	**1,23**
cell division cycle 45 homolog (S. cerevisiae)-like	Cdc45l	12544	**0,83**
cell division cycle 6 homolog (S. cerevisiae)	Cdc6	23834	**1,64**
cell division cycle associated 4	Cdca4	71963	**0,76**
cellular repressor of E1A-stimulated genes 1	Creg1	433375	**0,72**
centaurin, beta 2	Centb2	78618	**1,39**
centaurin, delta 1	Centd1	212285	**1,37**
centrin 2	Cetn2	26370	**0,71**
centromere protein A	Cenpa	12615	**0,71**
centromere protein B	Cenpb	12616	**1,34**
centromere protein H	Cenph	26886	**0,85**
centromere protein K	Cenpk	60411	**0,79**
centromere protein M	Cenpm	66570	**0,81**
centrosomal protein 164	Cep164	214552	**1,23**
centrosomal protein 170	Cep170	545389	**1,39**
centrosomal protein 290	Cep290	216274	**0,86**
centrosomal protein 55	Cep55	74107	**0,82**
centrosomal protein 63	Cep63	28135	**1,40**
centrosomal protein 72	Cep72	74470	**0,81**

cerebellin 2 precursor protein	Cbln2	12405	**1,27**
cerebral cavernous malformation 2 homolog (human)	Ccm2	216527	**0,80**
ceroid lipofuscinosis, neuronal 3, juvenile (Batten, Spielmeyer-Vogt disease)	Cln3	12752	**1,35**
ceroid-lipofuscinosis, neuronal 5	Cln5	211286	**0,75**
ceroid-lipofuscinosis, neuronal 8	Cln8	26889	**0,88**
chaperonin subunit 2 (beta)	Cct2	12461	**0,62**
chaperonin subunit 5 (epsilon)	Cct5	12465	**0,63**
chaperonin subunit 7 (eta)	Cct7	12468	**0,69**
checkpoint with forkhead and ring finger domains	Chfr	231600	**1,32**
chemokine (C-C motif) ligand 12	Ccl12	20293	**0,84**
chemokine (C-C motif) ligand 25	Ccl25	20300	**0,83**
chemokine (C-C motif) ligand 6	Ccl6	20305	**0,41**
chemokine (C-C motif) ligand 8	Ccl8	20307	**0,64**
chemokine (C-C motif) ligand 9	Ccl9	20308	**0,59**
chemokine (C-C motif) receptor 8	Ccr8	12776	**0,84**
chemokine (C-C motif) receptor-like 2	Ccrl2	54199	**0,84**
chemokine (C-X-C motif) ligand 1	Cxcl1	14825	**0,80**
chemokine (C-X-C motif) ligand 9	Cxcl9	17329	**0,80**
chemokine (C-X-C motif) receptor 3	Cxcr3	12766	**1,18**
chemokine-like factor	Cklf	75458	**0,83**
chloride channel 2	Clcn2	12724	**0,78**
chloride channel 4-2	Clcn4-2	12727	**1,21**
chloride channel calcium activated 2	Clca2	80797	**0,82**
chloride channel calcium activated 3	Clca3	23844	**0,68**
chloride intracellular channel 1	Clic1	114584	**0,58**
cholecystokinin	Cck	12424	**0,83**
cholecystokinin B receptor	Cckbr	12426	**1,39**
choline dehydrogenase	Chdh	218865	**1,52**
cholinergic receptor, muscarinic 4	Chrm4	12672	**0,81**
cholinergic receptor, nicotinic, epsilon polypeptide	Chrne	11448	**1,15**
chondroitin polymerizing factor	Chpf	74241	**1,18**
chondroitin sulfate N-acetylgalactosaminyltransferase 2	Csgalnact2	78752	**1,33**
chondroitin sulfate synthase 3	Chsy3	78923	**0,81**
chondrolectin	Chodl	246048	**1,39**
chromatin accessibility complex 1	Chrac1	93696	**0,71**
chromatin assembly factor 1, subunit A (p150)	Chaf1a	27221	**0,81**
chromatin licensing and DNA replication factor 1	Cdt1	67177	**0,77**
chromatin modifying protein 1B	Chmp1b	67064	**1,37**
chromatin modifying protein 2A	Chmp2a	68953	**0,55**
chromatin modifying protein 4B	Chmp4b	75608	**1,76**
chromatin modifying protein 4C	Chmp4c	66371	**1,31**
chromobox homolog 4 (Drosophila Pc class)	Cbx4	12418	**1,61**
chromodomain helicase DNA binding protein 3	Chd3	216848	**1,31**
chromodomain helicase DNA binding protein 5	Chd5	269610	**1,23**
chromodomain helicase DNA binding protein 6	Chd6	71389	**1,35**
chromodomain helicase DNA binding protein 7	Chd7	320790	**1,42**
chromodomain helicase DNA binding protein 8	Chd8	67772	**1,64**
chromogranin B	Chgb	12653	**0,65**
claudin 12	Cldn12	64945	**0,73**
claudin 15	Cldn15	60363	**0,58**
claudin 23	Cldn23	71908	**1,46**
claudin 6	Cldn6	54419	**0,81**
claudin 7	Cldn7	53624	**0,69**
claudin 8	Cldn8	54420	**0,64**
cleavage and polyadenylation specific factor 2	Cpsf2	51786	**0,82**
cleavage and polyadenylation specific factor 6	Cpsf6	432508	**1,42**
coactosin-like 1 (Dictyostelium)	Cotl1	72042	**1,20**
coagulation factor II (thrombin) receptor-like 1	F2rl1	14063	**1,59**
coatomer protein complex, subunit beta 2 (beta prime)	Copb2	50797	**0,64**
coatomer protein complex, subunit gamma	Copg	54161	**0,75**
coenzyme Q4 homolog (yeast)	Coq4	227683	**1,31**
coenzyme Q6 homolog (yeast)	Coq6	217707	**0,80**
coenzyme Q9 homolog (yeast)	Coq9	67914	**0,67**
cofactor of BRCA1	Cobra1	58202	**0,80**
coiled-coil domain containing 80	Ccdc80	67896	**0,85**
coiled-coil domain containing 85B	Ccdc85b	240514	**1,48**
coiled-coil domain containing 89	Ccdc89	70054	**0,83**
coiled-coil-helix-coiled-coil-helix domain containing 7	Chchd7	66433	**0,64**
coilin	Coil	12812	**0,80**
cold shock domain containing C2, RNA binding	Csdc2	105859	**1,55**
cold shock domain protein A	Csda	56449	**1,26**
colipase, pancreatic	Clps	109791	**0,57**
collagen, type IV, alpha 4	Col4a4	12829	**1,26**
collagen, type V, alpha 1	Col5a1	12831	**1,35**
collagen, type XIV, alpha 1	Col14a1	12818	**1,26**
collagen, type XVI, alpha 1	Col16a1	107581	**1,43**
collagen, type XVII, alpha 1	Col17a1	12821	**0,86**
collagen, type XXIV, alpha 1	Col24a1	71355	**0,85**
collagen, type XXVII, alpha 1	Col27a1	373864	**1,26**
collapsin response mediator protein 1	Crmp1	12933	**1,22**
colony stimulating factor 1 (macrophage)	Csf1	12977	**1,25**
colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)	Csf2ra	12982	**1,35**
complement component 2 (within H-2S)	C2	12263	**1,23**
complement component 4 binding protein	C4bp	12269	**0,78**
complexin 1	Cplx1	12889	**1,20**
component of oligomeric golgi complex 2	Cog2	76332	**0,77**

component of oligomeric golgi complex 3	Cog3	338337	**1,33**
component of oligomeric golgi complex 4	Cog4	102339	**0,73**
component of oligomeric golgi complex 6	Cog6	67542	**0,75**
connective tissue growth factor	Ctgf	14219	**1,53**
contactin 1	Cntn1	12805	**1,67**
copine VIII	Cpne8	66871	**0,80**
cordon-bleu	Cobl	12808	**1,73**
core 1 synthase, glycoprotein-N-acetylgalactosamine 3-beta-galactosyltransferase, 1	C1galt1	94192	**0,70**
core-binding factor, runt domain, alpha subunit 2, translocated to, 3 (human)	Cbfa2t3	12398	**1,28**
coronin, actin binding protein 1B	Coro1b	23789	**0,64**
cortactin binding protein 2	Cttnbp2	30785	**1,45**
corticotropin releasing hormone	Crh	12918	**0,80**
corticotropin releasing hormone receptor 1	Crhr1	12921	**1,19**
craniofacial development protein 1	Cfdp1	23837	**0,73**
creatine kinase, muscle	Ckm	12715	**1,34**
cryptochrome 2 (photolyase-like)	Cry2	12953	**1,37**
cullin associated and neddylation disassociated 1	Cand1	71902	**1,25**
cyclic nucleotide gated channel alpha 3	Cnga3	12790	**1,29**
cyclin A2	Ccna2	12428	**0,74**
cyclin B2	Ccnb2	12442	**0,65**
cyclin D binding myb-like transcription factor 1	Dmtf1	23857	**0,74**
cyclin D2	Ccnd2	12444	**0,69**
cyclin D3	Ccnd3	12445	**0,84**
cyclin G1	Ccng1	12450	**0,68**
cyclin G2	Ccng2	12452	**1,43**
cyclin I	Ccni	12453	**1,76**
cyclin T2	Ccnt2	72949	**0,82**
cyclin-dependent kinase 4	Cdk4	12567	**0,69**
cyclin-dependent kinase 7 (homolog of Xenopus MO15 cdk-activating kinase)	Cdk7	12572	**0,77**
cyclin-dependent kinase 9 (CDC2-related kinase)	Cdk9	107951	**1,42**
cyclin-dependent kinase inhibitor 1A (P21)	Cdkn1a	12575	**1,32**
cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4)	Cdkn2b	12579	**1,25**
cyclin-dependent kinase inhibitor 3	Cdkn3	72391	**0,71**
cyclin-dependent kinase-like 2 (CDC2-related kinase)	Cdkl2	53886	**1,25**
cylindromatosis (turban tumor syndrome)	Cyld	74256	**1,23**
cystathionine beta-synthase	Cbs	12411	**0,78**
cysteine-rich protein 1 (intestinal)	Crip1	12925	**0,57**
cysteine-rich with EGF-like domains 2	Creld2	76737	**0,67**
cysteinyl leukotriene receptor 1	Cysltr1	58861	**0,84**
cystin 1	Cys1	12879	**1,19**
cystinosis, nephropathic	Ctns	83429	**1,25**
cytidine monophosphate (UMP-CMP) kinase 2, mitochondrial	Cmpk2	22169	**1,36**
cytidine monophospho-N-acetylneuraminic acid hydroxylase	Cmah	12763	**0,71**
cytochrome P450, family 2, subfamily c, polypeptide 54	Cyp2c54	404195	**1,20**
cytochrome P450, family 2, subfamily c, polypeptide 55	Cyp2c55	72082	**0,86**
cytochrome P450, family 2, subfamily d, polypeptide 10	Cyp2d10	13101	**1,24**
cytochrome P450, family 2, subfamily d, polypeptide 22	Cyp2d22	56448	**1,27**
cytochrome P450, family 2, subfamily d, polypeptide 26	Cyp2d26	76279	**0,70**
cytochrome P450, family 2, subfamily d, polypeptide 9	Cyp2d9	13105	**1,29**
cytochrome P450, family 2, subfamily f, polypeptide 2	Cyp2f2	13107	**1,53**
cytochrome P450, family 2, subfamily j, polypeptide 6	Cyp2j6	13110	**1,49**
cytochrome P450, family 2, subfamily r, polypeptide 1	Cyp2r1	244209	**0,82**
cytochrome P450, family 2, subfamily s, polypeptide 1	Cyp2s1	74134	**1,66**
cytochrome P450, family 26, subfamily a, polypeptide 1	Cyp26a1	13082	**1,21**
cytochrome P450, family 3, subfamily a, polypeptide 11	Cyp3a11	13112	**1,31**
cytochrome P450, family 3, subfamily a, polypeptide 13	Cyp3a13	13113	**1,53**
cytochrome P450, family 3, subfamily a, polypeptide 25	Cyp3a25	56388	**1,77**
cytochrome P450, family 4, subfamily b, polypeptide 1	Cyp4b1	13120	**1,62**
cytochrome P450, family 4, subfamily f, polypeptide 16	Cyp4f16	70101	**1,45**
cytochrome P450, family 51	Cyp51	13121	**1,23**
cytochrome b-245, alpha polypeptide	Cyba	13057	**0,59**
cytochrome b-245, beta polypeptide	Cybb	13058	**1,22**
cytochrome b-5	Cyb5	109672	**0,68**
cytochrome c oxidase subunit IV isoform 1	Cox4i1	12857	**0,70**
cytochrome c oxidase, subunit VI a, polypeptide 2	Cox6a2	12862	**1,26**
cytochrome c oxidase, subunit VIIIa	Cox8a	12868	**0,56**
cytochrome c oxidase, subunit VIIa 1	Cox7a1	12865	**0,65**
cytochrome c oxidase, subunit VIc	Cox6c	12864	**0,68**
cytochrome c oxidase, subunit XVII assembly protein homolog (yeast)	Cox17	12856	**1,35**
cytochrome c-1	Cyc1	66445	**0,58**
cytokine induced apoptosis inhibitor 1	Ciapin1	109006	**0,80**
cytokine inducible SH2-containing protein	Cish	12700	**1,28**
cytokine like 1	Cytl1	231162	**0,87**
cytokine receptor-like factor 1	Crlf1	12931	**0,81**
cytoplasmic FMR1 interacting protein 1	Cyfip1	20430	**1,30**
cytoplasmic FMR1 interacting protein 2	Cyfip2	76884	**1,48**
cytoplasmic polyadenylation element binding protein 3	Cpeb3	208922	**1,37**
cytoskeleton-associated protein 4	Ckap4	216197	**0,79**
dCMP deaminase	Dctd	320685	**0,80**
deafness, autosomal dominant 5 homolog (human)	Dfna5h	54722	**0,81**
death associated protein 3	Dap3	65111	**1,34**
death associated protein kinase 1	Dapk1	69635	**1,29**
death effector domain-containing	Dedd	21945	**1,22**
death inducer-obliterator 1	Dido1	23856	**1,32**
decapping enzyme, scavenger	Dcps	69305	**0,78**
dedicator of cyto-kinesis 1	Dock1	330662	**0,84**

dedicator of cytokinesis 11	Dock11	75974	**1,41**
dedicator of cytokinesis 5	Dock5	68813	**1,35**
defective in sister chromatid cohesion 1 homolog (S. cerevisiae)	Dscc1	72107	**0,84**
degenerative spermatocyte homolog 1 (Drosophila)	Degs1	13244	**1,49**
degenerative spermatocyte homolog 2 (Drosophila), lipid desaturase	Degs2	70059	**0,64**
dehydrogenase/reductase member 2	Dhrs2	71412	**1,14**
deiodinase, iodothyronine, type I	Dio1	13370	**1,35**
deleted in liver cancer 1	Dlc1	50768	**1,24**
deleted in lymphocytic leukemia, 2	Dleu2	328425	**0,86**
deleted in malignant brain tumors 1	Dmbt1	12945	**0,73**
delta-like 1 (Drosophila)	Dll1	13388	**1,26**
delta-like 1 homolog (Drosophila)	Dlk1	13386	**1,67**
delta/notch-like EGF-related receptor	Dner	227325	**1,44**
deltex 3 homolog (Drosophila)	Dtx3	80904	**1,33**
density-regulated protein	Denr	68184	**0,85**
deoxycytidine kinase	Dck	13178	**1,46**
deoxyguanosine kinase	Dguok	27369	**0,77**
deoxyribonuclease 1-like 1	Dnase1l1	69537	**0,80**
deoxythymidylate kinase	Dtymk	21915	**0,74**
desmin	Des	13346	**1,36**
desmoplakin	Dsp	109620	**2,15**
desmuslin	Dmn	233335	**1,44**
development and differentiation enhancing factor 2	Ddef2	211914	**1,40**
developmentally regulated GTP binding protein 1	Drg1	13494	**0,70**
diacylglycerol kinase kappa	Dgkk	331374	**0,85**
diacylglycerol kinase zeta	Dgkz	104418	**0,84**
diacylglycerol kinase, delta	Dgkd	227333	**1,44**
diazepam binding inhibitor	Dbi	13167	**0,58**
dihydrolipoamide dehydrogenase	Dld	13382	**0,72**
dipeptidase 1 (renal)	Dpep1	13479	**1,66**
discoidin, CUB and LCCL domain containing 2	Dcbld2	73379	**1,51**
discs, large homolog 1 (Drosophila)	Dlg1	13383	**1,34**
discs, large homolog 3 (Drosophila)	Dlg3	53310	**1,46**
discs, large homolog 5 (Drosophila)	Dlg5	71228	**0,87**
discs, large homolog 7 (Drosophila)	Dlg7	218977	**0,81**
dishevelled associated activator of morphogenesis 2	Daam2	76441	**1,20**
disrupted in renal carcinoma 2 (human)	Dirc2	224132	**0,84**
docking protein 1	Dok1	13448	**1,26**
docking protein 7	Dok7	231134	**0,80**
dolichyl-phosphate mannosyltransferase polypeptide 3	Dpm3	68563	**0,68**
doublecortin domain containing 2a	Dcdc2a	195208	**1,28**
doublecortin-like kinase 1	Dclk1	13175	**0,87**
down-regulated by Ctnnb1, a	Drctnnb1a	84652	**1,22**
drebrin-like	Dbnl	13169	**0,71**
dual adaptor for phosphotyrosine and 3-phosphoinositides 1	Dapp1	26377	**0,86**
dual oxidase 1	Duox1	99439	**1,38**
dual specificity phosphatase 19	Dusp19	68082	**0,80**
dual specificity phosphatase 22	Dusp22	105352	**1,16**
dual specificity phosphatase 26 (putative)	Dusp26	66959	**1,41**
dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1b	Dyrk1b	13549	**1,19**
dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 2	Dyrk2	69181	**1,58**
dynactin 3	Dctn3	53598	**0,54**
dynactin 4	Dctn4	67665	**1,43**
dynamin 3	Dnm3	103967	**1,31**
dynein cytoplasmic 1 heavy chain 1	Dync1h1	13424	**1,58**
dynein cytoplasmic 1 intermediate chain 2	Dync1i2	13427	**1,26**
dynein cytoplasmic 2 heavy chain 1	Dync2h1	110350	**1,17**
dynein light chain roadblock-type 1	Dynlrb1	67068	**0,62**
dynein, axonemal, heavy chain 17	Dnahc17	69926	**0,85**
dynein, cytoplasmic 1 light intermediate chain 2	Dync1li2	234663	**1,35**
dyslexia susceptibility 1 candidate 1 homolog (human)	Dyx1c1	67685	**0,83**
dystrobrevin alpha	Dtna	13527	**1,51**
dystrophia myotonica-containing WD repeat motif	Dmwd	13401	**1,23**
early endosome antigen 1	Eea1	216238	**1,28**
echinoderm microtubule associated protein like 5	Eml5	319670	**1,29**
ecotropic viral integration site 1	Evi1	14013	**1,38**
ectonucleoside triphosphate diphosphohydrolase 2	Entpd2	12496	**1,28**
ectonucleoside triphosphate diphosphohydrolase 5	Entpd5	12499	**1,49**
ectonucleotide pyrophosphatase/phosphodiesterase 2	Enpp2	18606	**1,19**
elastin	Eln	13717	**1,21**
elongation factor RNA polymerase II 2	Ell2	192657	**1,34**
embryonal Fyn-associated substrate	Efs	13644	**1,25**
empty spiracles homolog 2 (Drosophila)	Emx2	13797	**0,82**
enabled homolog (Drosophila)	Enah	13800	**1,60**
endoglin	Eng	13805	**1,38**
endonuclease G	Endog	13804	**0,83**
endoplasmic reticulum (ER) to nucleus signalling 1	Ern1	78943	**1,44**
endothelial cell-specific molecule 1	Esm1	71690	**0,82**
endothelial differentiation, lysophosphatidic acid G-protein-coupled receptor, 2	Edg2	14745	**1,31**
endothelial differentiation, sphingolipid G-protein-coupled receptor, 3	Edg3	13610	**1,22**
endothelial differentiation, sphingolipid G-protein-coupled receptor, 5	Edg5	14739	**1,23**
endothelial differentiation-related factor 1	Edf1	59022	**0,60**
endothelial-specific receptor tyrosine kinase	Tek	21687	**0,85**
engulfment and cell motility 1, ced-12 homolog (C. elegans)	Elmo1	140580	**1,20**
enhancer of polycomb homolog 1 (Drosophila)	Epc1	13831	**1,34**
enhancer of polycomb homolog 2 (Drosophila)	Epc2	227867	**1,30**

enhancer of yellow 2 homolog (Drosophila)	Eny2	223527	**0,78**
enhancer trap locus 4	Etl4	208618	**1,22**
enoyl Coenzyme A hydratase, short chain, 1, mitochondrial	Echs1	93747	**0,57**
enoyl coenzyme A hydratase 1, peroxisomal	Ech1	51798	**0,60**
envoplakin	Evpl	14027	**1,26**
ependymin related protein 1 (zebrafish)	Epdr1	105298	**1,26**
ephrin A3	Efna3	13638	**1,31**
ephrin B1	Efnb1	13641	**1,76**
ephrin B2	Efnb2	13642	**1,96**
epidermal growth factor	Egf	13645	**0,85**
epidermal growth factor receptor pathway substrate 8	Eps8	13860	**1,50**
epithelial membrane protein 1	Emp1	13730	**1,30**
epithelial membrane protein 2	Emp2	13731	**0,84**
epoxide hydrolase 2, cytoplasmic	Ephx2	13850	**1,36**
epsin 1	Epn1	13854	**1,29**
erythrocyte protein band 4.1-like 1	Epb4.1l1	13821	**1,46**
erythrocyte protein band 4.1-like 3	Epb4.1l3	13823	**1,38**
erythrocyte protein band 4.1-like 4a	Epb4.1l4a	13824	**1,22**
erythrocyte protein band 4.9	Epb4.9	13829	**1,34**
establishment of cohesion 1 homolog 2 (S. cerevisiae)	Esco2	71988	**0,77**
estrogen related receptor, alpha	Esrra	26379	**1,52**
ethylmalonic encephalopathy 1	Ethe1	66071	**0,66**
ets variant gene 2	Etv2	14008	**0,60**
eukaryotic elongation factor, selenocysteine-tRNA-specific	Eefsec	65967	**0,82**
eukaryotic translation elongation factor 1 alpha 2	Eef1a2	13628	**1,41**
eukaryotic translation elongation factor 1 epsilon 1	Eef1e1	66143	**0,71**
eukaryotic translation elongation factor 2	Eef2	13629	**0,64**
eukaryotic translation initiation factor 2 alpha kinase 1	Eif2ak1	15467	**1,33**
eukaryotic translation initiation factor 2 alpha kinase 3	Eif2ak3	13666	**0,81**
eukaryotic translation initiation factor 2, subunit 2 (beta)	Eif2s2	67204	**1,80**
eukaryotic translation initiation factor 2, subunit 3, structural gene Y-linked	Eif2s3y	26908	**0,83**
eukaryotic translation initiation factor 2B, subunit 1 (alpha)	Eif2b1	209354	**0,59**
eukaryotic translation initiation factor 2B, subunit 5 epsilon	Eif2b5	224045	**0,77**
eukaryotic translation initiation factor 2C, 1	Eif2c1	236511	**1,28**
eukaryotic translation initiation factor 2C, 4	Eif2c4	76850	**1,37**
eukaryotic translation initiation factor 2a	Eif2a	229317	**0,80**
eukaryotic translation initiation factor 3, subunit C	Eif3c	56347	**0,71**
eukaryotic translation initiation factor 3, subunit E	Eif3e	16341	**0,69**
eukaryotic translation initiation factor 3, subunit E interacting protein	Eif3eip	223691	**0,58**
eukaryotic translation initiation factor 3, subunit F	Eif3f	66085	**0,65**
eukaryotic translation initiation factor 3, subunit G	Eif3g	53356	**0,67**
eukaryotic translation initiation factor 3, subunit I	Eif3i	54709	**0,63**
eukaryotic translation initiation factor 3, subunit K	Eif3k	73830	**0,62**
eukaryotic translation initiation factor 5B	Eif5b	226982	**1,95**
eukaryotic translation termination factor 1	Etf1	225363	**0,73**
excision repair cross-complementing rodent repair deficiency, complementation group 2	Ercc2	13871	**1,24**
excision repair cross-complementing rodent repair deficiency, complementation group 6	Ercc6	319955	**1,25**
exocyst complex component 2	Exoc2	66482	**1,39**
exocyst complex component 5	Exoc5	105504	**1,38**
exocyst complex component 7	Exoc7	53413	**0,83**
exosome component 4	Exosc4	109075	**0,78**
exosome component 7	Exosc7	66446	**0,73**
exostoses (multiple)-like 2	Extl2	58193	**1,25**
expressed sequence AA467197	AA467197	433470	**0,77**
expressed sequence AU040320	AU040320	100317	**1,36**
expressed sequence C80913	C80913	19777	**0,78**
extra spindle poles-like 1 (S. cerevisiae)	Espl1	105988	**0,84**
eyes absent 2 homolog (Drosophila)	Eya2	14049	**0,82**
eyes absent 3 homolog (Drosophila)	Eya3	14050	**1,21**
ezrin	Ezr	22350	**1,41**
far upstream element (FUSE) binding protein 1	Fubp1	51886	**1,72**
far upstream element (FUSE) binding protein 3	Fubp3	320267	**1,32**
fasciculation and elongation protein zeta 1 (zygin I)	Fez1	235180	**1,34**
fasciculation and elongation protein zeta 2 (zygin II)	Fez2	225020	**1,26**
fatty acid binding protein 2, intestinal	Fabp2	14079	**0,64**
fer (fms/fps related) protein kinase, testis specific 2	Fert2	14158	**0,83**
fer-1-like 3, myoferlin (C. elegans)	Fer1l3	226101	**0,82**
fermitin family homolog 2 (Drosophila)	Fermt2	218952	**1,32**
fibrinogen-like protein 2	Fgl2	14190	**1,29**
fibroblast growth factor 12	Fgf12	14167	**0,83**
fibroblast growth factor 13	Fgf13	14168	**1,51**
fibroblast growth factor binding protein 1	Fgfbp1	14181	**0,59**
fibroblast growth factor receptor substrate 2	Frs2	327826	**1,33**
fibulin 5	Fbln5	23876	**1,28**
ficolin A	Fcna	14133	**0,69**
filaggrin	Flg	14246	**0,78**
filamin C, gamma (actin binding protein 280)	Flnc	68794	**1,30**
filamin, alpha	Flna	192176	**1,48**
filamin, beta	Flnb	286940	**1,30**
fission 1 (mitochondrial outer membrane) homolog (yeast)	Fis1	66437	**0,64**
flap structure specific endonuclease 1	Fen1	14156	**0,76**
flavin containing monooxygenase 1	Fmo1	14261	**1,24**
flavin containing monooxygenase 5	Fmo5	14263	**1,41**
folliculin	Flcn	216805	**0,85**
folliculin interacting protein 2	Fnip2	329679	**1,47**
follistatin-like 1	Fstl1	14314	**1,29**

follistatin-like 3	Fstl3	83554	**1,25**
forkhead box A3	Foxa3	15377	**0,67**
forkhead box B1	Foxb1	64290	**1,31**
forkhead box I2	Foxi2	270004	**1,19**
forkhead box J2	Foxj2	60611	**1,46**
forkhead box M1	Foxm1	14235	**1,17**
forkhead box O1	Foxo1	56458	**1,38**
forkhead box O3a	Foxo3a	56484	**1,35**
forkhead box P2	Foxp2	114142	**1,48**
formin 2	Fmn2	54418	**1,26**
formin binding protein 1	Fnbp1	14269	**1,42**
formin-like 2	Fmnl2	71409	**0,84**
fos-like antigen 2	Fosl2	14284	**1,63**
four and a half LIM domains 1	Fhl1	14199	**1,25**
free fatty acid receptor 1	Ffar1	233081	**1,31**
free fatty acid receptor 2	Ffar2	233079	**0,74**
frequently rearranged in advanced T-cell lymphomas 2	Frat2	212398	**0,75**
frizzled homolog 1 (Drosophila)	Fzd1	14362	**0,86**
frizzled homolog 10 (Drosophila)	Fzd10	93897	**1,25**
frizzled homolog 4 (Drosophila)	Fzd4	14366	**1,20**
frizzled homolog 8 (Drosophila)	Fzd8	14370	**1,30**
fructose bisphosphatase 1	Fbp1	14121	**1,23**
fucose-1-phosphate guanylyltransferase	Fpgt	75540	**0,76**
fucosidase, alpha-L- 1, tissue	Fuca1	71665	**0,59**
fucosyltransferase 2	Fut2	14344	**0,68**
fucosyltransferase 7	Fut7	14347	**1,12**
fumarate hydratase 1	Fh1	14194	**0,61**
furin (paired basic amino acid cleaving enzyme)	Furin	18550	**1,59**
furry homolog-like (Drosophila)	Fryl	72313	**1,50**
fyn-related kinase	Frk	14302	**1,50**
galactokinase 1	Galk1	14635	**0,82**
galactokinase 2	Galk2	69976	**0,72**
galactose-4-epimerase, UDP	Gale	74246	**0,59**
galanin	Gal	14419	**1,58**
gamma-aminobutyric acid (GABA) B receptor 2	Gabbr2	242425	**1,29**
gamma-aminobutyric acid (GABA-A) receptor, subunit beta 2	Gabrb2	14401	**1,50**
gamma-aminobutyric acid (GABA-B) receptor, 1	Gabbr1	54393	**1,34**
gamma-aminobutyric acid receptor associated protein	Gabarap	56486	**0,59**
gamma-glutamyl carboxylase	Ggcx	56316	**0,85**
gamma-glutamyltransferase 1	Ggt1	14598	**1,66**
gamma-glutamyltransferase 6	Ggt6	71522	**1,42**
gamma-glutamyltransferase 7	Ggt7	207182	**1,17**
gap junction protein, gamma 1	Gjc1	14615	**1,43**
gasdermin A3	Gsdma3	450219	**1,18**
gastrin releasing peptide	Grp	225642	**1,42**
gastrin releasing peptide receptor	Grpr	14829	**0,80**
gene model 166, (NCBI)	Gm166	233899	**0,84**
gene model 459, (NCBI)	Gm459	243451	**0,82**
gene regulated by estrogen in breast cancer protein	Greb1	268527	**0,84**
gene trap locus 3	Gtl3	14894	**0,71**
gene trap locus F3b	Gtlf3b	24083	**1,21**
general transcription factor II E, polypeptide 1 (alpha subunit)	Gtf2e1	74197	**0,84**
general transcription factor II E, polypeptide 2 (beta subunit)	Gtf2e2	68153	**0,77**
general transcription factor II H, polypeptide 2	Gtf2h2	23894	**0,79**
general transcription factor II H, polypeptide 4	Gtf2h4	14885	**0,80**
general transcription factor IIB	Gtf2b	229906	**0,74**
general transcription factor IIF, polypeptide 2	Gtf2f2	68705	**0,76**
general transcription factor IIH, polypeptide 3	Gtf2h3	209357	**0,80**
general transcription factor IIH, polypeptide 5	Gtf2h5	66467	**0,73**
general transcription factor III A	Gtf3a	66596	**0,67**
general transcription factor III C 1	Gtf3c1	233863	**1,39**
general transcription factor IIIC, polypeptide 3	Gtf3c3	98488	**0,83**
geranylgeranyl diphosphate synthase 1	Ggps1	14593	**1,35**
germ cell-less homolog 1 (Drosophila)	Gmcl1	23885	**0,75**
germ cell-specific gene 2	Gsg2	14841	**0,84**
glial cell line derived neurotrophic factor	Gdnf	14573	**1,29**
glucagon	Gcg	14526	**0,58**
glucagon receptor	Gcgr	14527	**1,27**
glucocorticoid induced transcript 1	Glcci1	170772	**1,25**
glucocorticoid modulatory element binding protein 1	Gmeb1	56809	**1,19**
glucosamine	Gne	50798	**0,68**
glucosaminyl (N-acetyl) transferase 1, core 2	Gcnt1	14537	**1,37**
glucosidase 1	Gcs1	57377	**0,77**
glucuronidase, beta	Gusb	110006	**0,77**
glutamate dehydrogenase 1	Glud1	14661	**0,78**
glutamate receptor ionotropic, NMDA3A	Grin3a	242443	**1,48**
glutamate receptor, ionotropic, NMDA1 (zeta 1)	Grin1	14810	**1,30**
glutamate receptor, ionotropic, NMDA3B	Grin3b	170483	**1,35**
glutamate receptor, ionotropic, delta 2 (Grid2) interacting protein 1	Grid2ip	170935	**1,23**
glutamate receptor, ionotropic, kainate 5 (gamma 2)	Grik5	14809	**1,30**
glutamate-cysteine ligase, catalytic subunit	Gclc	14629	**1,87**
glutaminase	Gls	14660	**1,54**
glutaminyl-tRNA synthetase	Qars	97541	**0,70**
glutamyl aminopeptidase	Enpep	13809	**1,61**
glutaredoxin 5 homolog (S. cerevisiae)	Glrx5	73046	**1,42**
glutathione S-transferase kappa 1	Gstk1	76263	**0,64**

glutathione S-transferase, alpha 4	Gsta4	14860	**0,59**
glutathione S-transferase, mu 5	Gstm5	14866	**0,62**
glutathione S-transferase, theta 2	Gstt2	14872	**0,62**
glutathione peroxidase 1	Gpx1	14775	**0,62**
glutathione peroxidase 2	Gpx2	14776	**0,52**
glutathione transferase zeta 1 (maleylacetoacetate isomerase)	Gstz1	14874	**0,74**
glycerol kinase 5 (putative)	Gk5	235533	**0,85**
glycerol phosphate dehydrogenase 2, mitochondrial	Gpd2	14571	**1,49**
glyceronephosphate O-acyltransferase	Gnpat	14712	**0,76**
glycerophosphodiester phosphodiesterase 1	Gde1	56209	**0,74**
glycerophosphodiester phosphodiesterase domain containing 2	Gdpd2	71584	**1,21**
glycine amidinotransferase (L-arginine:glycine amidinotransferase)	Gatm	67092	**1,29**
glycolipid transfer protein	Gltp	56356	**1,46**
glycophorin C	Gypc	71683	**1,30**
glycoprotein 1b, alpha polypeptide	Gp1ba	14723	**0,81**
glycoprotein Ib, beta polypeptide	Gp1bb	14724	**1,37**
glypican 4	Gpc4	14735	**1,20**
golgi associated PDZ and coiled-coil motif containing	Gopc	94221	**0,81**
golgi autoantigen, golgin subfamily a, 1	Golga1	76899	**0,81**
golgi autoantigen, golgin subfamily a, 2	Golga2	99412	**1,52**
golgi integral membrane protein 4	Golim4	73124	**1,26**
golgi membrane protein 1	Golm1	105348	**0,55**
golgi-specific brefeldin A-resistance factor 1	Gbf1	107338	**1,31**
grainyhead-like 2 (Drosophila)	Grhl2	252973	**0,84**
granzyme A	Gzma	14938	**0,73**
granzyme B	Gzmb	14939	**0,81**
granzyme D	Gzmd	14941	**0,82**
granzyme F	Gzmf	14943	**0,82**
growth arrest and DNA-damage-inducible 45 alpha	Gadd45a	13197	**1,24**
growth arrest and DNA-damage-inducible, gamma interacting protein 1	Gadd45gip1	102060	**0,70**
growth arrest specific 1	Gas1	14451	**1,56**
growth arrest specific 2	Gas2	14453	**1,32**
growth differentiation factor 10	Gdf10	14560	**1,42**
growth differentiation factor 11	Gdf11	14561	**0,85**
growth factor independent 1	Gfi1	14581	**0,84**
growth factor receptor bound protein 14	Grb14	50915	**1,26**
growth factor, erv1 (S. cerevisiae)-like (augmenter of liver regeneration)	Gfer	11692	**0,72**
guanine deaminase	Gda	14544	**1,69**
guanine nucleotide binding protein (G protein), beta 5	Gnb5	14697	**1,29**
guanine nucleotide binding protein (G protein), beta polypeptide 2 like 1	Gnb2l1	14694	**1,44**
guanine nucleotide binding protein (G protein), gamma 11	Gng11	66066	**0,75**
guanine nucleotide binding protein (G protein), gamma 2	Gng2	14702	**1,33**
guanine nucleotide binding protein, alpha 11	Gna11	14672	**1,41**
guanine nucleotide binding protein, alpha 15	Gna15	14676	**1,31**
guanine nucleotide binding protein, alpha q polypeptide	Gnaq	14682	**1,15**
guanine nucleotide binding protein, alpha transducing 2	Gnat2	14686	**0,79**
guanine nucleotide binding protein, alpha transducing 3	Gnat3	242851	**0,79**
guanine nucleotide binding protein, alpha z subunit	Gnaz	14687	**1,35**
guanosine diphosphate (GDP) dissociation inhibitor 1	Gdi1	14567	**1,55**
guanosine diphosphate (GDP) dissociation inhibitor 2	Gdi2	14569	**1,28**
guanosine monophosphate reductase 2	Gmpr2	105446	**0,76**
guanylate cyclase activator 2a (guanylin)	Guca2a	14915	**0,54**
guanylate kinase 1	Guk1	14923	**0,64**
guanylate nucleotide binding protein 1	Gbp1	14468	**0,82**
gulonolactone (L-) oxidase	Gulo	268756	**0,85**
hairy and enhancer of split 5 (Drosophila)	Hes5	15208	**0,83**
hairy and enhancer of split 6 (Drosophila)	Hes6	55927	**0,77**
hairy/enhancer-of-split related with YRPW motif 1	Hey1	15213	**1,24**
headcase homolog (Drosophila)	Heca	380629	**1,37**
heart and neural crest derivatives expressed transcript 1	Hand1	15110	**1,30**
heart and neural crest derivatives expressed transcript 2	Hand2	15111	**1,63**
heat shock 105kDa/110kDa protein 1	Hsph1	15505	**0,68**
heat shock factor 1	Hsf1	15499	**0,87**
heat shock protein 1 (chaperonin 10)	Hspe1	15528	**0,57**
heat shock protein 12A	Hspa12a	73442	**1,38**
heat shock protein 14	Hspa14	50497	**0,79**
heat shock protein 2	Hspa2	15512	**1,25**
heat shock protein 5	Hspa5	14828	**0,66**
heat shock protein 8	Hspb8	80888	**1,38**
hect (homologous to the E6-AP (UBE3A) carboxyl terminus) domain and RCC1 (CHC1)-like domain (RLD) 1	Herc1	235439	**1,38**
hect domain and RLD 3	Herc3	73998	**1,36**
hect domain and RLD 5	Herc5	67138	**0,83**
hedgehog acyltransferase-like	Hhatl	74770	**1,25**
helicase with zinc finger domain	Helz	78455	**1,69**
helicase-like transcription factor	Hltf	20585	**0,80**
hematopoietic SH2 domain containing	Hsh2d	209488	**0,82**
hematopoietically expressed homeobox	Hhex	15242	**1,18**
heme binding protein 1	Hebp1	15199	**1,26**
hemochromatosis	Hfe	15216	**0,77**
heparan sulfate (glucosamine) 3-O-sulfotransferase 3B1	Hs3st3b1	54710	**0,87**
heparan sulfate 6-O-sulfotransferase 1	Hs6st1	50785	**0,79**
hepatic leukemia factor	Hlf	217082	**1,31**
hepatocyte growth factor activator	Hgfac	54426	**0,56**
hepatoma derived growth factor-like 1	Hdgfl1	15192	**1,26**
hepatoma-derived growth factor	Hdgf	15191	**1,43**
hepatoma-derived growth factor, related protein 3	Hdgfrp3	29877	**0,85**

Addendum

hephaestin	Heph	15203	**1,44**
heterogeneous nuclear ribonucleoprotein K	Hnrpk	15387	**1,26**
hexosaminidase A	Hexa	15211	**1,39**
hexose-6-phosphate dehydrogenase (glucose 1-dehydrogenase)	H6pd	100198	**0,78**
high density lipoprotein (HDL) binding protein	Hdlbp	110611	**0,67**
high mobility group 20A	Hmg20a	66867	**0,83**
high mobility group AT-hook 2	Hmga2	15364	**0,85**
high mobility group box transcription factor 1	Hbp1	73389	**0,74**
high mobility group nucleosomal binding domain 3	Hmgn3	94353	**1,46**
hippocalcin-like 4	Hpcal4	170638	**1,15**
histidine triad nucleotide binding protein 1	Hint1	15254	**0,61**
histidine-rich glycoprotein	Hrg	94175	**1,57**
histocompatibility 2, O region alpha locus	H2-Oa	15001	**1,22**
histone H1-like protein in spermatids 1	Hils1	54388	**1,28**
histone cluster 1, H2ac	Hist1h2ac	319164	**0,74**
histone deacetylase 11	Hdac11	232232	**0,80**
histone deacetylase 9	Hdac9	79221	**1,31**
homeo box A11	Hoxa11	15396	**1,22**
homeo box A5	Hoxa5	15402	**1,50**
homeo box B4	Hoxb4	15412	**1,25**
homeo box B5	Hoxb5	15413	**1,79**
homeo box B8	Hoxb8	15416	**1,55**
homeo box C13	Hoxc13	15422	**1,19**
homeo box C9	Hoxc9	15427	**1,20**
homeo box D10	Hoxd10	15430	**1,49**
homeo box D12	Hoxd12	15432	**1,18**
homeo box D13	Hoxd13	15433	**1,36**
homeo box D9	Hoxd9	15438	**1,36**
hook homolog 1 (Drosophila)	Hook1	77963	**1,54**
hormonally up-regulated Neu-associated kinase	Hunk	26559	**1,19**
host cell factor C1 regulator 1 (XPO1-dependent)	Hcfc1r1	353502	**1,34**
hyaluronoglucosaminidase 1	Hyal1	15586	**1,30**
hydrogen voltage-gated channel 1	Hvcn1	74096	**1,24**
hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2	Hsd3b2	15493	**1,33**
hydroxyacyl glutathione hydrolase	Hagh	14651	**0,67**
hydroxyacyl-Coenzyme A dehydrogenase	Hadh	15107	**0,80**
hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase (trifunctional protein), alpha subunit	Hadha	97212	**0,69**
hydroxymethylbilane synthase	Hmbs	15288	**0,65**
hydroxysteroid (17-beta) dehydrogenase 11	Hsd17b11	114664	**1,26**
hydroxysteroid (17-beta) dehydrogenase 2	Hsd17b2	15486	**0,74**
hypermethylated in cancer 1	Hic1	15248	**1,19**
hyperpolarization-activated, cyclic nucleotide-gated K+ 4	Hcn4	330953	**1,30**
hypocretin (orexin) receptor 2	Hcrtr2	387285	**0,81**
hypoxanthine guanine phosphoribosyl transferase 1	Hprt1	15452	**0,77**
hypoxia-inducible factor 1, alpha subunit inhibitor	Hif1an	319594	**1,73**
iduronate 2-sulfatase	Ids	15931	**1,49**
iduronidase, alpha-L-	Idua	15932	**1,20**
immediate early response 5	Ier5	15939	**1,34**
immunity-related GTPase family, M	Irgm	15944	**0,77**
immunoglobulin (CD79A) binding protein 1	Igbp1	18518	**0,71**
immunoglobulin heavy constant gamma 1 (G1m marker)	Ighg1	16017	**0,62**
immunoglobulin joining chain	Igj	16069	**0,53**
immunoglobulin superfamily containing leucine-rich repeat	Islr	26968	**1,33**
immunoglobulin superfamily, member 8	Igsf8	140559	**1,27**
immunoglobulin superfamily, member 9	Igsf9	93842	**1,29**
imprinted gene in the Prader-Willi syndrome region	Ipw	16353	**0,81**
inactive X specific transcripts	Xist	213742	**0,89**
influenza virus NS1A binding protein	Ivns1abp	117198	**0,81**
inhibitor of DNA binding 4	Id4	15904	**1,40**
inhibitor of growth family, member 5	Ing5	66262	**1,23**
inhibitor of kappa light polypeptide enhancer in B-cells, kinase complex-associated protein	Ikbkap	230233	**1,30**
inhibitor of kappaB kinase beta	Ikbkb	16150	**1,55**
inosine triphosphatase (nucleoside triphosphate pyrophosphatase)	Itpa	16434	**0,69**
inositol 1,4,5-trisphosphate 3-kinase A	Itpka	228550	**0,83**
inositol 1,4,5-trisphosphate 3-kinase B	Itpkb	320404	**1,42**
inositol 1,4,5-trisphosphate 3-kinase C	Itpkc	233011	**1,28**
inositol polyphosphate phosphatase-like 1	Inppl1	16332	**1,26**
inositol polyphosphate-5-phosphatase B	Inpp5b	16330	**0,82**
inositol polyphosphate-5-phosphatase F	Inpp5f	101490	**1,40**
inscuteable homolog (Drosophila)	Insc	233752	**0,82**
insulin II	Ins2	16334	**1,25**
insulin degrading enzyme	Ide	15925	**0,85**
insulin induced gene 2	Insig2	72999	**1,23**
insulin-like 6	Insl6	27356	**0,73**
insulin-like growth factor 2 receptor	Igf2r	16004	**1,32**
insulin-like growth factor binding protein 2	Igfbp2	16008	**1,32**
insulin-like growth factor binding protein 3	Igfbp3	16009	**0,77**
insulin-like growth factor binding protein 5	Igfbp5	16011	**1,63**
insulin-like growth factor binding protein 6	Igfbp6	16012	**1,45**
integral membrane protein 2B	Itm2b	16432	**1,22**
integrator complex subunit 6	Ints6	18130	**1,38**
integrin alpha 6	Itga6	16403	**1,61**
integrin alpha V	Itgav	16410	**1,55**
integrin beta 1 binding protein 2	Itgb1bp2	26549	**1,26**
integrin binding sialoprotein	Ibsp	15891	**1,15**

interferon activated gene 204	Ifi204	15951	**0,82**
interferon gamma	Ifng	15978	**0,82**
interferon gamma inducible protein 47	Ifi47	15953	**0,75**
interferon gamma receptor 2	Ifngr2	15980	**0,68**
interferon regulatory factor 1	Irf1	16362	**1,34**
interferon regulatory factor 6	Irf6	54139	**0,75**
interferon regulatory factor 7	Irf7	54123	**0,80**
interferon regulatory factor 9	Irf9	16391	**1,31**
interferon-induced protein 35	Ifi35	70110	**0,75**
interferon-induced protein 44	Ifi44	99899	**1,37**
interferon-induced protein with tetratricopeptide repeats 1	Ifit1	15957	**1,27**
interferon-related developmental regulator 1	Ifrd1	15982	**1,38**
interferon-stimulated protein	Isg20	57444	**0,66**
interleukin 1 receptor, type I	Il1r1	16177	**0,79**
interleukin 11	Il11	16156	**1,35**
interleukin 17 receptor C	Il17rc	171095	**1,25**
interleukin 17F	Il17f	257630	**1,39**
interleukin 20	Il20	58181	**1,20**
interleukin 22 receptor, alpha 2	Il22ra2	237310	**1,30**
interleukin 28 receptor alpha	Il28ra	242700	**1,39**
interleukin 28B	Il28b	338374	**1,23**
interleukin 31	Il31	76399	**0,83**
interleukin 4 induced 1	Il4i1	14204	**1,22**
interleukin 6 signal transducer	Il6st	16195	**1,44**
interleukin 9 receptor	Il9r	16199	**1,19**
interleukin-1 receptor-associated kinase 3	Irak3	73914	**0,85**
intestine specific homeobox	Isx	71597	**1,53**
intraflagellar transport 140 homolog (Chlamydomonas)	Ift140	106633	**0,85**
intraflagellar transport 172 homolog (Chlamydomonas)	Ift172	67661	**0,68**
intraflagellar transport 52 homolog (Chlamydomonas)	Ift52	245866	**0,80**
intraflagellar transport 74 homolog (Chlamydomonas)	Ift74	67694	**0,82**
iodotyrosine deiodinase	Iyd	70337	**1,27**
iron responsive element binding protein 2	Ireb2	64602	**0,86**
islet amyloid polypeptide	Iapp	15874	**0,80**
isocitrate dehydrogenase 3 (NAD+) alpha	Idh3a	67834	**0,77**
itchy, E3 ubiquitin protein ligase	Itch	16396	**1,34**
jagged 1	Jag1	16449	**1,23**
jumonji domain containing 1A	Jmjd1a	104263	**0,81**
jumonji domain containing 1C	Jmjd1c	108829	**1,62**
jumonji domain containing 2A	Jmjd2a	230674	**1,22**
jumonji domain containing 2C	Jmjd2c	76804	**1,26**
jumonji, AT rich interactive domain 1C (Rbp2 like)	Jarid1c	20591	**1,28**
jumonji, AT rich interactive domain 1D (Rbp2 like)	Jarid1d	20592	**0,82**
jumping translocation breakpoint	Jtb	23922	**0,73**
junction plakoglobin	Jup	16480	**1,23**
junction-mediating and regulatory protein	Jmy	57748	**1,32**
junctophilin 2	Jph2	59091	**1,25**
junctophilin 4	Jph4	319984	**1,26**
kalirin, RhoGEF kinase	Kalrn	545156	**1,80**
karyopherin (importin) alpha 1	Kpna1	16646	**0,87**
karyopherin (importin) alpha 4	Kpna4	16649	**1,35**
karyopherin (importin) alpha 6	Kpna6	16650	**1,38**
karyopherin (importin) beta 1	Kpnb1	16211	**1,26**
kelch domain containing 3	Klhdc3	71765	**1,31**
kelch-like 11 (Drosophila)	Klhl11	217194	**1,21**
keratin 19	Krt19	16669	**0,49**
keratin 2	Krt2	16681	**0,80**
keratin 20	Krt20	66809	**1,22**
keratin 80	Krt80	74127	**1,23**
keratinocyte associated protein 2	Krtcap2	66059	**0,58**
killer cell lectin-like receptor, subfamily D, member 1	Klrd1	16643	**0,82**
kinase insert domain protein receptor	Kdr	16542	**1,46**
kinase suppressor of ras 2	Ksr2	333050	**1,20**
kinesin family member 11	Kif11	16551	**0,81**
kinesin family member 13A	Kif13a	16553	**0,80**
kinesin family member 14	Kif14	381293	**0,85**
kinesin family member 17	Kif17	16559	**1,23**
kinesin family member 1A	Kif1a	16560	**1,21**
kinesin family member 1B	Kif1b	16561	**1,28**
kinesin family member 20A	Kif20a	19348	**0,85**
kinesin family member 3B	Kif3b	16569	**0,84**
kinesin family member 3C	Kif3c	16570	**1,28**
kinesin family member 5B	Kif5b	16573	**1,39**
kinesin family member 5C	Kif5c	16574	**1,35**
kinesin family member C2	Kifc2	16581	**1,53**
kinesin light chain 1	Klc1	16593	**1,62**
kinesin light chain 2	Klc2	16594	**0,84**
kit ligand	Kitl	17311	**1,43**
kringle containing transmembrane protein 2	Kremen2	73016	**0,84**
l(3)mbt-like 3 (Drosophila)	L3mbtl3	237339	**1,32**
lactoperoxidase	Lpo	76113	**0,71**
lamin A	Lmna	16905	**1,17**
lamin B1	Lmnb1	16906	**1,31**
laminin, alpha 3	Lama3	16774	**0,85**
large subunit GTPase 1 homolog (S. cerevisiae)	Lsg1	224092	**0,87**
latexin	Lxn	17035	**0,78**

latrophilin 1	Lphn1	330814	**1,20**
layilin	Layn	244864	**1,20**
lectin, galactose binding, soluble 3	Lgals3	16854	**0,84**
lectin, galactose binding, soluble 4	Lgals4	16855	**0,71**
lectin, galactose binding, soluble 7	Lgals7	16858	**1,51**
lectin, mannose-binding, 1	Lman1	70361	**0,76**
lethal giant larvae homolog 1 (Drosophila)	Llgl1	16897	**1,33**
lethal giant larvae homolog 2 (Drosophila)	Llgl2	217325	**1,55**
leucine rich repeat (in FLII) interacting protein 1	Lrrfip1	16978	**1,50**
leucine rich repeat and fibronectin type III domain containing 3	Lrfn3	233067	**0,83**
leucine rich repeat containing 10	Lrrc10	237560	**0,84**
leucine rich repeat containing 17	Lrrc17	74511	**0,82**
leucine rich repeat containing 25	Lrrc25	211228	**1,22**
leucine rich repeat containing 29	Lrrc29	234684	**0,80**
leucine rich repeat containing 4	Lrrc4	192198	**0,83**
leucine rich repeat containing 8 family, member C	Lrrc8c	100604	**1,35**
leucine rich repeat protein 1, neuronal	Lrrn1	16979	**0,84**
leucine zipper and CTNNBIP1 domain containing	Lzic	69151	**1,14**
leucine zipper-EF-hand containing transmembrane protein 1	Letm1	56384	**0,72**
leucine-rich repeat LGI family, member 1	Lgi1	56839	**1,17**
leucine-rich repeats and immunoglobulin-like domains 2	Lrig2	269473	**1,30**
leucine-rich repeats and immunoglobulin-like domains 3	Lrig3	320398	**1,24**
leucine-zipper-like transcriptional regulator, 1	Lztr1	66863	**0,81**
leucyl/cystinyl aminopeptidase	Lnpep	240028	**1,64**
leukocyte receptor cluster (LRC) member 8	Leng8	232798	**1,38**
leukotriene B4 12-hydroxydehydrogenase	Ltb4dh	67103	**0,71**
leupaxin	Lpxn	107321	**1,31**
ligand dependent nuclear receptor corepressor	Lcor	212391	**1,53**
ligand of numb-protein X 2	Lnx2	140887	**1,30**
like-glycosyltransferase	Large	16795	**1,31**
limb region 1	Lmbr1	56873	**1,28**
limb-bud and heart	Lbh	77889	**1,41**
lin-7 homolog B (C. elegans)	Lin7b	22342	**1,41**
lipase maturation factor 1	Lmf1	76483	**0,83**
lipase, hepatic	Lipc	15450	**0,86**
lipin 2	Lpin2	64898	**1,53**
lipin 3	Lpin3	64899	**0,84**
lipocalin 2	Lcn2	16819	**0,86**
lipoic acid synthetase	Lias	79464	**0,86**
lipoma HMGIC fusion partner-like 3	Lhfpl3	269629	**0,84**
lipoma HMGIC fusion partner-like protein 4	Lhfpl4	269788	**1,23**
lon peptidase 1, mitochondrial	Lonp1	74142	**0,78**
loss of heterozygosity, 12, chromosomal region 1 homolog (human)	Loh12cr1	67774	**1,23**
low density lipoprotein receptor adaptor protein 1	Ldlrap1	100017	**0,78**
low density lipoprotein receptor-related protein 1	Lrp1	16971	**1,17**
low density lipoprotein receptor-related protein 11	Lrp11	237253	**1,28**
low density lipoprotein receptor-related protein 4	Lrp4	228357	**1,37**
low density lipoprotein-related protein 12	Lrp12	239393	**1,60**
lymphatic vessel endothelial hyaluronan receptor 1	Lyve1	114332	**1,33**
lymphocyte antigen 6 complex, locus G6D	Ly6g6d	114654	**0,83**
lymphocyte antigen 75	Ly75	17076	**1,35**
lymphocyte antigen 96	Ly96	17087	**0,77**
lymphoid-restricted membrane protein	Lrmp	16970	**0,78**
lymphotoxin B	Ltb	16994	**1,19**
lysocardiolipin acyltransferase	Lycat	225010	**1,44**
lysophospholipase 2	Lypla2	26394	**1,72**
lysophospholipase 3	Lypla3	192654	**0,84**
lysophospholipase-like 1	Lyplal1	226791	**0,84**
lysosomal acid lipase A	Lipa	16889	**1,40**
lysosomal-associated membrane protein 2	Lamp2	16784	**1,29**
lysosomal-associated protein transmembrane 5	Laptm5	16792	**1,33**
lysyl oxidase-like 3	Loxl3	16950	**1,51**
lysyl oxidase-like 4	Loxl4	67573	**0,79**
mab-21-like 2 (C. elegans)	Mab21l2	23937	**1,40**
makorin, ring finger protein, 1	Mkrn1	54484	**1,30**
malate dehydrogenase 1, NAD (soluble)	Mdh1	17449	**0,82**
male enhanced antigen 1	Mea1	17256	**0,65**
male-specific lethal 2-like 1 (Drosophila)	Msl2l1	77853	**1,35**
malic enzyme 1, NADP(+)-dependent, cytosolic	Me1	17436	**1,50**
malignant T cell amplified sequence 2	Mcts2	66405	**0,77**
malonyl CoA:ACP acyltransferase (mitochondrial)	Mcat	223722	**0,83**
mannose-6-phosphate receptor binding protein 1	M6prbp1	66905	**0,75**
mannosidase 2, alpha 1	Man2a1	17158	**1,37**
mannosidase 2, alpha 2	Man2a2	140481	**1,22**
mannoside acetylglucosaminyltransferase 3	Mgat3	17309	**0,80**
mannoside acetylglucosaminyltransferase 5	Mgat5	107895	**1,47**
mast cell protease 1	Mcpt1	17224	**0,83**
mast cell protease 2	Mcpt2	17225	**0,80**
mastermind like 3 (Drosophila)	Maml3	433586	**1,39**
matrix metallopeptidase 12	Mmp12	17381	**0,86**
matrix metallopeptidase 13	Mmp13	17386	**0,83**
matrix metallopeptidase 15	Mmp15	17388	**1,25**
matrix metallopeptidase 17	Mmp17	23948	**1,15**
max binding protein	Mnt	17428	**1,46**
mcf.2 transforming sequence	Mcf2	109904	**0,83**
mcf.2 transforming sequence-like	Mcf2l	17207	**0,74**

mediator complex subunit 13	Med13	327987	**1,41**
mediator complex subunit 17	Med17	234959	**0,81**
mediator complex subunit 20	Med20	56771	**0,77**
mediator complex subunit 21	Med21	108098	**0,71**
mediator complex subunit 22	Med22	20933	**1,23**
mediator of RNA polymerase II transcription, subunit 11 homolog (S. cerevisiae)	Med11	66172	**0,79**
mediator of RNA polymerase II transcription, subunit 18 homolog (yeast)	Med18	67219	**2,12**
mediator of RNA polymerase II transcription, subunit 19 homolog (yeast)	Med19	381379	**0,83**
mediator of RNA polymerase II transcription, subunit 25 homolog (yeast)	Med25	75613	**0,87**
mediator of RNA polymerase II transcription, subunit 6 homolog (yeast)	Med6	69792	**0,78**
megalencephalic leukoencephalopathy with subcortical cysts 1 homolog (human)	Mlc1	170790	**1,20**
melanin-concentrating hormone receptor 1	Mchr1	207911	**1,23**
melanocyte proliferating gene 1	Myg1	60315	**0,76**
melanoma antigen, family A, 9	Magea9	195772	**1,41**
melanoma cell adhesion molecule	Mcam	84004	**1,32**
melanoma inhibitory activity 1	Mia1	12587	**0,81**
membrane associated guanylate kinase, WW and PDZ domain containing 3	Magi3	99470	**1,37**
membrane protein, palmitoylated 5 (MAGUK p55 subfamily member 5)	Mpp5	56217	**1,54**
membrane protein, palmitoylated 6 (MAGUK p55 subfamily member 6)	Mpp6	56524	**1,61**
membrane protein, palmitoylated 7 (MAGUK p55 subfamily member 7)	Mpp7	75739	**0,87**
membrane-associated ring finger (C3HC4) 2	March2	224703	**1,30**
membrane-associated ring finger (C3HC4) 8	March8	71779	**1,32**
membrane-spanning 4-domains, subfamily A, member 1	Ms4a1	12482	**1,53**
membrane-spanning 4-domains, subfamily A, member 6D	Ms4a6d	68774	**0,83**
membrane-spanning 4-domains, subfamily A, member 7	Ms4a7	109225	**0,66**
mesoderm specific transcript	Mest	17294	**1,23**
mesothelin	Msln	56047	**1,22**
metal response element binding transcription factor 1	Mtf1	17764	**1,37**
metallothionein 1	Mt1	17748	**1,17**
metallothionein 3	Mt3	17751	**0,83**
metastasis suppressor 1	Mtss1	211401	**1,45**
metaxin 2	Mtx2	53375	**0,70**
metaxin 3	Mtx3	382793	**0,84**
methionine aminopeptidase 2	Metap2	56307	**1,28**
methionine sulfoxide reductase B3	Msrb3	320183	**1,33**
methyl CpG binding protein 2	Mecp2	17257	**1,26**
methyl-CpG binding domain protein 2	Mbd2	17191	**1,23**
methyl-CpG binding domain protein 4	Mbd4	17193	**1,29**
methylmalonic aciduria cblC type, with homocystinuria	Mmachc	67096	**0,84**
methylmalonyl CoA epimerase	Mcee	73724	**0,61**
methyltransferase like 2	Mettl2	52686	**0,81**
microsomal glutathione S-transferase 3	Mgst3	66447	**0,39**
microtubule-actin crosslinking factor 1	Macf1	11426	**1,45**
microtubule-associated protein 1 A	Mtap1a	17754	**1,28**
microtubule-associated protein 4	Mtap4	17758	**1,24**
microtubule-associated protein, RP/EB family, member 3	Mapre3	100732	**1,30**
midline 1	Mid1	17318	**1,75**
midnolin	Midn	59090	**1,57**
milk fat globule-EGF factor 8 protein	Mfge8	17304	**1,33**
minichromosome maintenance complex component 9	Mcm9	71567	**0,83**
minichromosome maintenance deficient 2 mitotin (S. cerevisiae)	Mcm2	17216	**0,75**
minichromosome maintenance deficient 5, cell division cycle 46 (S. cerevisiae)	Mcm5	17218	**0,75**
minichromosome maintenance deficient 7 (S. cerevisiae)	Mcm7	17220	**0,72**
mitochondrial carrier homolog 1 (C. elegans)	Mtch1	56462	**0,71**
mitochondrial intermediate peptidase	Mipep	70478	**0,72**
mitochondrial ribosomal protein L12	Mrpl12	56282	**0,64**
mitochondrial ribosomal protein S11	Mrps11	67994	**0,71**
mitochondrial ribosomal protein S12	Mrps12	24030	**0,75**
mitochondrial ribosomal protein S22	Mrps22	64655	**0,60**
mitochondrial ribosomal protein S23	Mrps23	64656	**0,65**
mitochondrial ribosomal protein S27	Mrps27	218506	**0,81**
mitochondrial ribosomal protein S30	Mrps30	59054	**0,77**
mitochondrial ribosomal protein S35	Mrps35	232536	**0,67**
mitochondrial ribosome recycling factor	Mrrf	67871	**0,79**
mitochondrial trans-2-enoyl-CoA reductase	Mecr	26922	**0,74**
mitofusin 2	Mfn2	170731	**1,35**
mitogen-activated protein kinase 15	Mapk15	332110	**1,73**
mitogen-activated protein kinase 6	Mapk6	50772	**1,43**
mitogen-activated protein kinase 8 interacting protein 3	Mapk8ip3	30957	**1,23**
mitogen-activated protein kinase kinase 4	Map2k4	26398	**1,45**
mitogen-activated protein kinase kinase kinase 3	Map3k3	26406	**1,26**
mitogen-activated protein kinase kinase kinase 5	Map3k5	26408	**1,30**
mitogen-activated protein kinase kinase kinase 7	Map3k7	26409	**0,87**
mitogen-activated protein kinase kinase kinase 7 interacting protein 3	Map3k7ip3	66724	**1,26**
mitogen-activated protein kinase kinase kinase kinase 3	Map4k3	225028	**0,76**
molybdenum cofactor sulfurase	Mocos	68591	**1,29**
monoamine oxidase A	Maoa	17161	**1,94**
mucin 15	Muc15	269328	**0,80**
mucin 2	Muc2	17831	**0,58**
mucin 4	Muc4	140474	**0,80**
multimerin 1	Mmrn1	70945	**0,85**
multiple EGF-like-domains 6	Megf6	230971	**1,14**
multiple coagulation factor deficiency 2	Mcfd2	193813	**0,83**
muscleblind-like 3 (Drosophila)	Mbnl3	171170	**0,81**
muskelin 1, intracellular mediator containing kelch motifs	Mkln1	27418	**0,77**
mutL homolog 1 (E. coli)	Mlh1	17350	**0,85**

mutS homolog 2 (E. coli)	Msh2	17685	**0,79**
mutS homolog 6 (E. coli)	Msh6	17688	**0,80**
muted	Muted	17828	**0,82**
myb-like, SWIRM and MPN domains 1	Mysm1	320713	**0,84**
myelin and lymphocyte protein, T-cell differentiation protein	Mal	17153	**1,56**
myelocytomatosis oncogene	Myc	17869	**0,81**
myeloid cell leukemia sequence 1	Mcl1	17210	**1,40**
myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 11	Mllt11	56772	**1,40**
myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 4	Mllt4	17356	**1,39**
myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 6	Mllt6	246198	**1,30**
myocyte enhancer factor 2C	Mef2c	17260	**1,25**
myocyte enhancer factor 2D	Mef2d	17261	**1,63**
myomesin 1	Myom1	17929	**1,36**
myosin IE	Myo1e	71602	**1,32**
myosin IXa	Myo9a	270163	**1,34**
myosin VC	Myo5c	208943	**1,69**
myosin VI	Myo6	17920	**1,39**
myosin VIIA and Rab interacting protein	Myrip	245049	**0,85**
myosin XVIIIa	Myo18a	360013	**1,46**
myosin light chain, regulatory B	Mylc2b	67938	**1,16**
myosin regulatory light chain interacting protein	Mylip	218203	**1,30**
myosin, heavy polypeptide 11, smooth muscle	Myh11	17880	**1,43**
myosin, heavy polypeptide 14	Myh14	71960	**1,60**
myosin, light polypeptide 7, regulatory	Myl7	17898	**0,80**
myosin, light polypeptide kinase	Mylk	107589	**1,47**
myosin, light polypeptide kinase 2, skeletal muscle	Mylk2	228785	**1,29**
myotilin	Myot	58916	**0,86**
myotrophin	Mtpn	14489	**0,74**
myotubularin related protein 11	Mtmr11	194126	**1,19**
myotubularin related protein 3	Mtmr3	74302	**1,28**
myotubularin related protein 4	Mtmr4	170749	**1,42**
myotubularin related protein 6	Mtmr6	219135	**1,20**
myotubularin related protein 7	Mtmr7	54384	**1,18**
myozenin 1	Myoz1	59011	**1,29**
myxovirus (influenza virus) resistance 1	Mx1	17857	**0,85**
naked cuticle 2 homolog (Drosophila)	Nkd2	72293	**1,31**
nardilysin, N-arginine dibasic convertase, NRD convertase 1	Nrd1	230598	**0,79**
natriuretic peptide receptor 2	Npr2	230103	**1,18**
natriuretic peptide receptor 3	Npr3	18162	**0,85**
nebulin	Neb	17996	**0,85**
necdin	Ndn	17984	**1,71**
neogenin	Neo1	18007	**1,42**
nephroblastoma overexpressed gene	Nov	18133	**0,47**
nestin	Nes	18008	**1,25**
neuralized-like 2 (Drosophila)	Neurl2	415115	**1,22**
neuraminidase 1	Neu1	18010	**1,56**
neurexophilin 2	Nxph2	18232	**1,44**
neurexophilin 3	Nxph3	104079	**1,33**
neuroblastoma ras oncogene	Nras	18176	**0,82**
neurofilament, light polypeptide	Nefl	18039	**1,38**
neurogenic differentiation 1	Neurod1	18012	**0,85**
neuroglobin	Ngb	64242	**1,30**
neuroguidin, EIF4E binding protein	Ngdn	68966	**0,73**
neuroligin 2	Nlgn2	216856	**1,22**
neuromedin U	Nmu	56183	**1,53**
neuron navigator 1	Nav1	215690	**1,37**
neuron navigator 3	Nav3	260315	**1,17**
neuron specific gene family member 1	Nsg1	18196	**1,31**
neuronal pentraxin 1	Nptx1	18164	**1,33**
neuronal pentraxin receptor	Nptxr	73340	**1,27**
neuronatin	Nnat	18111	**1,32**
neuropilin (NRP) and tolloid (TLL)-like 2	Neto2	74513	**0,88**
neuropilin 2	Nrp2	18187	**1,25**
neuroplastin	Nptn	20320	**1,41**
neurotensin	Nts	67405	**0,64**
neutrophil cytosolic factor 4	Ncf4	17972	**1,13**
niban protein	Niban	63913	**1,43**
nibrin	Nbn	27354	**0,81**
nidogen 1	Nid1	18073	**0,84**
nischarin	Nisch	64652	**1,21**
nodal	Nodal	18119	**1,36**
nodal modulator 1	Nomo1	211548	**0,81**
non imprinted in Prader-Willi/Angelman syndrome 2 homolog (human)	Nipa2	93790	**1,36**
non-metastatic cells 1, protein (NM23A) expressed in	Nme1	18102	**0,71**
non-metastatic cells 4, protein expressed in	Nme4	56520	**0,85**
nuclear distribution gene E-like homolog 1 (A. nidulans)	Ndel1	83431	**0,74**
nuclear factor I/B	Nfib	18028	**1,34**
nuclear factor of activated T-cells 5	Nfat5	54446	**1,81**
nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	Nfkbia	18035	**1,49**
nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta	Nfkbiz	80859	**1,35**
nuclear factor related to kappa B binding protein	Nfrkb	235134	**1,34**
nuclear factor, erythroid derived 2, like 2	Nfe2l2	18024	**1,26**
nuclear factor, interleukin 3, regulated	Nfil3	18030	**0,80**
nuclear fragile X mental retardation protein interacting protein 2	Nufip2	68564	**1,57**
nuclear import 7 homolog (S. cerevisiae)	Nip7	66164	**0,72**
nuclear pore membrane protein 121	Pom121	107939	**1,62**

nuclear prelamin A recognition factor	Narf	67608	**1,77**
nuclear protein 1	Nupr1	56312	**0,52**
nuclear protein localization 4 homolog (S. cerevisiae)	Nploc4	217365	**0,82**
nuclear receptor binding protein 2	Nrbp2	223649	**1,32**
nuclear receptor coactivator 2	Ncoa2	17978	**1,33**
nuclear receptor coactivator 6	Ncoa6	56406	**1,49**
nuclear receptor interacting protein 2	Nrip2	60345	**1,34**
nuclear receptor subfamily 0, group B, member 2	Nr0b2	23957	**1,27**
nuclear receptor subfamily 1, group D, member 2	Nr1d2	353187	**1,47**
nuclear receptor subfamily 2, group F, member 2	Nr2f2	11819	**0,83**
nuclear transcription factor-Y beta	Nfyb	18045	**0,82**
nucleobindin 2	Nucb2	53322	**0,80**
nucleolar protein 5	Nol5	55989	**0,83**
nucleolar protein family A, member 2	Nola2	52530	**0,48**
nucleolar protein family A, member 3	Nola3	66181	**0,56**
nucleophosmin/nucleoplasmin 2	Npm2	328440	**1,24**
nucleoplasmin 3	Npm3	18150	**1,64**
nucleoporin 107	Nup107	103468	**0,84**
nucleoporin 133	Nup133	234865	**0,85**
nucleoporin 155	Nup155	170762	**0,87**
nucleoporin 37	Nup37	69736	**0,77**
nucleoporin 98	Nup98	269966	**1,41**
nucleosome assembly protein 1-like 4	Nap1l4	17955	**0,68**
nucleosome assembly protein 1-like 5	Nap1l5	58243	**1,35**
nucleotide binding protein 1	Nubp1	26425	**0,70**
nucleotide-binding oligomerization domain containing 1	Nod1	107607	**1,30**
nudix (nucleoside diphosphate linked moiety X)-type motif 1	Nudt1	17766	**0,71**
nudix (nucleoside diphosphate linked moiety X)-type motif 16-like 1	Nudt16l1	66911	**0,82**
nudix (nucleoside diphosphate linked moiety X)-type motif 6	Nudt6	229228	**0,85**
nudix (nucleotide diphosphate linked moiety X)-type motif 3	Nudt3	56409	**1,31**
occludin	Ocln	18260	**0,70**
olfactomedin-like 3	Olfml3	99543	**1,28**
olfactory receptor 1508	Olfr1508	57270	**1,27**
olfactory receptor 78	Olfr78	170639	**0,87**
oligodendrocyte transcription factor 2	Olig2	50913	**0,81**
oligophrenin 1	Ophn1	94190	**0,86**
one cut domain, family member 2	Onecut2	225631	**1,32**
oocyte expressed protein homolog (dog)	Ooep	67968	**1,46**
oocyte maturation, alpha	Omt2a	18379	**0,80**
oocyte maturation, beta	Omt2b	382088	**0,82**
open reading frame 9	ORF9	52793	**0,61**
opioid growth factor receptor-like 1	Ogfrl1	70155	**1,42**
opposite strand transcription unit to Stag3	Gats	80909	**1,55**
opsin 3	Opn3	13603	**1,18**
opsin 5	Opn5	353344	**0,83**
optic atrophy 1 homolog (human)	Opa1	74143	**1,54**
opticin	Optc	269120	**1,39**
optineurin	Optn	71648	**1,34**
origin recognition complex, subunit 2-like (S. cerevisiae)	Orc2l	18393	**0,73**
origin recognition complex, subunit 3-like (S. cerevisiae)	Orc3l	50793	**0,84**
origin recognition complex, subunit 5-like (S. cerevisiae)	Orc5l	26429	**0,82**
origin recognition complex, subunit 6-like (S. cerevisiae)	Orc6l	56452	**0,83**
orthodenticle homolog 1 (Drosophila)	Otx1	18423	**1,39**
osteoclast stimulating factor 1	Ostf1	20409	**0,67**
osteopetrosis associated transmembrane protein 1	Ostm1	14628	**1,27**
ovo-like 2 (Drosophila)	Ovol2	107586	**0,83**
oxidative stress induced growth inhibitor 1	Osgin1	71839	**1,34**
oxidative-stress responsive 1	Oxsr1	108737	**1,35**
oxysterol binding protein 2	Osbp2	74309	**1,47**
oxysterol binding protein-like 11	Osbpl11	106326	**1,30**
oxysterol binding protein-like 2	Osbpl2	228983	**0,69**
oxysterol binding protein-like 3	Osbpl3	71720	**1,48**
p21 (CDKN1A)-activated kinase 1	Pak1	18479	**0,75**
p21 (CDKN1A)-activated kinase 2	Pak2	224105	**1,25**
p21 (CDKN1A)-activated kinase 4	Pak4	70584	**1,28**
p53 and DNA damage regulated 1	Pdrg1	68559	**0,78**
paired immunoglobin-like type 2 receptor alpha	Pilra	231805	**0,87**
paired-like homeobox 2a	Phox2a	11859	**1,34**
palladin, cytoskeletal associated protein	Palld	72333	**1,26**
pallidin	Pldn	18457	**0,84**
palmitoyl-protein thioesterase 1	Ppt1	19063	**0,77**
palmitoyl-protein thioesterase 2	Ppt2	54397	**1,34**
pancreatic lipase-related protein 2	Pnliprp2	18947	**0,61**
pannexin 1	Panx1	55991	**1,37**
pannexin 2	Panx2	406218	**1,23**
par-3 (partitioning defective 3) homolog (C. elegans)	Pard3	93742	**1,26**
paralemmin	Palm	18483	**1,24**
paraoxonase 3	Pon3	269823	**0,66**
paraspeckle protein 1	Pspc1	66645	**1,28**
patatin-like phospholipase domain containing 7	Pnpla7	241274	**0,84**
patched homolog 1	Ptch1	19206	**1,34**
paternally expressed 3	Peg3	18616	**1,40**
paxillin	Pxn	19303	**0,83**
pellino 2	Peli2	93834	**1,21**
pelota homolog (Drosophila)	Pelo	105083	**1,37**
peptidase (mitochondrial processing) beta	Pmpcb	73078	**0,70**

peptide YY	Pyy	217212	**0,61**
peptidoglycan recognition protein 1	Pglyrp1	21946	**0,63**
peptidyl-prolyl isomerase G (cyclophilin G)	Ppig	228005	**1,54**
peptidyl-tRNA hydrolase 2	Ptrh2	217057	**0,82**
peptidylprolyl isomerase (cyclophilin) like 5	Ppil5	69706	**1,41**
peptidylprolyl isomerase B	Ppib	19035	**0,49**
peptidylprolyl isomerase C	Ppic	19038	**1,24**
peptidylprolyl isomerase F (cyclophilin F)	Ppif	105675	**0,68**
per-pentamer repeat gene	Ppnr	26930	**1,59**
pericentriolar material 1	Pcm1	18536	**1,15**
period homolog 1 (Drosophila)	Per1	18626	**1,26**
period homolog 3 (Drosophila)	Per3	18628	**1,27**
peripheral myelin protein	Pmp22	18858	**1,50**
peripheral myelin protein 2	Pmp2	18857	**1,36**
peripherin	Prph	19132	**1,57**
perlecan (heparan sulfate proteoglycan 2)	Hspg2	15530	**1,19**
peroxiredoxin 1	Prdx1	18477	**0,67**
peroxiredoxin 2	Prdx2	21672	**0,79**
peroxiredoxin 3	Prdx3	11757	**0,67**
peroxiredoxin 4	Prdx4	53381	**0,63**
peroxiredoxin 5	Prdx5	54683	**0,63**
peroxisomal biogenesis factor 11b	Pex11b	18632	**1,19**
peroxisomal biogenesis factor 3	Pex3	56535	**0,83**
peroxisomal delta3, delta2-enoyl-Coenzyme A isomerase	Peci	23986	**0,78**
peroxisomal membrane protein 2	Pxmp2	19301	**1,17**
peroxisomal membrane protein 4	Pxmp4	59038	**0,80**
peroxisome biogenesis factor 19	Pex19	19298	**1,29**
peroxisome proliferative activated receptor, gamma, coactivator 1 alpha	Ppargc1a	19017	**1,66**
peroxisome proliferative activated receptor, gamma, coactivator 1 beta	Ppargc1b	170826	**2,07**
peroxisome proliferator activated receptor alpha	Ppara	19013	**1,66**
peroxisome proliferator activated receptor gamma	Pparg	19016	**0,76**
phosphatase and actin regulator 4	Phactr4	100169	**1,39**
phosphate regulating gene with homologies to endopeptidases on the X chromosome (hypophosphatemia, vitamin D resistant rickets)	Phex	18675	**0,85**
phosphatidylinositol 3 kinase, regulatory subunit, polypeptide 3 (p55)	Pik3r3	18710	**1,22**
phosphatidylinositol 3-kinase, C2 domain containing, gamma polypeptide	Pik3c2g	18705	**0,80**
phosphatidylinositol 3-kinase, catalytic, alpha polypeptide	Pik3ca	18706	**1,38**
phosphatidylinositol 3-kinase, regulatory subunit, polypeptide 2 (p85 beta)	Pik3r2	18709	**1,19**
phosphatidylinositol glycan anchor biosynthesis, class C	Pigc	67292	**0,79**
phosphatidylinositol transfer protein, alpha	Pitpna	18738	**1,26**
phosphatidylinositol transfer protein, membrane-associated 2	Pitpnm2	19679	**1,31**
phosphatidylinositol-3-phosphate/phosphatidylinositol 5-kinase, type III	Pip5k3	18711	**1,50**
phosphatidylinositol-4-phosphate 5-kinase, type 1 beta	Pip5k1b	18719	**0,78**
phosphatidylinositol-4-phosphate 5-kinase, type 1 gamma	Pip5k1c	18717	**1,23**
phosphodiesterase 1B, Ca2+-calmodulin dependent	Pde1b	18574	**1,17**
phosphodiesterase 2A, cGMP-stimulated	Pde2a	207728	**0,72**
phosphodiesterase 3B, cGMP-inhibited	Pde3b	18576	**1,22**
phosphodiesterase 8A	Pde8a	18584	**1,18**
phosphoenolpyruvate carboxykinase 1, cytosolic	Pck1	18534	**0,72**
phosphofructokinase, liver, B-type	Pfkl	18641	**1,60**
phosphofructokinase, muscle	Pfkm	18642	**1,27**
phosphofurin acidic cluster sorting protein 1	Pacs1	107975	**1,26**
phosphoglucomutase 1	Pgm1	66681	**0,77**
phosphoglucomutase 2	Pgm2	72157	**0,77**
phosphoglucomutase 3	Pgm3	109785	**0,62**
phosphoglucomutase 5	Pgm5	226041	**1,40**
phosphohistidine phosphatase 1	Phpt1	75454	**0,67**
phosphoinositide-3-kinase adaptor protein 1	Pik3ap1	83490	**1,20**
phospholamban	Pln	18821	**1,26**
phospholipase A2 receptor 1	Pla2r1	18779	**1,31**
phospholipase A2, group IIF	Pla2g2f	26971	**0,88**
phospholipase A2, group VI	Pla2g6	53357	**1,43**
phospholipase A2, group X	Pla2g10	26565	**0,57**
phospholipase A2, group XIIA	Pla2g12a	66350	**0,84**
phospholipase A2, group XIIB	Pla2g12b	69836	**0,81**
phospholipase C, beta 1	Plcb1	18795	**1,24**
phospholipase C, beta 2	Plcb2	18796	**1,20**
phospholipase C, beta 3	Plcb3	18797	**1,33**
phospholipase C, epsilon 1	Plce1	74055	**1,56**
phospholipase C, gamma 1	Plcg1	18803	**1,22**
phospholipase D1	Pld1	18805	**0,84**
phospholipid scramblase 3	Plscr3	70310	**1,50**
phospholipid transfer protein	Pltp	18830	**0,87**
phosphorylase kinase beta	Phkb	102093	**1,34**
phosphorylase kinase, gamma 2 (testis)	Phkg2	68961	**1,19**
phosphoserine aminotransferase 1	Psat1	107272	**0,84**
phosphoserine phosphatase	Psph	100678	**0,85**
pituitary tumor-transforming 1 interacting protein	Pttg1ip	108705	**1,28**
placenta-specific 8	Plac8	231507	**0,60**
plakophilin 1	Pkp1	18772	**1,37**
plakophilin 3	Pkp3	56460	**1,38**
plakophilin 4	Pkp4	227937	**1,33**
plasma membrane associated protein, S3-12	S3-12	57435	**1,25**
plasma membrane proteolipid	Pllp	67801	**0,68**
plasminogen activator, tissue	Plat	18791	**1,25**
plastin 3 (T-isoform)	Pls3	102866	**1,41**

platelet derived growth factor receptor, beta polypeptide	Pdgfrb	18596	**1,17**
platelet derived growth factor, alpha	Pdgfa	18590	**1,66**
platelet endothelial aggregation receptor 1	Pear1	73182	**0,83**
platelet factor 4	Pf4	56744	**0,82**
platelet-activating factor receptor	Ptafr	19204	**1,26**
platelet-derived growth factor receptor-like	Pdgfrl	68797	**0,79**
platelet-derived growth factor, C polypeptide	Pdgfc	54635	**1,62**
pleckstrin 2	Plek2	27260	**1,21**
pleckstrin and Sec7 domain containing	Psd	73728	**1,37**
pleckstrin homology domain containing, family B (evectins) member 1	Plekhb1	27276	**1,22**
pleckstrin homology domain containing, family B (evectins) member 2	Plekhb2	226971	**0,70**
pleckstrin homology domain containing, family G (with RhoGef domain) member 2	Plekhg2	101497	**1,35**
pleckstrin homology domain containing, family G (with RhoGef domain) member 5	Plekhg5	269608	**1,28**
pleckstrin homology domain containing, family M (with RUN domain) member 1	Plekhm1	353047	**1,28**
pleckstrin homology domain containing, family O member 1	Plekho1	67220	**1,41**
pleckstrin homology domain interacting protein	Phip	83946	**1,33**
pleckstrin homology, Sec7 and coiled-coil domains, binding protein	Pscdbp	227929	**1,21**
pleckstrin homology-like domain, family A, member 1	Phlda1	21664	**1,27**
pleckstrin homology-like domain, family B, member 1	Phldb1	102693	**1,28**
pleckstrin homology-like domain, family B, member 2	Phldb2	208177	**1,39**
pleiotrophin	Ptn	19242	**1,53**
plexin A3	Plxna3	18846	**1,30**
plexin A4	Plxna4	243743	**1,60**
plexin B2	Plxnb2	140570	**1,27**
podocan	Podn	242608	**1,20**
podoplanin	Pdpn	14726	**1,35**
poliovirus receptor-related 2	Pvrl2	19294	**1,35**
poliovirus receptor-related 3	Pvrl3	58998	**1,38**
polo-like kinase 2 (Drosophila)	Plk2	20620	**0,78**
poly (ADP-ribose) polymerase family, member 14	Parp14	547253	**1,31**
poly A binding protein, cytoplasmic 5	Pabpc5	93728	**0,81**
poly(A) binding protein, nuclear 1	Pabpn1	54196	**1,82**
poly(A)-specific ribonuclease (deadenylation nuclease)	Parn	74108	**0,86**
poly(rC) binding protein 2	Pcbp2	18521	**1,26**
polyadenylate-binding protein-interacting protein 2	Paip2	67869	**0,72**
polycomb group ring finger 2	Pcgf2	22658	**1,37**
polycystic kidney disease 1 homolog	Pkd1	18763	**1,25**
polyhomeotic-like 3 (Drosophila)	Phc3	241915	**1,21**
polymerase (DNA directed), alpha 1	Pola1	18968	**0,78**
polymerase (DNA directed), alpha 2	Pola2	18969	**0,84**
polymerase (DNA directed), beta	Polb	18970	**0,78**
polymerase (DNA directed), delta 2, regulatory subunit	Pold2	18972	**0,72**
polymerase (DNA directed), epsilon 2 (p59 subunit)	Pole2	18974	**0,79**
polymerase (DNA directed), epsilon 3 (p17 subunit)	Pole3	59001	**0,80**
polymerase (DNA-directed), delta 3, accessory subunit	Pold3	67967	**1,34**
polymerase (DNA-directed), delta interacting protein 2	Poldip2	67811	**0,77**
polymerase (RNA) II (DNA directed) polypeptide E	Polr2e	66420	**0,62**
polymerase (RNA) II (DNA directed) polypeptide F	Polr2f	69833	**0,60**
polymerase (RNA) III (DNA directed) polypeptide E	Polr3e	26939	**1,26**
polymeric immunoglobulin receptor	Pigr	18703	**0,56**
post-GPI attachment to proteins 1	Pgap1	241062	**1,35**
potassium channel modulatory factor 1	Kcmf1	74287	**0,86**
potassium channel, subfamily K, member 1	Kcnk1	16525	**0,65**
potassium channel, subfamily K, member 5	Kcnk5	16529	**0,81**
potassium inwardly rectifying channel, subfamily J, member 11	Kcnj11	16514	**1,32**
potassium inwardly-rectifying channel, subfamily J, member 12	Kcnj12	16515	**1,21**
potassium inwardly-rectifying channel, subfamily K, member 6	Kcnk6	52150	**0,63**
potassium voltage gated channel, Shab-related subfamily, member 1	Kcnb1	16500	**1,21**
potassium voltage-gated channel, Isk-related subfamily, gene 2	Kcne2	246133	**0,86**
potassium voltage-gated channel, Isk-related subfamily, gene 3	Kcne3	57442	**0,50**
potassium voltage-gated channel, Isk-related subfamily, gene 4	Kcne4	57814	**1,23**
potassium voltage-gated channel, Isk-related subfamily, member 1	Kcne1	16509	**0,82**
potassium voltage-gated channel, subfamily H (eag-related), member 3	Kcnh3	16512	**1,25**
praja1, RING-H2 motif containing	Pja1	18744	**1,26**
pre B-cell leukemia transcription factor 1	Pbx1	18514	**1,50**
pre-B lymphocyte gene 3	Vpreb3	22364	**1,21**
prefoldin 4	Pfdn4	109054	**0,69**
prenyl (solanesyl) diphosphate synthase, subunit 2	Pdss2	71365	**1,70**
prenylcysteine oxidase 1	Pcyox1	66881	**0,77**
preproenkephalin 1	Penk1	18619	**1,54**
processing of precursor 5, ribonuclease P/MRP family (S. cerevisiae)	Pop5	117109	**0,60**
processing of precursor 7, ribonuclease P family, (S. cerevisiae)	Pop7	74097	**1,30**
procollagen C-endopeptidase enhancer 2	Pcolce2	76477	**1,24**
procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha 1 polypeptide	P4ha1	18451	**0,87**
profilin 2	Pfn2	18645	**1,47**
programmed cell death 10	Pdcd10	56426	**1,53**
prohibitin 2	Phb2	12034	**0,61**
proliferation-associated 2G4	Pa2g4	18813	**1,13**
proline rich 7 (synaptic)	Prr7	432763	**1,41**
proline rich protein HaeIII subfamily 1	Prh1	19131	**1,20**
proline-rich acidic protein 1	Prap1	22264	**0,70**
proline-rich nuclear receptor coactivator 1	Pnrc1	108767	**1,43**
prolyl endopeptidase-like	Prepl	213760	**0,76**
prolylcarboxypeptidase (angiotensinase C)	Prcp	72461	**1,36**
prominin 1	Prom1	19126	**1,29**
propionyl Coenzyme A carboxylase, beta polypeptide	Pccb	66904	**0,67**

proprotein convertase subtilisin/kexin type 4	Pcsk4	18551	**1,24**
proprotein convertase subtilisin/kexin type 5	Pcsk5	18552	**1,53**
proprotein convertase subtilisin/kexin type 9	Pcsk9	100102	**1,21**
prostaglandin E receptor 4 (subtype EP4)	Ptger4	19219	**1,31**
prostaglandin E synthase 2	Ptges2	96979	**0,73**
prostaglandin I receptor (IP)	Ptgir	19222	**1,25**
protamine 3	Prm3	19120	**1,18**
protease, serine, 16 (thymus)	Prss16	54373	**0,86**
protease, serine, 23	Prss23	76453	**1,30**
protease, serine, 33	Prss33	353130	**0,85**
proteasome (prosome, macropain) 26S subunit, ATPase 2	Psmc2	19181	**0,62**
proteasome (prosome, macropain) 26S subunit, ATPase 3	Psmc3	19182	**0,66**
proteasome (prosome, macropain) 26S subunit, ATPase, 4	Psmc4	23996	**0,75**
proteasome (prosome, macropain) 26S subunit, non-ATPase, 10	Psmd10	53380	**0,73**
proteasome (prosome, macropain) 26S subunit, non-ATPase, 5	Psmd5	66998	**0,79**
proteasome (prosome, macropain) 26S subunit, non-ATPase, 8	Psmd8	57296	**0,56**
proteasome (prosome, macropain) subunit, alpha type 1	Psma1	26440	**0,61**
proteasome (prosome, macropain) subunit, alpha type 2	Psma2	19166	**0,60**
proteasome (prosome, macropain) subunit, alpha type 6	Psma6	26443	**0,57**
proteasome (prosome, macropain) subunit, alpha type 7	Psma7	26444	**0,56**
proteasome (prosome, macropain) subunit, beta type 10	Psmb10	19171	**0,60**
proteasome (prosome, macropain) subunit, beta type 3	Psmb3	26446	**0,49**
proteasome (prosome, macropain) subunit, beta type 6	Psmb6	19175	**0,57**
proteasome (prosome, macropain) subunit, beta type 8 (large multifunctional peptidase 7)	Psmb8	16913	**0,67**
protein (peptidyl-prolyl cis/trans isomerase) NIMA-interacting 1	Pin1	23988	**0,65**
protein arginine N-methyltransferase 2	Prmt2	15468	**1,26**
protein arginine N-methyltransferase 3	Prmt3	71974	**0,85**
protein arginine N-methyltransferase 7	Prmt7	214572	**0,83**
protein disulfide isomerase associated 3	Pdia3	14827	**0,53**
protein disulfide isomerase associated 5	Pdia5	72599	**0,60**
protein disulfide isomerase associated 6	Pdia6	71853	**0,60**
protein inhibitor of activated STAT 1	Pias1	56469	**1,24**
protein inhibitor of activated STAT 2	Pias2	17344	**1,30**
protein kinase C and casein kinase substrate in neurons 2	Pacsin2	23970	**1,38**
protein kinase C, epsilon	Prkce	18754	**1,48**
protein kinase C, iota	Prkci	18759	**1,21**
protein kinase C, theta	Prkcq	18761	**1,23**
protein kinase D2	Prkd2	101540	**0,89**
protein kinase, X-linked	Prkx	19108	**1,34**
protein kinase, cAMP dependent regulatory, type I beta	Prkar1b	19085	**1,48**
protein kinase, cAMP dependent regulatory, type I, alpha	Prkar1a	19084	**1,37**
protein kinase, cAMP dependent regulatory, type II alpha	Prkar2a	19087	**1,31**
protein kinase, cGMP-dependent, type I	Prkg1	19091	**1,46**
protein kinase, cGMP-dependent, type II	Prkg2	19092	**1,49**
protein phosphatase 1, catalytic subunit, alpha isoform	Ppp1ca	19045	**0,49**
protein phosphatase 1, catalytic subunit, beta isoform	Ppp1cb	19046	**1,29**
protein phosphatase 1, regulatory (inhibitor) subunit 16A	Ppp1r16a	73062	**1,24**
protein phosphatase 1, regulatory (inhibitor) subunit 1A	Ppp1r1a	58200	**1,22**
protein phosphatase 1, regulatory (inhibitor) subunit 7	Ppp1r7	66385	**1,20**
protein phosphatase 1, regulatory (inhibitor) subunit 9A	Ppp1r9a	243725	**1,34**
protein phosphatase 1A, magnesium dependent, alpha isoform	Ppm1a	19042	**1,33**
protein phosphatase 1B, magnesium dependent, beta isoform	Ppm1b	19043	**1,47**
protein phosphatase 2, regulatory subunit B", gamma	Ppp2r3c	59032	**0,77**
protein phosphatase 3, catalytic subunit, alpha isoform	Ppp3ca	19055	**1,27**
protein phosphatase 5, catalytic subunit	Ppp5c	19060	**0,80**
protein regulator of cytokinesis 1	Prc1	233406	**0,83**
protein tyrosine phosphatase, mitochondrial 1	Ptpmt1	66461	**0,66**
protein tyrosine phosphatase, non-receptor type 13	Ptpn13	19249	**1,23**
protein tyrosine phosphatase, non-receptor type 3	Ptpn3	545622	**1,25**
protein tyrosine phosphatase, non-receptor type 5	Ptpn5	19259	**1,13**
protein tyrosine phosphatase, receptor type Z, polypeptide 1	Ptprz1	19283	**1,50**
protein tyrosine phosphatase, receptor type, A	Ptpra	19262	**0,77**
protein tyrosine phosphatase, receptor type, D	Ptprd	19266	**1,45**
protein tyrosine phosphatase, receptor type, F	Ptprf	19268	**0,70**
protein tyrosine phosphatase, receptor type, K	Ptprk	19272	**0,82**
protein tyrosine phosphatase, receptor type, N	Ptprn	19275	**1,31**
protein tyrosine phosphatase, receptor type, O	Ptpro	19277	**0,80**
protein tyrosine phosphatase, receptor type, S	Ptprs	19280	**1,48**
protein-L-isoaspartate (D-aspartate) O-methyltransferase 1	Pcmt1	18537	**1,21**
protein-kinase, interferon-inducible double stranded RNA dependent inhibitor, repressor of (P58 repressor)	Prkrir	72981	**0,79**
protocadherin 1	Pcdh1	75599	**1,33**
protocadherin 12	Pcdh12	53601	**0,85**
protocadherin 15	Pcdh15	11994	**1,21**
protocadherin 17	Pcdh17	219228	**1,64**
protocadherin 8	Pcdh8	18530	**0,83**
protocadherin alpha 4	Pcdha4	12936	**1,56**
protoporphyrinogen oxidase	Ppox	19044	**0,87**
proviral integration site 2	Pim2	18715	**1,25**
pterin 4 alpha carbinolamine dehydratase/dimerization cofactor of hepatocyte nuclear factor 1 alpha (TCF1) 2	Pcbd2	72562	**0,70**
purine-nucleoside phosphorylase	Pnp	18950	**0,63**
purinergic receptor P2X, ligand-gated ion channel 4	P2rx4	18438	**0,82**
purinergic receptor P2X-like 1, orphan receptor	P2rxl1	18440	**1,26**
purinergic receptor P2Y, G-protein coupled, 5	P2ry5	67168	**0,80**
putative homeodomain transcription factor 1	Phtf1	18685	**1,36**
pyridoxal (pyridoxine, vitamin B6) phosphatase	Pdxp	57028	**1,25**
pyridoxine 5'-phosphate oxidase	Pnpo	103711	**1,36**

pyrophosphatase (inorganic) 1	Ppa1	67895	**0,60**
pyrroline-5-carboxylate reductase 1	Pycr1	209027	**0,79**
pyrroline-5-carboxylate reductase-like	Pycrl	66194	**0,69**
pyruvate dehydrogenase kinase, isoenzyme 4	Pdk4	27273	**1,79**
queuine tRNA-ribosyltransferase 1	Qtrt1	60507	**0,74**
rad and gem related GTP binding protein 2	Rem2	140743	**1,39**
ral guanine nucleotide dissociation stimulator-like 3	Rgl3	71746	**0,86**
ras responsive element binding protein 1	Rreb1	68750	**1,39**
rearranged L-myc fusion sequence	Rlf	109263	**1,27**
receptor (TNFRSF)-interacting serine-threonine kinase 1	Ripk1	19766	**0,87**
receptor (calcitonin) activity modifying protein 1	Ramp1	51801	**0,65**
receptor (calcitonin) activity modifying protein 3	Ramp3	56089	**1,17**
receptor tyrosine kinase-like orphan receptor 2	Ror2	26564	**1,51**
receptor-interacting serine-threonine kinase 3	Ripk3	56532	**0,79**
recombination activating gene 1 activating protein 1	Rag1ap1	19729	**0,62**
recombination signal binding protein for immunoglobulin kappa J region	Rbpj	19664	**1,23**
reelin	Reln	19699	**1,27**
regenerating islet-derived 3 beta	Reg3b	18489	**0,62**
regenerating islet-derived family, member 4	Reg4	67709	**0,41**
regulating synaptic membrane exocytosis 1	Rims1	116837	**1,61**
regulator of G-protein signaling 13	Rgs13	246709	**0,71**
regulator of G-protein signaling 17	Rgs17	56533	**0,82**
regulator of G-protein signaling 5	Rgs5	19737	**1,47**
regulator of G-protein signalling 7 binding protein	Rgs7bp	52882	**1,31**
regulator of calcineurin 2	Rcan2	53901	**1,27**
regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 2	Rcbtb2	105670	**0,83**
related RAS viral (r-ras) oncogene homolog 2	Rras2	66922	**1,18**
renin binding protein	Renbp	19703	**1,20**
replication factor C (activator 1) 3	Rfc3	69263	**0,77**
replication factor C (activator 1) 4	Rfc4	106344	**0,68**
replication initiator 1	Repin1	58887	**1,45**
reproductive homeobox 6	Rhox6	19202	**1,44**
resistance to inhibitors of cholinesterase 8 homolog B (C. elegans)	Ric8b	237422	**0,85**
resistin	Retn	57264	**1,19**
resistin like beta	Retnlb	57263	**0,26**
ret proto-oncogene	Ret	19713	**1,56**
reticulon 1	Rtn1	104001	**1,53**
reticulon 3	Rtn3	20168	**1,34**
reticulon 4	Rtn4	68585	**1,43**
retinaldehyde binding protein 1	Rlbp1	19771	**0,82**
retinitis pigmentosa 9 (human)	rp9	55934	**0,81**
retinitis pigmentosa GTPase regulator interacting protein 1	Rpgrip1	77945	**1,57**
retinoblastoma 1	Rb1	19645	**1,47**
retinoblastoma binding protein 4	Rbbp4	19646	**1,79**
retinoblastoma-like 2	Rbl2	19651	**0,82**
retinoic acid induced 14	Rai14	75646	**1,57**
retinoic acid induced 2	Rai2	24004	**0,83**
retinoic acid receptor, gamma	Rarg	19411	**1,38**
retinol binding protein 3, interstitial	Rbp3	19661	**1,29**
retinol binding protein 4, plasma	Rbp4	19662	**0,63**
retinol binding protein 7, cellular	Rbp7	63954	**0,80**
retinol dehydrogenase 11	Rdh11	17252	**0,82**
retinol dehydrogenase 14 (all-trans and 9-cis)	Rdh14	105014	**0,74**
retinol saturase (all trans retinol 13,14 reductase)	Retsat	67442	**0,63**
reversion-inducing-cysteine-rich protein with kazal motifs	Reck	53614	**1,34**
rhodopsin	Rho	212541	**0,84**
riboflavin kinase	Rfk	54391	**1,38**
ribonuclease P 21 subunit (human)	Rpp21	67676	**0,70**
ribonuclease P 40 subunit (human)	Rpp40	208366	**0,86**
ribonuclease P/MRP 38 subunit (human)	Rpp38	227522	**0,84**
ribonuclease/angiogenin inhibitor 1	Rnh1	107702	**0,64**
ribonucleotide reductase M2 B (TP53 inducible)	Rrm2b	382985	**0,89**
ribosomal L1 domain containing 1	Rsl1d1	66409	**0,68**
ribosomal protein L14	Rpl14	67115	**0,79**
ribosomal protein L21	Rpl21	19933	**0,87**
ribosomal protein L22	Rpl22	19934	**0,71**
ribosomal protein L26	Rpl26	19941	**0,77**
ribosomal protein S3	Rps3	27050	**0,87**
ribosomal protein S5	Rps5	20103	**0,69**
ribosomal protein S6 kinase, polypeptide 1	Rps6kb1	72508	**1,25**
ribosomal protein S6 kinase, polypeptide 4	Rps6ka4	56613	**1,27**
ribosome binding protein 1	Rrbp1	81910	**0,71**
ring finger 111	Rnf111	93836	**1,26**
ring finger and CCCH-type zinc finger domains 2	Rc3h2	319817	**1,43**
ring finger and FYVE like domain containing protein	Rffl	67338	**1,25**
ring finger protein 128	Rnf128	66889	**1,30**
ring finger protein 2	Rnf2	19821	**1,37**
ring finger protein 41	Rnf41	67588	**1,22**
ring finger protein 8	Rnf8	58230	**1,31**
ripply2 homolog (zebrafish)	Ripply2	382089	**0,80**
runt related transcription factor 2	Runx2	12393	**0,86**
salvador homolog 1 (Drosophila)	Sav1	64010	**0,81**
sarcoglycan, alpha (dystrophin-associated glycoprotein)	Sgca	20391	**1,29**
sarcolemma associated protein	Slmap	83997	**1,31**
sarcospan	Sspn	16651	**1,28**
scavenger receptor class B, member 1	Scarb1	20778	**0,86**

scavenger receptor class B, member 2	Scarb2	12492	**1,46**
scavenger receptor cysteine rich domain containing, group B (4 domains)	Srcrb4d	109267	**1,36**
schlafen 4	Slfn4	20558	**1,49**
sclerostin domain containing 1	Sostdc1	66042	**1,22**
scribbled homolog (Drosophila)	Scrib	105782	**1,45**
secernin 1	Scrn1	69938	**1,21**
secreted frizzled-related sequence protein 5	Sfrp5	54612	**1,31**
secretin	Sct	20287	**0,74**
secretogranin II	Scg2	20254	**1,65**
secretogranin III	Scg3	20255	**1,48**
secretory carrier membrane protein 2	Scamp2	24044	**1,32**
selenium binding protein 1	Selenbp1	20341	**0,88**
selenoprotein M	Selm	114679	**0,55**
sema domain, immunoglobulin domain (Ig), and GPI membrane anchor, (semaphorin) 7A	Sema7a	20361	**1,19**
sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3C	Sema3c	20348	**1,42**
sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4C	Sema4c	20353	**1,15**
sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6C	Sema6c	20360	**1,34**
senataxin	Setx	269254	**1,34**
septin 11	Sept11	52398	**1,23**
septin 3	Sept3	24050	**1,34**
septin 4	Sept4	18952	**0,84**
serine (or cysteine) peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 12	Serpina12	68054	**1,27**
serine (or cysteine) peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 9	Serpina9	71907	**1,32**
serine (or cysteine) peptidase inhibitor, clade B, member 1a	Serpinb1a	66222	**0,53**
serine (or cysteine) peptidase inhibitor, clade B, member 7	Serpinb7	116872	**0,82**
serine (or cysteine) peptidase inhibitor, clade E, member 2	Serpine2	20720	**1,69**
serine hydroxymethyltransferase 1 (soluble)	Shmt1	20425	**0,72**
serine palmitoyltransferase, long chain base subunit 2	Sptlc2	20773	**0,77**
serine peptidase inhibitor, Kazal type 3	Spink3	20730	**0,69**
serine protease inhibitor, Kunitz type 1	Spint1	20732	**1,51**
serine/arginine repetitive matrix 2	Srrm2	75956	**1,89**
serine/arginine-rich protein specific kinase 1	Srpk1	20815	**1,41**
serine/threonine kinase 10	Stk10	20868	**1,60**
serine/threonine kinase 11	Stk11	20869	**0,74**
serine/threonine kinase 16	Stk16	20872	**0,76**
serine/threonine kinase 17b (apoptosis-inducing)	Stk17b	98267	**1,38**
serine/threonine kinase 35	Stk35	67333	**1,95**
serine/threonine kinase 38	Stk38	106504	**1,41**
serine/threonine kinase 38 like	Stk38l	232533	**0,80**
serologically defined colon cancer antigen 1	Sdccag1	66244	**0,75**
serum amyloid A 1	Saa1	20208	**0,64**
serum amyloid A 3	Saa3	20210	**1,38**
serum deprivation response	Sdpr	20324	**1,58**
serum response factor binding protein 1	Srfbp1	67222	**0,89**
serum/glucocorticoid regulated kinase 2	Sgk2	27219	**1,90**
sestrin 3	Sesn3	75747	**1,40**
short stature homeobox 2	Shox2	20429	**0,84**
shugoshin-like 1 (S. pombe)	Sgol1	72415	**0,83**
sialic acid binding Ig-like lectin H	Siglech	233274	**0,84**
signal recognition particle 14	Srp14	20813	**0,77**
signal recognition particle 19	Srp19	66384	**0,75**
signal recognition particle 9	Srp9	27058	**0,72**
signal recognition particle receptor, B subunit	Srprb	20818	**1,31**
signal sequence receptor, beta	Ssr2	66256	**0,60**
signal sequence receptor, delta	Ssr4	20832	**1,19**
signal transducer and activator of transcription 1	Stat1	20846	**0,78**
signal transducing adaptor molecule (SH3 domain and ITAM motif) 2	Stam2	56324	**0,81**
signal-induced proliferation-associated 1 like 1	Sipa1l1	217692	**1,64**
sine oculis-binding protein homolog (Drosophila)	Sobp	109205	**1,77**
sine oculis-related homeobox 2 homolog (Drosophila)	Six2	20472	**1,20**
sine oculis-related homeobox 5 homolog (Drosophila)	Six5	20475	**1,34**
single-strand selective monofunctional uracil DNA glycosylase	Smug1	71726	**0,76**
single-stranded DNA binding protein 2	Ssbp2	66970	**1,34**
sirtuin 4 (silent mating type information regulation 2 homolog) 4 (S. cerevisiae)	Sirt4	75387	**0,84**
six transmembrane epithelial antigen of prostate 2	Steap2	74051	**0,86**
six transmembrane epithelial antigen of the prostate 1	Steap1	70358	**0,78**
slingshot homolog 1 (Drosophila)	Ssh1	231637	**1,42**
slit homolog 2 (Drosophila)	Slit2	20563	**1,31**
small chemokine (C-C motif) ligand 11	Ccl11	20292	**0,77**
small nuclear RNA activating complex, polypeptide 3	Snapc3	77634	**0,87**
smoothelin	Smtn	29856	**1,35**
smu-1 suppressor of mec-8 and unc-52 homolog (C. elegans)	Smu1	74255	**0,78**
sodium channel, nonvoltage-gated 1 beta	Scnn1b	20277	**1,14**
sodium channel, nonvoltage-gated, type I, alpha	Scnn1a	20276	**1,25**
sodium channel, voltage-gated, type I, alpha	Scn1a	20265	**1,43**
sodium channel, voltage-gated, type I, beta	Scn1b	20266	**1,45**
sodium channel, voltage-gated, type II, beta	Scn2b	72821	**1,35**
solute carrier family 1 (glutamate transporter), member 7	Slc1a7	242607	**1,23**
solute carrier family 1 (glutamate/neutral amino acid transporter), member 4	Slc1a4	55963	**0,78**
solute carrier family 10, member 2	Slc10a2	20494	**1,70**
solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1	Slc11a1	18173	**0,82**
solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	Slc11a2	18174	**0,80**
solute carrier family 12 (potassium/chloride transporters), member 8	Slc12a8	171286	**0,62**
solute carrier family 12 (potassium/chloride transporters), member 9	Slc12a9	83704	**1,19**
solute carrier family 12, member 7	Slc12a7	20499	**1,40**
solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 2	Slc13a2	20500	**1,56**

solute carrier family 13 (sodium/sulphate symporters), member 1	Slc13a1	55961	**1,77**
solute carrier family 15 (H+/peptide transporter), member 2	Slc15a2	57738	**1,77**
solute carrier family 15 (oligopeptide transporter), member 1	Slc15a1	56643	**1,35**
solute carrier family 15, member 4	Slc15a4	100561	**0,87**
solute carrier family 16 (monocarboxylic acid transporters), member 5	Slc16a5	217316	**1,23**
solute carrier family 16 (monocarboxylic acid transporters), member 7	Slc16a7	20503	**0,82**
solute carrier family 17 (anion/sugar transporter), member 5	Slc17a5	235504	**1,39**
solute carrier family 18 (vesicular monoamine), member 1	Slc18a1	110877	**0,83**
solute carrier family 19 (sodium/hydrogen exchanger), member 1	Slc19a1	20509	**1,15**
solute carrier family 19 (thiamine transporter), member 2	Slc19a2	116914	**1,21**
solute carrier family 2 (facilitated glucose transporter), member 5	Slc2a5	56485	**1,22**
solute carrier family 2 (facilitated glucose transporter), member 9	Slc2a9	117591	**1,25**
solute carrier family 22 (organic cation transporter), member 17	Slc22a17	59049	**1,29**
solute carrier family 22, member 23	Slc22a23	73102	**1,56**
solute carrier family 24 (sodium/potassium/calcium exchanger), member 3	Slc24a3	94249	**1,49**
solute carrier family 25 (mitochondrial carnitine/acylcarnitine translocase), member 20	Slc25a20	57279	**1,41**
solute carrier family 25 (mitochondrial carrier, peroxisomal membrane protein), member 17	Slc25a17	20524	**0,80**
solute carrier family 25 (mitochondrial carrier, phosphate carrier), member 3	Slc25a3	18674	**0,87**
solute carrier family 25 (mitochondrial thiamine pyrophosphate carrier), member 19	Slc25a19	67283	**0,83**
solute carrier family 25, member 32	Slc25a32	69906	**0,83**
solute carrier family 25, member 37	Slc25a37	67712	**1,51**
solute carrier family 25, member 38	Slc25a38	208638	**0,84**
solute carrier family 25, member 42	Slc25a42	73095	**1,24**
solute carrier family 25, member 45	Slc25a45	107375	**0,87**
solute carrier family 25, member 46	Slc25a46	67453	**0,78**
solute carrier family 26 (sulfate transporter), member 2	Slc26a2	13521	**2,36**
solute carrier family 27 (fatty acid transporter), member 4	Slc27a4	26569	**1,48**
solute carrier family 3, member 1	Slc3a1	20532	**1,32**
solute carrier family 30 (zinc transporter), member 3	Slc30a3	22784	**1,26**
solute carrier family 30 (zinc transporter), member 4	Slc30a4	22785	**1,39**
solute carrier family 34 (sodium phosphate), member 2	Slc34a2	20531	**0,82**
solute carrier family 35 (UDP-galactose transporter), member A2	Slc35a2	22232	**0,78**
solute carrier family 35 (UDP-glucuronic acid/UDP-N-acetylgalactosamine dual transporter), member D1	Slc35d1	242585	**1,43**
solute carrier family 35, member C1	Slc35c1	228368	**0,69**
solute carrier family 35, member D3	Slc35d3	76157	**1,35**
solute carrier family 35, member F2	Slc35f2	72022	**0,84**
solute carrier family 35, member F5	Slc35f5	74150	**0,83**
solute carrier family 38, member 10	Slc38a10	72055	**0,75**
solute carrier family 38, member 2	Slc38a2	67760	**1,49**
solute carrier family 38, member 5	Slc38a5	209837	**0,84**
solute carrier family 38, member 7	Slc38a7	234595	**1,20**
solute carrier family 39 (metal ion transporter), member 6	Slc39a6	106957	**1,24**
solute carrier family 39 (metal ion transporter), member 8	Slc39a8	67547	**0,81**
solute carrier family 4 (anion exchanger), member 1, adaptor protein	Slc4a1ap	20534	**1,20**
solute carrier family 4 (anion exchanger), member 2	Slc4a2	20535	**1,44**
solute carrier family 40 (iron-regulated transporter), member 1	Slc40a1	53945	**1,46**
solute carrier family 43, member 1	Slc43a1	72401	**0,87**
solute carrier family 5 (choline transporter), member 7	Slc5a7	63993	**0,85**
solute carrier family 5 (inositol transporters), member 3	Slc5a3	53881	**0,71**
solute carrier family 5 (sodium/glucose cotransporter), member 1	Slc5a1	20537	**1,44**
solute carrier family 6 (neurotransmitter transporter, betaine/GABA), member 12	Slc6a12	14411	**1,33**
solute carrier family 6 (neurotransmitter transporter, taurine), member 6	Slc6a6	21366	**1,55**
solute carrier family 7 (cationic amino acid transporter, y+ system), member 1	Slc7a1	11987	**1,36**
solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	Slc7a5	20539	**1,25**
solute carrier family 7 (cationic amino acid transporter, y+ system), member 9	Slc7a9	30962	**1,29**
solute carrier family 9 (sodium/hydrogen exchanger), member 1	Slc9a1	20544	**1,30**
solute carrier family 9 (sodium/hydrogen exchanger), member 2	Slc9a2	226999	**1,48**
solute carrier family 9 (sodium/hydrogen exchanger), member 3	Slc9a3	105243	**1,41**
solute carrier family 9 (sodium/hydrogen exchanger), member 3 regulator 2	Slc9a3r2	65962	**1,23**
solute carrier family 9 (sodium/hydrogen exchanger), member 6	Slc9a6	236794	**1,31**
solute carrier organic anion transporter family, member 2a1	Slco2a1	24059	**1,37**
solute carrier organic anion transporter family, member 4a1	Slco4a1	108115	**1,18**
somatostatin	Sst	20604	**1,38**
somatostatin receptor 1	Sstr1	20605	**1,76**
sonic hedgehog	Shh	20423	**1,20**
sorbin and SH3 domain containing 1	Sorbs1	20411	**1,92**
sorbin and SH3 domain containing 3	Sorbs3	20410	**1,24**
sorbitol dehydrogenase	Sord	20322	**0,70**
sortilin 1	Sort1	20661	**1,19**
sortilin-related receptor, LDLR class A repeats-containing	Sorl1	20660	**1,51**
sorting nexin 12	Snx12	55988	**1,29**
sorting nexin 14	Snx14	244962	**0,75**
sorting nexin 15	Snx15	69024	**1,26**
sorting nexin 17	Snx17	266781	**1,23**
sorting nexin 19	Snx19	102607	**1,20**
sorting nexin 5	Snx5	69178	**0,74**
sorting nexin 6	Snx6	72183	**0,78**
spastic paraplegia 21 homolog (human)	Spg21	27965	**0,73**
spastic paraplegia 3A homolog (human)	Spg3a	73991	**1,31**
special AT-rich sequence binding protein 1	Satb1	20230	**1,44**
spectrin alpha 1	Spna1	20739	**0,76**
spectrin beta 2	Spnb2	20742	**1,32**
spectrin beta 3	Spnb3	20743	**1,22**
sperm associated antigen 9	Spag9	70834	**1,44**
spermatogenesis associated 6	Spata6	67946	**1,20**
spermatogenesis associated, serine-rich 2	Spats2	72572	**0,86**

spermine oxidase	Smox	228608	**0,83**
sphingomyelin synthase 1	Sgms1	208449	**1,23**
sphingosine-1-phosphate phosphatase 1	Sgpp1	81535	**1,20**
spinster homolog 3 (Drosophila)	Spns3	77577	**1,22**
splicing factor proline/glutamine rich (polypyrimidine tract binding protein associated)	Sfpq	71514	**1,40**
splicing factor, arginine/serine-rich 12	Sfrs12	218543	**1,36**
splicing factor, arginine/serine-rich 4 (SRp75)	Sfrs4	57317	**1,59**
split hand/foot malformation (ectrodactyly) type 1	Shfm1	20422	**0,66**
sprouty homolog 4 (Drosophila)	Spry4	24066	**1,19**
sprouty protein with EVH-1 domain 1, related sequence	Spred1	114715	**0,86**
sprouty-related, EVH1 domain containing 3	Spred3	101809	**1,18**
squamous cell carcinoma antigen recognized by T-cells 1	Sart1	20227	**1,28**
src family associated phosphoprotein 2	Skap2	54353	**1,30**
src homology 2 domain-containing transforming protein B	Shb	230126	**1,27**
src homology 2 domain-containing transforming protein C1	Shc1	20416	**1,44**
src-like adaptor	Sla	20491	**0,86**
src-related kinase lacking C-terminal regulatory tyrosine and N-terminal myristylation sites	Srms	20811	**1,19**
stathmin-like 2	Stmn2	20257	**1,44**
stathmin-like 3	Stmn3	20262	**1,43**
sterile alpha motif domain containing 9-like	Samd9l	209086	**0,74**
steroid receptor RNA activator 1	Sra1	24068	**0,56**
sterol regulatory element binding factor 2	Srebf2	20788	**1,42**
sterol regulatory element binding transcription factor 1	Srebf1	20787	**1,45**
stimulated by retinoic acid 13	Stra13	20892	**0,62**
stress 70 protein chaperone, microsome-associated, human homolog	Stch	110920	**0,85**
stress-induced phosphoprotein 1	Stip1	20867	**0,73**
stromal antigen 2	Stag2	20843	**0,76**
stromal cell derived factor 2	Sdf2	20316	**0,60**
stromal cell-derived factor 2-like 1	Sdf2l1	64136	**0,69**
stromal interaction molecule 1	Stim1	20866	**0,80**
stromal interaction molecule 2	Stim2	116873	**1,35**
stromal membrane-associated protein 1	Smap1	98366	**1,34**
structure specific recognition protein 1	Ssrp1	20833	**0,80**
succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	Sdhb	67680	**0,59**
succinate dehydrogenase complex, subunit D, integral membrane protein	Sdhd	66925	**0,57**
succinate-CoA ligase, GDP-forming, alpha subunit	Suclg1	56451	**0,48**
sulfatase 1	Sulf1	240725	**1,28**
sulfiredoxin 1 homolog (S. cerevisiae)	Srxn1	76650	**1,37**
sulfotransferase family 1A, phenol-preferring, member 1	Sult1a1	20887	**0,50**
sulfotransferase family 1B, member 1	Sult1b1	56362	**0,64**
sulfotransferase family 4A, member 1	Sult4a1	29859	**1,18**
sulfotransferase family, cytosolic, 1C, member 2	Sult1c2	69083	**0,63**
supervillin	Svil	225115	**1,34**
suppression of tumorigenicity 7-like	St7l	229681	**0,73**
suppressor of cytokine signaling 7	Socs7	192157	**1,33**
suppressor of fused homolog (Drosophila)	Sufu	24069	**1,30**
suppressor of var1, 3-like 1 (S. cerevisiae)	Supv3l1	338359	**0,76**
suppressor of variegation 4-20 homolog 2 (Drosophila)	Suv420h2	232811	**1,32**
suppressor of zeste 12 homolog (Drosophila)	Suz12	52615	**0,81**
surfeit gene 1	Surf1	20930	**0,60**
surfeit gene 2	Surf2	20931	**0,83**
sushi domain containing 2	Susd2	71733	**1,21**
sushi-repeat-containing protein, X-linked 2	Srpx2	68792	**0,84**
symplekin	Sympk	68188	**0,84**
synapsin I	Syn1	20964	**1,27**
synapsin II	Syn2	20965	**1,31**
synapsin III	Syn3	27204	**1,30**
synaptic nuclear envelope 1	Syne1	64009	**1,23**
synaptic vesicle glycoprotein 2 a	Sv2a	64051	**1,46**
synaptogyrin 1	Syngr1	20972	**1,35**
synaptogyrin 3	Syngr3	20974	**1,20**
synaptojanin 1	Synj1	104015	**1,44**
synaptojanin 2 binding protein	Synj2bp	24071	**0,79**
synaptopodin 2	Synpo2	118449	**1,44**
synaptosomal-associated protein 25	Snap25	20614	**1,53**
synaptosomal-associated protein 91	Snap91	20616	**1,36**
synaptotagmin I	Syt1	20979	**1,47**
synaptotagmin V	Syt5	53420	**1,23**
synaptotagmin VIII	Syt8	55925	**1,23**
synaptotagmin XI	Syt11	229521	**1,24**
synaptotagmin XVII	Syt17	110058	**1,26**
synaptotagmin binding, cytoplasmic RNA interacting protein	Syncrip	56403	**1,40**
synaptotagmin-like 1	Sytl1	269589	**0,79**
synaptotagmin-like 4	Sytl4	27359	**0,76**
syncoilin	Sync	68828	**1,35**
syndecan 2	Sdc2	15529	**0,83**
syndecan 3	Sdc3	20970	**1,43**
synovial sarcoma, X breakpoint 2 interacting protein	Ssx2ip	99167	**1,29**
syntaxin 12	Stx12	100226	**0,77**
syntaxin 17	Stx17	67727	**0,77**
syntaxin 18	Stx18	71116	**0,81**
syntaxin 2	Stx2	13852	**1,25**
syntaxin 3	Stx3	20908	**0,68**
syntaxin 5A	Stx5a	56389	**0,77**
syntaxin 6	Stx6	58244	**0,87**
syntaxin binding protein 1	Stxbp1	20910	**1,33**

syntaxin binding protein 5 (tomosyn)	Stxbp5	78808	**1,21**
tRNA aspartic acid methyltransferase 1	Trdmt1	13434	**0,82**
tRNA nucleotidyl transferase, CCA-adding, 1	Trnt1	70047	**0,86**
tRNA selenocysteine associated protein 1	Trspap1	71787	**0,77**
tachykinin 1	Tac1	21333	**1,78**
tachykinin receptor 1	Tacr1	21336	**1,28**
tachykinin receptor 2	Tacr2	21337	**1,31**
talin 1	Tln1	21894	**1,26**
tandem C2 domains, nuclear	Tc2n	74413	**0,78**
target of myb1-like 2 (chicken)	Tom1l2	216810	**1,85**
taxilin alpha	Txlna	109658	**0,86**
teashirt zinc finger family member 1	Tshz1	110796	**1,45**
teashirt zinc finger family member 2	Tshz2	228911	**1,43**
telomerase associated protein 1	Tep1	21745	**1,51**
telomeric repeat binding factor 2	Terf2	21750	**1,39**
tenascin C	Tnc	21923	**1,32**
tensin 1	Tns1	21961	**1,48**
tensin 3	Tns3	319939	**1,59**
tensin 4	Tns4	217169	**1,51**
testis-specific protein, Y-encoded-like 1	Tspyl1	22110	**1,27**
testis-specific protein, Y-encoded-like 5	Tspyl5	239364	**1,32**
tet oncogene family member 2	Tet2	214133	**1,40**
tetraspanin 1	Tspan1	66805	**1,33**
tetraspanin 13	Tspan13	66109	**0,48**
tetraspanin 14	Tspan14	52588	**0,82**
tetraspanin 2	Tspan2	70747	**1,24**
tetraspanin 3	Tspan3	56434	**1,23**
tetraspanin 4	Tspan4	64540	**1,22**
tetraspanin 7	Tspan7	21912	**1,33**
tetraspanin 9	Tspan9	109246	**1,30**
tetratricopeptide repeat domain 27	Ttc27	74196	**0,83**
tetratricopeptide repeat domain 4	Ttc4	72354	**0,85**
thimet oligopeptidase 1	Thop1	50492	**0,84**
thioesterase superfamily member 2	Them2	66834	**0,67**
thioredoxin domain containing 12 (endoplasmic reticulum)	Txndc12	66073	**0,67**
thioredoxin domain containing 17	Txndc17	52700	**0,59**
thioredoxin domain containing 4 (endoplasmic reticulum)	Txndc4	76299	**0,67**
thioredoxin domain containing 5	Txndc5	105245	**0,52**
thioredoxin reductase 1	Txnrd1	50493	**0,69**
thioredoxin reductase 2	Txnrd2	26462	**1,33**
thioredoxin reductase 3	Txnrd3	232223	**1,35**
thioredoxin-like 1	Txnl1	53382	**1,36**
three prime histone mRNA exonuclease 1	Thex1	67276	**0,81**
threonyl-tRNA synthetase	Tars	110960	**0,74**
thromboxane A2 receptor	Tbxa2r	21390	**1,24**
thymidine kinase 2, mitochondrial	Tk2	57813	**0,82**
thymopoietin	Tmpo	21917	**0,79**
thymus cell antigen 1, theta	Thy1	21838	**1,25**
thyroid hormone receptor alpha	Thra	21833	**1,36**
thyroid hormone receptor associated protein 3	Thrap3	230753	**1,74**
thyroid hormone receptor interactor 11	Trip11	109181	**0,81**
thyroid hormone receptor interactor 4	Trip4	56404	**0,85**
thyrotroph embryonic factor	Tef	21685	**1,57**
thyrotropin releasing hormone receptor 2	Trhr2	170732	**1,33**
tight junction protein 1	Tjp1	21872	**1,36**
tissue factor pathway inhibitor 2	Tfpi2	21789	**0,73**
tissue inhibitor of metalloproteinase 3	Timp3	21859	**1,41**
titin	Ttn	22138	**1,19**
toll interacting protein	Tollip	54473	**1,29**
toll-like receptor 1	Tlr1	21897	**1,55**
toll-like receptor 11	Tlr11	239081	**1,22**
toll-like receptor 2	Tlr2	24088	**0,80**
toll-like receptor 3	Tlr3	142980	**0,85**
toll-like receptor 4	Tlr4	21898	**0,81**
topoisomerase (DNA) II beta	Top2b	21974	**0,85**
topoisomerase (DNA) II beta binding protein	Topbp1	235559	**0,80**
torsin family 1, member B	Tor1b	30934	**1,59**
trafficking protein particle complex 1	Trappc1	245828	**0,74**
trafficking protein particle complex 4	Trappc4	60409	**0,74**
trans-acting transcription factor 5	Sp5	64406	**0,80**
transaldolase 1	Taldo1	21351	**0,75**
transcription elongation factor A (SII), 3	Tcea3	21401	**0,70**
transcription elongation factor B (SIII), polypeptide 1	Tceb1	67923	**1,28**
transcription elongation factor B (SIII), polypeptide 3	Tceb3	27224	**0,79**
transcription factor 19	Tcf19	106795	**0,79**
transcription factor 3	Tcf3	21415	**1,46**
transcription factor 7, T-cell specific	Tcf7	21414	**1,21**
transcription factor A, mitochondrial	Tfam	21780	**0,77**
transcription factor B1, mitochondrial	Tfb1m	224481	**0,84**
transcription factor CP2	Tcfcp2	21422	**1,51**
transcription factor CP2-like 1	Tcfcp2l1	81879	**1,40**
transcription factor Dp 2	Tfdp2	211586	**1,40**
transcription factor EB	Tcfeb	21425	**1,37**
transcriptional regulator, SIN3A (yeast)	Sin3a	20466	**0,81**
transducer of ErbB-2.1	Tob1	22057	**1,63**
transducin-like enhancer of split 4, homolog of Drosophila E(spl)	Tle4	21888	**1,35**

transferrin receptor	Tfrc	22042	**0,61**
transformation related protein 53 binding protein 2	Trp53bp2	209456	**1,25**
transformation related protein 53 inducible nuclear protein 1	Trp53inp1	60599	**1,44**
transformation/transcription domain-associated protein	Trrap	100683	**1,43**
transforming growth factor beta 1 induced transcript 1	Tgfb1i1	21804	**1,36**
transforming growth factor beta regulated gene 1	Tbrg1	21376	**0,57**
transforming growth factor beta regulated gene 4	Tbrg4	21379	**0,84**
transforming growth factor, beta 2	Tgfb2	21808	**1,37**
transforming growth factor, beta induced	Tgfbi	21810	**1,29**
transforming growth factor, beta receptor II	Tgfbr2	21813	**0,73**
transforming growth factor, beta receptor associated protein 1	Tgfbrap1	73122	**1,29**
transforming, acidic coiled-coil containing protein 2	Tacc2	57752	**1,60**
transgelin	Tagln	21345	**1,42**
transgelin 3	Tagln3	56370	**1,30**
transient receptor potential cation channel, subfamily A, member 1	Trpa1	277328	**0,85**
transient receptor potential cation channel, subfamily C, member 2	Trpc2	22064	**1,28**
transient receptor potential cation channel, subfamily C, member 5	Trpc5	22067	**0,82**
transient receptor potential cation channel, subfamily M, member 2	Trpm2	28240	**1,17**
transient receptor potential cation channel, subfamily M, member 3	Trpm3	226025	**1,20**
transient receptor potential cation channel, subfamily M, member 6	Trpm6	225997	**1,55**
transient receptor potential cation channel, subfamily V, member 1	Trpv1	193034	**0,85**
transient receptor potential cation channel, subfamily V, member 5	Trpv5	194352	**0,80**
translin-associated factor X	Tsnax	53424	**0,84**
translocase of inner mitochondrial membrane 13 homolog (yeast)	Timm13	30055	**0,60**
translocase of inner mitochondrial membrane 22 homolog (yeast)	Timm22	56322	**0,77**
translocase of inner mitochondrial membrane 44	Timm44	21856	**0,79**
translocase of inner mitochondrial membrane 8 homolog b (yeast)	Timm8b	30057	**0,62**
translocase of outer mitochondrial membrane 34	Tomm34	67145	**1,27**
translocated promoter region	Tpr	108989	**0,77**
translocator protein	Tspo	12257	**0,58**
transmembrane 4 superfamily member 4	Tm4sf4	229302	**1,43**
transmembrane BAX inhibitor motif containing 1	Tmbim1	69660	**1,45**
transmembrane emp24 domain containing 3	Tmed3	66111	**0,69**
transmembrane emp24 protein transport domain containing 7	Tmed7	66676	**0,75**
transmembrane protease, serine 2	Tmprss2	50528	**0,62**
transmembrane protease, serine 5 (spinesin)	Tmprss5	80893	**1,24**
transmembrane protease, serine 8 (intestinal)	Tmprss8	30943	**0,62**
transmembrane protein 111	Tmem111	66087	**1,33**
transmembrane protein 143	Tmem143	70209	**1,28**
transmembrane protein 158	Tmem158	72309	**1,48**
transmembrane protein 159	Tmem159	233806	**0,78**
transmembrane protein 165	Tmem165	21982	**0,73**
transmembrane protein 16F	Tmem16f	105722	**1,49**
transmembrane protein 16g	Tmem16g	404545	**0,88**
transmembrane protein 176B	Tmem176b	65963	**0,62**
transmembrane protein 25	Tmem25	71687	**1,19**
transmembrane protein 30A	Tmem30a	69981	**1,64**
transmembrane protein 30B	Tmem30b	238257	**1,46**
transmembrane protein 30C	Tmem30c	71027	**0,84**
transmembrane protein 46	Tmem46	219134	**0,82**
transmembrane protein 48	Tmem48	72787	**0,86**
transmembrane protein 49	Tmem49	75909	**0,72**
transmembrane protein 55b	Tmem55b	219024	**1,38**
transmembrane protein 57	Tmem57	66146	**1,25**
transmembrane protein 69	Tmem69	230657	**0,82**
transmembrane protein 9	Tmem9	66241	**0,83**
transmembrane protein with EGF-like and two follistatin-like domains 1	Tmeff1	230157	**0,85**
transmembrane serine protease 6	Tmprss6	71753	**1,21**
trefoil factor 1	Tff1	21784	**1,21**
trefoil factor 2 (spasmolytic protein 1)	Tff2	21785	**0,81**
trefoil factor 3, intestinal	Tff3	21786	**0,54**
tribbles homolog 1 (Drosophila)	Trib1	211770	**0,84**
trichorhinophalangeal syndrome I (human)	Trps1	83925	**1,35**
triggering receptor expressed on myeloid cells-like 1	Treml1	71326	**1,37**
trinucleotide repeat containing 4	Tnrc4	78784	**1,36**
trinucleotide repeat containing 6a	Tnrc6a	233833	**1,67**
tripartite motif-containing 11	Trim11	94091	**1,18**
tripartite motif-containing 14	Trim14	74735	**0,77**
tripartite motif-containing 16	Trim16	94092	**0,79**
tripartite motif-containing 2	Trim2	80890	**0,68**
tripartite motif-containing 3	Trim3	55992	**1,15**
tripartite motif-containing 33	Trim33	94093	**1,35**
tripartite motif-containing 36	Trim36	28105	**1,54**
tripartite motif-containing 37	Trim37	68729	**0,79**
tripartite motif-containing 54	Trim54	58522	**1,22**
tripeptidyl peptidase I	Tpp1	12751	**1,44**
trophinin associated protein	Troap	78733	**0,83**
tropomodulin 2	Tmod2	50876	**1,46**
tryptase gamma 1	Tpsg1	26945	**0,65**
tryptophan hydroxylase 1	Tph1	21990	**0,76**
tryptophanyl-tRNA synthetase	Wars	22375	**0,71**
tubby-like protein 2	Tulp2	56734	**0,86**
tuberous sclerosis 2	Tsc2	22084	**0,85**
tubulin folding cofactor E-like	Tbcel	272589	**1,38**
tumor necrosis factor (ligand) superfamily, member 10	Tnfsf10	22035	**1,25**
tumor necrosis factor (ligand) superfamily, member 12	Tnfsf12	21944	**0,61**

tumor necrosis factor receptor superfamily, member 13c	Tnfrsf13c	72049	**1,35**
tumor necrosis factor receptor superfamily, member 18	Tnfrsf18	21936	**0,82**
tumor necrosis factor receptor superfamily, member 1a	Tnfrsf1a	21937	**1,33**
tumor necrosis factor receptor superfamily, member 1b	Tnfrsf1b	21938	**0,83**
tumor necrosis factor, alpha-induced protein 1 (endothelial)	Tnfaip1	21927	**1,47**
tumor necrosis factor, alpha-induced protein 3	Tnfaip3	21929	**1,16**
tumor protein D52-like 1	Tpd52l1	21987	**0,69**
tumor suppressor candidate 4	Tusc4	56032	**0,80**
tweety homolog 2 (Drosophila)	Ttyh2	117160	**1,17**
tweety homolog 3 (Drosophila)	Ttyh3	78339	**1,72**
two pore channel 1	Tpcn1	252972	**1,88**
tyrosine aminotransferase	Tat	234724	**1,22**
tyrosine kinase, non-receptor, 1	Tnk1	83813	**1,32**
ubinuclein 1	Ubn1	170644	**1,65**
ubiquilin 2	Ubqln2	54609	**1,55**
ubiquilin 4	Ubqln4	94232	**1,25**
ubiquinol cytochrome c reductase core protein 2	Uqcrc2	67003	**1,29**
ubiquinol-cytochrome c reductase core protein 1	Uqcrc1	22273	**0,57**
ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1	Uqcrfs1	66694	**0,64**
ubiquitin associated and SH3 domain containing, A	Ubash3a	328795	**1,29**
ubiquitin associated domain containing 1	Ubac1	98766	**0,79**
ubiquitin associated protein 2-like	Ubap2l	74383	**0,84**
ubiquitin carboxy-terminal hydrolase L1	Uchl1	22223	**1,41**
ubiquitin protein ligase E3 component n-recognin 1	Ubr1	22222	**0,85**
ubiquitin protein ligase E3 component n-recognin 2	Ubr2	224826	**1,81**
ubiquitin protein ligase E3 component n-recognin 4	Ubr4	69116	**1,45**
ubiquitin protein ligase E3 component n-recognin 5	Ubr5	70790	**1,42**
ubiquitin specific peptidase 2	Usp2	53376	**2,02**
ubiquitin specific peptidase 25	Usp25	30940	**1,43**
ubiquitin specific peptidase 3	Usp3	235441	**0,79**
ubiquitin specific peptidase 31	Usp31	76179	**1,22**
ubiquitin specific peptidase 33	Usp33	170822	**1,28**
ubiquitin specific peptidase 42	Usp42	76800	**1,32**
ubiquitin-conjugating enzyme E2, J1	Ube2j1	56228	**0,84**
ubiquitin-conjugating enzyme E2, J2 homolog (yeast)	Ube2j2	140499	**1,79**
ubiquitin-conjugating enzyme E2B, RAD6 homology (S. cerevisiae)	Ube2b	22210	**0,84**
ubiquitin-conjugating enzyme E2D 2	Ube2d2	56550	**1,32**
ubiquitin-conjugating enzyme E2E 2 (UBC4/5 homolog, yeast)	Ube2e2	218793	**1,23**
ubiquitin-conjugating enzyme E2G 2	Ube2g2	22213	**1,23**
ubiquitin-conjugating enzyme E2R 2	Ube2r2	67615	**1,54**
ubiquitin-like 4	Ubl4	27643	**0,72**
ubiquitin-like 5	Ubl5	66177	**0,56**
ubiquitin-like modifier activating enzyme 1	Uba1	22201	**0,69**
ubiquitin-like modifier activating enzyme 3	Uba3	22200	**0,63**
ubiquitously transcribed tetratricopeptide repeat gene, X chromosome	Utx	22289	**1,32**
ubiquitously transcribed tetratricopeptide repeat gene, Y chromosome	Uty	22290	**0,85**
unc-45 homolog B (C. elegans)	Unc45b	217012	**1,26**
unc-5 homolog A (C. elegans)	Unc5a	107448	**0,81**
unc-84 homolog B (C. elegans)	Unc84b	223697	**1,56**
unc-93 homolog B1 (C. elegans)	Unc93b1	54445	**1,29**
unconventional SNARE in the ER 1 homolog (S. cerevisiae)	Use1	67023	**0,50**
upstream binding transcription factor, RNA polymerase I	Ubtf	21429	**1,41**
uridine-cytidine kinase 2	Uck2	80914	**0,76**
uroporphyrinogen III synthase	Uros	22276	**0,83**
uroporphyrinogen decarboxylase	Urod	22275	**0,74**
v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	Kras	16653	**1,24**
v-abl Abelson murine leukemia viral oncogene homolog 2 (arg, Abelson-related gene)	Abl2	11352	**1,42**
v-crk sarcoma virus CT10 oncogene homolog (avian)	Crk	12928	**0,69**
v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)	Erbb2	13866	**1,42**
v-maf musculoaponeurotic fibrosarcoma oncogene family, protein B (avian)	Mafb	16658	**1,22**
v-maf musculoaponeurotic fibrosarcoma oncogene family, protein K (avian)	Mafk	17135	**1,29**
v-myc myelocytomatosis viral oncogene homolog 1, lung carcinoma derived (avian)	Mycl1	16918	**0,83**
v-myc myelocytomatosis viral related oncogene, neuroblastoma derived (avian)	Mycn	18109	**0,84**
v-raf-leukemia viral oncogene 1	Raf1	110157	**0,80**
v-ral simian leukemia viral oncogene homolog A (ras related)	Rala	56044	**1,55**
v-ral simian leukemia viral oncogene homolog B (ras related)	Ralb	64143	**0,74**
vaccinia related kinase 2	Vrk2	69922	**0,80**
vacuolar protein sorting 16 (yeast)	Vps16	80743	**0,85**
vacuolar protein sorting 26 homolog B (yeast)	Vps26b	69091	**1,25**
vacuolar protein sorting 28 (yeast)	Vps28	66914	**0,60**
vacuolar protein sorting 35	Vps35	65114	**0,70**
vacuolar protein sorting 37C (yeast)	Vps37c	107305	**1,59**
vacuolar protein sorting 39 (yeast)	Vps39	269338	**1,40**
vacuolar protein sorting 41 (yeast)	Vps41	218035	**0,83**
vang-like 1 (van gogh, Drosophila)	Vangl1	229658	**1,17**
vanin 3	Vnn3	26464	**1,16**
vascular cell adhesion molecule 1	Vcam1	22329	**1,33**
vasoactive intestinal polypeptide	Vip	22353	**1,52**
vasorin	Vasn	246154	**1,17**
vav 3 oncogene	Vav3	57257	**0,84**
versican	Vcan	13003	**0,88**
vesicle amine transport protein 1 homolog (T californica)	Vat1	26949	**1,21**
vesicle transport through interaction with t-SNAREs homolog 1A (yeast)	Vti1a	53611	**1,30**
vesicle-associated membrane protein 1	Vamp1	22317	**1,28**
vesicle-associated membrane protein 4	Vamp4	53330	**1,30**
vesicle-associated membrane protein 7	Vamp7	20955	**0,81**

vesicle-associated membrane protein 8	Vamp8	22320	**0,62**
vesicle-associated membrane protein, associated protein A	Vapa	30960	**1,26**
vesicle-associated membrane protein, associated protein B and C	Vapb	56491	**1,28**
villin 1	Vil1	22349	**1,20**
vitamin D receptor	Vdr	22337	**1,64**
vomeronasal 1 receptor, A1	V1ra1	22296	**0,82**
vomeronasal 1, receptor B2	V1rb2	24112	**0,82**
von Hippel-Lindau syndrome homolog	Vhlh	22346	**1,37**
von Willebrand factor A domain containing 2	Vwa2	240675	**0,82**
wingless-related MMTV integration site 3A	Wnt3a	22416	**1,19**
wingless-related MMTV integration site 6	Wnt6	22420	**1,21**
wingless-type MMTV integration site 9A	Wnt9a	216795	**1,20**
xenotropic and polytropic retrovirus receptor 1	Xpr1	19775	**1,53**
xylulokinase homolog (H. influenzae)	Xylb	102448	**1,19**
yes-associated protein 1	Yap1	22601	**1,29**
zinc binding alcohol dehydrogenase, domain containing 2	Zadh2	225791	**1,34**
zinc finger (CCCH type), RNA binding motif and serine/arginine rich 1	Zrsr1	22183	**1,34**
zinc finger CCCH type, antiviral 1	Zc3hav1	78781	**1,47**
zinc finger E-box binding homeobox 1	Zeb1	21417	**1,40**
zinc finger E-box binding homeobox 2	Zeb2	24136	**0,84**
zinc finger and AT hook domain containing	Zfat	380993	**1,33**
zinc finger and BTB domain containing 1	Zbtb1	268564	**1,16**
zinc finger and BTB domain containing 20	Zbtb20	56490	**1,60**
zinc finger and BTB domain containing 22	Zbtb22	81630	**1,24**
zinc finger and BTB domain containing 4	Zbtb4	75580	**1,26**
zinc finger and BTB domain containing 6	Zbtb6	241322	**0,85**
zinc finger and BTB domain containing 7B	Zbtb7b	22724	**1,19**
zinc finger and BTB domain containing 7a	Zbtb7a	16969	**1,87**
zinc finger and SCAN domain containing 21	Zscan21	22697	**1,32**
zinc finger protein 110	Zfp110	65020	**0,81**
zinc finger protein 148	Zfp148	22661	**0,76**
zinc finger protein 2	Zfp2	22678	**0,80**
zinc finger protein 260	Zfp260	26466	**0,79**
zinc finger protein 263	Zfp263	74120	**0,85**
zinc finger protein 282	Zfp282	101095	**0,84**
zinc finger protein 292	Zfp292	30046	**0,87**
zinc finger protein 318	Zfp318	57908	**1,24**
zinc finger protein 36	Zfp36	22695	**1,41**
zinc finger protein 362	Zfp362	230761	**1,24**
zinc finger protein 367	Zfp367	238673	**1,35**
zinc finger protein 386 (Kruppel-like)	Zfp386	56220	**0,77**
zinc finger protein 467	Zfp467	68910	**1,30**
zinc finger protein 503	Zfp503	218820	**1,70**
zinc finger protein 523	Zfp523	224656	**1,31**
zinc finger protein 53	Zfp53	24132	**1,57**
zinc finger protein 54	Zfp54	22712	**0,83**
zinc finger protein 60	Zfp60	22718	**0,83**
zinc finger protein 639	Zfp639	67778	**0,86**
zinc finger protein 650	Zfp650	68795	**1,26**
zinc finger protein 664	Zfp664	269704	**0,77**
zinc finger protein 7	Zfp7	223669	**0,87**
zinc finger protein 810	Zfp810	235050	**0,80**
zinc finger protein 87	Zfp87	170763	**1,29**
zinc finger protein 9	Zfp9	22750	**0,84**
zinc finger protein X-linked	Zfx	22764	**1,27**
zinc finger protein, multitype 2	Zfpm2	22762	**1,27**
zinc finger with KRAB and SCAN domains 14	Zkscan14	67235	**0,84**
zinc finger, CCCH-type with G patch domain	Zgpat	229007	**0,81**
zinc finger, CCHC domain containing 11	Zcchc11	230594	**1,65**
zinc finger, DHHC domain containing 5	Zdhhc5	228136	**0,80**
zinc finger, DHHC domain containing 8	Zdhhc8	27801	**1,34**
zinc finger, DHHC domain containing 9	Zdhhc9	208884	**1,39**
zinc finger, FYVE domain containing 20	Zfyve20	78287	**0,90**
zinc finger, FYVE domain containing 9	Zfyve9	230597	**1,21**
zinc finger, HIT domain containing 1	Znhit1	70103	**0,68**
zinc finger, HIT type 3	Znhit3	448850	**0,73**
zinc finger, RAN-binding domain containing 1	Zranb1	360216	**1,27**
zinc finger, RAN-binding domain containing 2	Zranb2	53861	**1,34**
zinc finger, SWIM domain containing 6	Zswim6	67263	**1,45**
zinc finger, matrin-like	Zfml	18139	**0,85**
zinc fingers and homeoboxes 1	Zhx1	22770	**0,81**
zona pellucida glycoprotein 2	Zp2	22787	**1,21**

Table 22: Gene targets in the therapy group (high dose flavone) filtered according to GO "glucose metabolic process"

gene name	gene symbol	reg. fac.
2,3-bisphosphoglycerate mutase	Bpgm	**0,71**
aldolase 3, C isoform	Aldoc	**1,27**
Bcl-associated death promoter	Bad	**0,69**
fructose bisphosphatase 1	Fbp1	**1,23**
glycerol phosphate dehydrogenase 2, mitochondrial	Gpd2	**1,49**
hexose-6-phosphate dehydrogenase (glucose 1-dehydrogenase)	H6pd	**0,78**
insulin II	Ins2	**1,25**
malate dehydrogenase 1, NAD (soluble)	Mdh1	**0,82**
peroxisome proliferator activated receptor alpha	Ppara	**1,66**
phosphatidylinositol 3-kinase, catalytic, alpha polypeptide	Pik3ca	**1,38**
phosphoenolpyruvate carboxykinase 1, cytosolic	Pck1	**0,72**
phosphofructokinase, liver, B-type	Pfkl	**1,60**
phosphofructokinase, muscle	Pfkm	**1,27**
phosphoglucomutase 1	Pgm1	**0,77**
phosphoglucomutase 2	Pgm2	**0,77**
phosphoglucomutase 3	Pgm3	**0,62**
phosphoglucomutase 5	Pgm5	**1,40**
pyruvate dehydrogenase kinase, isoenzyme 4	Pdk4	**1,79**
transaldolase 1	Taldo1	**0,75**

Table 23: Gene targets in the therapy group (high dose flavone) filtered according to GO "fatty acid metabolic process"

gene name	gene symbol	reg. fac.
acetoacetyl-CoA synthetase	Aacs	**0,76**
acyl-CoA synthetase long-chain family member 3	Acsl3	**1,75**
acyl-CoA synthetase long-chain family member 4	Acsl4	**1,33**
acyl-CoA synthetase medium-chain family member 3	Acsm3	**0,62**
acyl-CoA thioesterase 11	Acot11	**1,63**
acyl-CoA thioesterase 4	Acot4	**1,36**
acyl-CoA thioesterase 8	Acot8	**0,82**
acyl-Coenzyme A dehydrogenase, short/branched chain	Acadsb	**1,37**
acyl-Coenzyme A dehydrogenase, very long chain	Acadvl	**0,77**
acyl-Coenzyme A oxidase 2, branched chain	Acox2	**1,23**
angiotensinogen (serpin peptidase inhibitor, clade A, member 8)	Agt	**0,78**
ankyrin repeat domain 23	Ankrd23	**1,17**
arachidonate lipoxygenase 3	Aloxe3	**1,23**
arginyl aminopeptidase (aminopeptidase B)	Rnpep	**0,71**
carboxylesterase 3	Ces3	**0,86**
caveolin, caveolae protein 1	Cav1	**1,41**
cytochrome b-5	Cyb5	**0,68**
degenerative spermatocyte homolog 1 (Drosophila)	Degs1	**1,49**
ELOVL family member 6, elongation of long chain fatty acids (yeast)	Elovl6	**1,28**
enoyl coenzyme A hydratase 1, peroxisomal	Ech1	**0,60**
enoyl Coenzyme A hydratase, short chain, 1, mitochondrial	Echs1	**0,57**
hydroxyacyl-Coenzyme A dehydrogenase	Hadh	**0,80**
hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase (trifunctional protein), alpha subunit	Hadha	**0,69**
lysophospholipase 2	Lypla2	**1,72**
lysophospholipase 3	Lypla3	**0,84**
malonyl CoA:ACP acyltransferase (mitochondrial)	Mcat	**0,83**
mitochondrial trans-2-enoyl-CoA reductase	Mecr	**0,74**
peroxisome proliferator activated receptor alpha	Ppara	**1,66**
podoplanin	Pdpn	**1,35**
propionyl Coenzyme A carboxylase, beta polypeptide	Pccb	**0,67**
prostaglandin E synthase 2	Ptges2	**0,73**
solute carrier family 27 (fatty acid transporter), member 4	Slc27a4	**1,48**
tumor necrosis factor receptor superfamily, member 1a	Tnfrsf1a	**1,33**

Table 24: Gene targets in the therapy group (high dose flavone) filtered according to GO "amino acid metabolic process"

gene name	gene symbol	reg. fac.
4-hydroxyphenylpyruvate dioxygenase-like	Hpdl	**0,85**
4-hydroxyphenylpyruvic acid dioxygenase	Hpd	**0,55**
6-pyruvoyl-tetrahydropterin synthase	Pts	**0,72**
acireductone dioxygenase 1	Adi1	**0,73**

aldehyde dehydrogenase family 6, subfamily A1	Aldh6a1	**1,45**
arginase type II	Arg2	**0,74**
arginyl-tRNA synthetase	Rars	**0,73**
arginyl-tRNA synthetase 2, mitochondrial (putative)	Rars2	**0,71**
asparagine synthetase	Asns	**0,69**
aspartyl-tRNA synthetase	Dars	**0,69**
aspartyl-tRNA synthetase 2 (mitochondrial)	Dars2	**0,87**
ATPase, Cu++ transporting, alpha polypeptide	Atp7a	**1,57**
ceroid lipofuscinosis, neuronal 3, juvenile (Batten, Spielmeyer-Vogt disease)	Cln3	**1,35**
cystathionine beta-synthase	Cbs	**0,78**
glutamate dehydrogenase 1	Glud1	**0,78**
glutaminase	Gls	**1,54**
glutathione transferase zeta 1 (maleylacetoacetate isomerase)	Gstz1	**0,74**
interleukin 4 induced 1	Il4i1	**1,22**
N-acetylglutamate synthase	Nags	**0,87**
PDZ domain containing 2	Pdzd2	**1,27**
phosphoserine aminotransferase 1	Psat1	**0,84**
phosphoserine phosphatase	Psph	**0,85**
pyrroline-5-carboxylate reductase 1	Pycr1	**0,79**
pyrroline-5-carboxylate reductase-like	Pycrl	**0,69**
serine hydroxymethyltransferase 1 (soluble)	Shmt1	**0,72**
threonyl-tRNA synthetase	Tars	**0,74**
tryptophan hydroxylase 1	Tph1	**0,76**
tryptophanyl-tRNA synthetase	Wars	**0,71**
tyrosine aminotransferase	Tat	**1,22**

Table 25: Gene targets in the therapy group (high dose flavone) filtered according to GO "tricarboxylic acid cycle"

gene name	gene symbol	**reg. fac.**
fumarate hydratase 1	Fh1	**0,61**
isocitrate dehydrogenase 3 (NAD+) alpha	Idh3a	**0,77**
malate dehydrogenase 1, NAD (soluble)	Mdh1	**0,82**
succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	Sdhb	**0,59**
succinate dehydrogenase complex, subunit D, integral membrane protein	Sdhd	**0,57**
succinate-CoA ligase, GDP-forming, alpha subunit	Suclg1	**0,48**

Table 26: Gene targets in the therapy group (high dose flavone) filtered according to GO "electron transport chain"

gene name	gene symbol	**reg. fac.**
dihydrolipoamide dehydrogenase	Dld	**0,72**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5	Ndufa5	**0,70**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7 (B14.5a)	Ndufa7	**0,47**
NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9	Ndufb9	**0,55**
NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2	Ndufc2	**0,51**
NADH dehydrogenase (ubiquinone) Fe-S protein 4	Ndufs4	**0,58**
NADH dehydrogenase (ubiquinone) Fe-S protein 7	Ndufs7	**0,60**
NADH dehydrogenase (ubiquinone) flavoprotein 1	Ndufv1	**0,64**
peroxisome proliferative activated receptor, gamma, coactivator 1 alpha	Ppargc1a	**1,66**

Table 27: Gene targets in the therapy group (high dose flavone) filtered according to GO "transporters"

gene name	gene symbol	**reg. fac.**
5-hydroxytryptamine (serotonin) receptor 3A	Htr3a	**1,27**
acetyl-Coenzyme A carboxylase beta	Acacb	**1,28**
adaptor protein complex AP-1, sigma 1	Ap1s1	**1,19**
adaptor protein complex AP-2, alpha 2 subunit	Ap2a2	**0,83**
adaptor-related protein complex 1, sigma 2 subunit	Ap1s2	**1,26**
adaptor-related protein complex 3, beta 1 subunit	Ap3b1	**0,85**
adaptor-related protein complex 3, beta 2 subunit	Ap3b2	**1,16**
adipose differentiation related protein	Adfp	**1,33**
ADP-ribosylation factor 2	Arf2	**0,83**
ADP-ribosylation factor interacting protein 1	Arfip1	**1,25**
advanced glycosylation end product-specific receptor	Ager	**1,29**
aftiphilin	Aftph	**1,40**
amiloride-sensitive cation channel 2, neuronal	Accn2	**1,23**
amphiphysin	Amph	**1,24**
amyloid beta (A4) precursor protein-binding, family B, member 2	Apbb2	**1,28**
angiotensin II receptor, type 1a	Agtr1a	**1,26**

ankyrin 1, erythroid	Ank1	**1,34**
ankyrin repeat domain 27 (VPS9 domain)	Ankrd27	**1,28**
apolipoprotein B	Apob	**1,57**
aquaporin 1	Aqp1	**0,62**
aquaporin 4	Aqp4	**1,33**
archain 1	Arcn1	**0,80**
ATP synthase, H+ transporting mitochondrial F1 complex, beta subunit	Atp5b	**0,57**
ATP synthase, H+ transporting, mitochondrial F1 complex, alpha subunit, isoform 1	Atp5a1	**0,60**
ATP synthase, H+ transporting, mitochondrial F1 complex, delta subunit	Atp5d	**0,54**
ATPase type 13A2	Atp13a2	**1,26**
ATPase, aminophospholipid transporter (APLT), class I, type 8A, member 1	Atp8a1	**1,37**
ATPase, Ca++ transporting, type 2C, member 2	Atp2c2	**0,69**
ATPase, class VI, type 11A	Atp11a	**1,44**
ATPase, class VI, type 11B	Atp11b	**1,33**
Atpase, class VI, type 11C	Atp11c	**0,85**
ATPase, Cu++ transporting, alpha polypeptide	Atp7a	**1,57**
ATPase, H+ transporting, lysosomal accessory protein 1	Atp6ap1	**1,34**
ATPase, H+ transporting, lysosomal V0 subunit A2	Atp6v0a2	**1,62**
ATPase, H+ transporting, lysosomal V0 subunit B	Atp6v0b	**1,24**
ATPase, H+ transporting, lysosomal V0 subunit E	Atp6v0e	**0,71**
ATPase, H+ transporting, lysosomal V0 subunit E2	Atp6v0e2	**1,39**
ATPase, H+ transporting, lysosomal V1 subunit B2	Atp6v1b2	**1,32**
ATPase, H+ transporting, lysosomal V1 subunit C1	Atp6v1c1	**1,23**
ATPase, H+ transporting, lysosomal V1 subunit H	Atp6v1h	**0,77**
ATPase, H+/K+ transporting, nongastric, alpha polypeptide	Atp12a	**1,57**
ATP-binding cassette, sub-family A (ABC1), member 7	Abca7	**1,53**
ATP-binding cassette, sub-family A (ABC1), member 8a	Abca8a	**1,42**
ATP-binding cassette, sub-family B (MDR/TAP), member 1A	Abcb1a	**1,60**
ATP-binding cassette, sub-family B (MDR/TAP), member 1B	Abcb1b	**1,25**
ATP-binding cassette, sub-family B (MDR/TAP), member 6	Abcb6	**1,50**
ATP-binding cassette, sub-family B (MDR/TAP), member 7	Abcb7	**0,86**
ATP-binding cassette, sub-family B (MDR/TAP), member 8	Abcb8	**0,82**
ATP-binding cassette, sub-family C (CFTR/MRP), member 1	Abcc1	**1,41**
ATP-binding cassette, sub-family C (CFTR/MRP), member 12	Abcc12	**1,33**
ATP-binding cassette, sub-family C (CFTR/MRP), member 3	Abcc3	**1,39**
ATP-binding cassette, sub-family C (CFTR/MRP), member 4	Abcc4	**1,30**
ATP-binding cassette, sub-family C (CFTR/MRP), member 9	Abcc9	**1,25**
ATP-binding cassette, sub-family D (ALD), member 2	Abcd2	**0,87**
ATP-binding cassette, sub-family G (WHITE), member 2	Abcg2	**0,82**
ATX1 (antioxidant protein 1) homolog 1 (yeast)	Atox1	**0,56**
autophagy-related 10 (yeast)	Atg10	**1,55**
autophagy-related 4B (yeast)	Atg4b	**1,24**
autophagy-related 9A (yeast)	Atg9a	**1,23**
basic helix-loop-helix domain containing, class B, 8	Bhlhb8	**0,79**
B-box and SPRY domain containing	Bspry	**0,74**
BCL2/adenovirus E1B interacting protein 1, NIP1	Bnip1	**0,80**
beta-site APP-cleaving enzyme 2	Bace2	**0,65**
bicaudal D homolog 2 (Drosophila)	Bicd2	**1,27**
blocked early in transport 1 homolog (S. cerevisiae)-like	Bet1l	**0,84**
cadherin 17	Cdh17	**1,31**
calcium channel, voltage-dependent, alpha2/delta subunit 1	Cacna2d1	**1,39**
calcium channel, voltage-dependent, beta 4 subunit	Cacnb4	**0,85**
calcium/calmodulin-dependent protein kinase II gamma	Camk2g	**1,30**
caseinolytic peptidase X (E.coli)	Clpx	**1,30**
caspase 1	Casp1	**0,64**
catenin (cadherin associated protein), beta 1	Ctnnb1	**0,65**
caveolin, caveolae protein 1	Cav1	**1,41**
CD47 antigen (Rh-related antigen, integrin-associated signal transducer)	Cd47	**1,31**
CDC42 small effector 2	Cdc42se2	**1,26**
centrosomal protein 290	Cep290	**0,86**
ceroid lipofuscinosis, neuronal 3, juvenile (Batten, Spielmeyer-Vogt disease)	Cln3	**1,35**
ceroid-lipofuscinosis, neuronal 8	Cln8	**0,88**
chloride channel 2	Clcn2	**0,78**
chloride channel 4-2	Clcn4-2	**1,21**
chloride channel calcium activated 2	Clca2	**0,82**
chloride channel calcium activated 3	Clca3	**0,68**
chloride intracellular channel 1	Clic1	**0,58**
cholinergic receptor, nicotinic, epsilon polypeptide	Chrne	**1,15**
chromatin modifying protein 1B	Chmp1b	**1,37**
chromatin modifying protein 2A	Chmp2a	**0,55**
chromatin modifying protein 4B	Chmp4b	**1,76**
chromatin modifying protein 4C	Chmp4c	**1,31**
coatomer protein complex, subunit beta 2 (beta prime)	Copb2	**0,64**
coatomer protein complex, subunit gamma	Copg	**0,75**
collagen, type IV, alpha 4	Col4a4	**1,26**
collagen, type V, alpha 1	Col5a1	**1,35**
collagen, type XIV, alpha 1	Col14a1	**1,26**

collagen, type XVI, alpha 1	Col16a1	**1,43**
collagen, type XVII, alpha 1	Col17a1	**0,86**
collagen, type XXIV, alpha 1	Col24a1	**0,85**
collagen, type XXVII, alpha 1	Col27a1	**1,26**
complexin 1	Cplx1	**1,20**
component of oligomeric golgi complex 2	Cog2	**0,77**
component of oligomeric golgi complex 3	Cog3	**1,33**
component of oligomeric golgi complex 4	Cog4	**0,73**
component of oligomeric golgi complex 6	Cog6	**0,75**
cryptochrome 2 (photolyase-like)	Cry2	**1,37**
cyclic nucleotide gated channel alpha 3	Cnga3	**1,29**
cystinosis, nephropathic	Ctns	**1,25**
cytidine monophospho-N-acetylneuraminic acid hydroxylase	Cmah	**0,71**
cytochrome b-245, alpha polypeptide	Cyba	**0,59**
cytochrome b-245, beta polypeptide	Cybb	**1,22**
cytochrome b-5	Cyb5	**0,68**
cytochrome c oxidase, subunit XVII assembly protein homolog (yeast)	Cox17	**1,35**
cytochrome c-1	Cyc1	**0,58**
dedicator of cyto-kinesis 1	Dock1	**0,84**
DENN/MADD domain containing 1A	Dennd1a	**1,31**
diazepam binding inhibitor	Dbi	**0,58**
disrupted in renal carcinoma 2 (human)	Dirc2	**0,84**
DNA segment, Chr 3, University of California at Los Angeles 1	D3Ucla1	**0,54**
DnaJ (Hsp40) homolog, subfamily C, member 14	Dnajc14	**1,57**
DnaJ (Hsp40) homolog, subfamily C, member 19	Dnajc19	**1,58**
drebrin-like	Dbnl	**0,71**
dynamin 3	Dnm3	**1,31**
dynein cytoplasmic 1 heavy chain 1	Dync1h1	**1,58**
dynein cytoplasmic 2 heavy chain 1	Dync2h1	**1,17**
dynein light chain roadblock-type 1	Dynlrb1	**0,62**
dynein, axonemal, heavy chain 17	Dnahc17	**0,85**
ELKS/RAB6-interacting/CAST family member 1	Erc1	**1,24**
enabled homolog (Drosophila)	Enah	**1,60**
endothelial differentiation, sphingolipid G-protein-coupled receptor, 3	Edg3	**1,22**
engulfment and cell motility 1, ced-12 homolog (C. elegans)	Elmo1	**1,20**
epsin 1	Epn1	**1,29**
Erbb2 interacting protein	Erbb2ip	**1,82**
ERGIC and golgi 2	Ergic2	**0,81**
eukaryotic translation initiation factor 2 alpha kinase 3	Eif2ak3	**0,81**
exocyst complex component 2	Exoc2	**1,39**
exocyst complex component 5	Exoc5	**1,38**
exocyst complex component 7	Exoc7	**0,83**
fatty acid binding protein 2, intestinal	Fabp2	**0,64**
Fc receptor, IgG, high affinity I	Fcgr1	**0,82**
ficolin A	Fcna	**0,69**
filamin, alpha	Flna	**1,48**
forkhead box O3a	Foxo3a	**1,35**
formin binding protein 1	Fnbp1	**1,42**
free fatty acid receptor 1	Ffar1	**1,31**
FXYD domain-containing ion transport regulator 3	Fxyd3	**0,50**
FXYD domain-containing ion transport regulator 6	Fxyd6	**1,32**
G protein-coupled receptor associated sorting protein 1	Gprasp1	**1,50**
gamma-aminobutyric acid (GABA-A) receptor, subunit beta 2	Gabrb2	**1,50**
gamma-aminobutyric acid receptor associated protein	Gabarap	**0,59**
GATA binding protein 2	Gata2	**1,26**
glucagon	Gcg	**0,58**
glutamate dehydrogenase 1	Glud1	**0,78**
glutamate receptor ionotropic, NMDA3A	Grin3a	**1,48**
glutamate receptor, ionotropic, kainate 5 (gamma 2)	Grik5	**1,30**
glutamate receptor, ionotropic, NMDA1 (zeta 1)	Grin1	**1,30**
glutamate receptor, ionotropic, NMDA3B	Grin3b	**1,35**
glutathione S-transferase kappa 1	Gstk1	**0,64**
glycolipid transfer protein	Gltp	**1,46**
golgi associated PDZ and coiled-coil motif containing	Gopc	**0,81**
golgi integral membrane protein 4	Golim4	**1,26**
GRP1 (general receptor for phosphoinositides 1)-associated scaffold protein	Grasp	**1,26**
guanosine diphosphate (GDP) dissociation inhibitor 1	Gdi1	**1,55**
guanosine diphosphate (GDP) dissociation inhibitor 2	Gdi2	**1,28**
HECT, UBA and WWE domain containing 1	Huwe1	**1,29**
hephaestin	Heph	**1,44**
HGF-regulated tyrosine kinase substrate	Hgs	**1,31**
high density lipoprotein (HDL) binding protein	Hdlbp	**0,67**
hydrogen voltage-gated channel 1	Hvcn1	**1,24**
hyperpolarization-activated, cyclic nucleotide-gated K+ 4	Hcn4	**1,30**
immunoglobulin heavy constant gamma 1 (G1m marker)	Ighg1	**0,62**
insulin II	Ins2	**1,25**
insulin-like growth factor 2 receptor	Igf2r	**1,32**

integrin alpha V	Itgav	**1,55**
interferon gamma	Ifng	**0,82**
interleukin 20	Il20	**1,20**
K+ voltage-gated channel, subfamily S, 1	Kcns1	**1,25**
karyopherin (importin) alpha 1	Kpna1	**0,87**
karyopherin (importin) alpha 4	Kpna4	**1,35**
karyopherin (importin) alpha 6	Kpna6	**1,38**
karyopherin (importin) beta 1	Kpnb1	**1,26**
KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	Kdelr3	**0,64**
keratin 20	Krt20	**1,22**
kinesin family member 11	Kif11	**0,81**
kinesin family member 13A	Kif13a	**0,80**
kinesin family member 17	Kif17	**1,23**
kinesin family member 1A	Kif1a	**1,21**
kinesin family member 1B	Kif1b	**1,28**
kinesin family member 20A	Kif20a	**0,85**
kinesin family member 3B	Kif3b	**0,84**
kinesin family member 3C	Kif3c	**1,28**
kinesin family member 5B	Kif5b	**1,39**
kinesin family member 5C	Kif5c	**1,35**
kinesin family member C2	Kifc2	**1,53**
kinesin light chain 1	Klc1	**1,62**
kinesin light chain 2	Klc2	**0,84**
large subunit GTPase 1 homolog (S. cerevisiae)	Lsg1	**0,87**
lectin, mannose-binding, 1	Lman1	**0,76**
lin-7 homolog B (C. elegans)	Lin7b	**1,41**
lipase maturation factor 1	Lmf1	**0,83**
lipase, hepatic	Lipc	**0,86**
lipocalin 2	Lcn2	**0,86**
low density lipoprotein receptor adaptor protein 1	Ldlrap1	**0,78**
low density lipoprotein receptor-related protein 1	Lrp1	**1,17**
low density lipoprotein receptor-related protein 11	Lrp11	**1,28**
low density lipoprotein receptor-related protein 4	Lrp4	**1,37**
low density lipoprotein-related protein 12	Lrp12	**1,60**
LPS-responsive beige-like anchor	Lrba	**1,33**
lymphatic vessel endothelial hyaluronan receptor 1	Lyve1	**1,33**
lymphocyte antigen 75	Ly75	**1,35**
lysosomal-associated protein transmembrane 5	Laptm5	**1,33**
mannose-6-phosphate receptor binding protein 1	M6prbp1	**0,75**
megalencephalic leukoencephalopathy with subcortical cysts 1 homolog (human)	Mlc1	**1,20**
membrane-associated ring finger (C3HC4) 2	March2	**1,30**
metaxin 2	Mtx2	**0,70**
microtubule-actin crosslinking factor 1	Macf1	**1,45**
milk fat globule-EGF factor 8 protein	Mfge8	**1,33**
mitochondrial carrier homolog 1 (C. elegans)	Mtch1	**0,71**
mitochondrial ribosomal protein S23	Mrps23	**0,65**
mitogen-activated protein kinase 8 interacting protein 3	Mapk8ip3	**1,23**
MON2 homolog (yeast)	Mon2	**1,28**
multiple coagulation factor deficiency 2	Mcfd2	**0,83**
muted	Muted	**0,82**
myosin VI	Myo6	**1,39**
myosin VIIA and Rab interacting protein	Myrip	**0,85**
myosin, heavy polypeptide 14	Myh14	**1,60**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 10	Ndufa10	**0,67**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13	Ndufa13	**0,75**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2	Ndufa2	**0,70**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 3	Ndufa3	**0,55**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4	Ndufa4	**0,57**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5	Ndufa5	**0,70**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6 (B14)	Ndufa6	**0,65**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7 (B14.5a)	Ndufa7	**0,47**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8	Ndufa8	**0,61**
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9	Ndufa9	**0,55**
NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 10	Ndufb10	**0,66**
NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 11	Ndufb11	**0,53**
NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5	Ndufb5	**0,51**
NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6	Ndufb6	**0,56**
NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9	Ndufb9	**0,55**
NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2	Ndufc2	**0,51**
NADH dehydrogenase (ubiquinone) Fe-S protein 4	Ndufs4	**0,58**
NADH dehydrogenase (ubiquinone) Fe-S protein 6	Ndufs6	**0,66**
NADH dehydrogenase (ubiquinone) Fe-S protein 7	Ndufs7	**0,60**
NADH dehydrogenase (ubiquinone) Fe-S protein 8	Ndufs8	**0,45**
NADH dehydrogenase (ubiquinone) flavoprotein 1	Ndufv1	**0,64**
NADH dehydrogenase (ubiquinone) flavoprotein 2	Ndufv2	**0,62**
naked cuticle 2 homolog (Drosophila)	Nkd2	**1,31**
neuroglobin	Ngb	**1,30**

Niemann Pick type C2	Npc2	**0,69**
NMD3 homolog (S. cerevisiae)	Nmd3	**0,73**
nuclear distribution gene E-like homolog 1 (A. nidulans)	Ndel1	**0,74**
nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	Nfkbia	**1,49**
nuclear pore membrane protein 121	Pom121	**1,62**
nucleoporin 107	Nup107	**0,84**
nucleoporin 133	Nup133	**0,85**
nucleoporin 155	Nup155	**0,87**
nucleoporin 37	Nup37	**0,77**
open reading frame 9	ORF9	**0,61**
oxysterol binding protein 2	Osbp2	**1,47**
oxysterol binding protein-like 11	Osbpl11	**1,30**
oxysterol binding protein-like 2	Osbpl2	**0,69**
oxysterol binding protein-like 3	Osbpl3	**1,48**
P140 gene	RP23-157O10.7	**1,36**
pallidin	Pldn	**0,84**
palmitoyl-protein thioesterase 1	Ppt1	**0,77**
pannexin 1	Panx1	**1,37**
PDZ domain containing 11	Pdzd11	**0,73**
peripheral myelin protein 2	Pmp2	**1,36**
peroxiredoxin 1	Prdx1	**0,67**
peroxisome proliferator activated receptor gamma	Pparg	**0,76**
phosphatidylinositol transfer protein, alpha	Pitpna	**1,26**
phosphatidylinositol transfer protein, membrane-associated 2	Pitpnm2	**1,31**
phosphodiesterase 3B, cGMP-inhibited	Pde3b	**1,22**
phosphofurin acidic cluster sorting protein 1	Pacs1	**1,26**
phosphoglucomutase 1	Pgm1	**0,77**
phospholamban	Pln	**1,26**
phospholipase A2 receptor 1	Pla2r1	**1,31**
phospholipid transfer protein	Pltp	**0,87**
plasma membrane proteolipid	Pllp	**0,68**
podoplanin	Pdpn	**1,35**
polycystic kidney disease 1 homolog	Pkd1	**1,25**
polymerase (DNA directed), alpha 2	Pola2	**0,84**
post-GPI attachment to proteins 1	Pgap1	**1,35**
potassium channel, subfamily K, member 1	Kcnk1	**0,65**
potassium channel, subfamily K, member 5	Kcnk5	**0,81**
potassium inwardly rectifying channel, subfamily J, member 11	Kcnj11	**1,32**
potassium inwardly-rectifying channel, subfamily J, member 12	Kcnj12	**1,21**
potassium inwardly-rectifying channel, subfamily K, member 6	Kcnk6	**0,63**
potassium voltage gated channel, Shab-related subfamily, member 1	Kcnb1	**1,21**
potassium voltage-gated channel, Isk-related subfamily, gene 2	Kcne2	**0,86**
potassium voltage-gated channel, Isk-related subfamily, gene 3	Kcne3	**0,50**
potassium voltage-gated channel, Isk-related subfamily, gene 4	Kcne4	**1,23**
potassium voltage-gated channel, Isk-related subfamily, member 1	Kcne1	**0,82**
potassium voltage-gated channel, subfamily H (eag-related), member 3	Kcnh3	**1,25**
proprotein convertase subtilisin/kexin type 4	Pcsk4	**1,24**
protein kinase C and casein kinase substrate in neurons 2	Pacsin2	**1,38**
protein phosphatase 3, catalytic subunit, alpha isoform	Ppp3ca	**1,27**
PTEN induced putative kinase 1	Pink1	**1,45**
purinergic receptor P2X, ligand-gated ion channel 4	P2rx4	**0,82**
purinergic receptor P2X-like 1, orphan receptor	P2rxl1	**1,26**
RAB guanine nucleotide exchange factor (GEF) 1	Rabgef1	**0,85**
Rab interacting lysosomal protein	Rilp	**1,19**
RAB1, member RAS oncogene family	Rab1	**0,67**
RAB11 family interacting protein 1 (class I)	Rab11fip1	**1,21**
RAB11 family interacting protein 5 (class I)	Rab11fip5	**1,38**
RAB15, member RAS oncogene family	Rab15	**0,64**
RAB17, member RAS oncogene family	Rab17	**1,47**
RAB18, member RAS oncogene family	Rab18	**1,30**
RAB20, member RAS oncogene family	Rab20	**0,76**
RAB21, member RAS oncogene family	Rab21	**1,23**
RAB25, member RAS oncogene family	Rab25	**0,49**
RAB27A, member RAS oncogene family	Rab27a	**0,85**
RAB27b, member RAS oncogene family	Rab27b	**0,72**
RAB33B, member of RAS oncogene family	Rab33b	**1,37**
RAB37, member of RAS oncogene family	Rab37	**0,84**
RAB3A, member RAS oncogene family	Rab3a	**1,23**
RAB3D, member RAS oncogene family	Rab3d	**0,76**
Rab40c, member RAS oncogene family	Rab40c	**0,87**
RAB4A, member RAS oncogene family	Rab4a	**0,81**
RAB6B, member RAS oncogene family	Rab6b	**1,56**
RAB7, member RAS oncogene family-like 1	Rab7l1	**0,73**
RAB9, member RAS oncogene family	Rab9	**1,30**
Rac GTPase-activating protein 1	Racgap1	**0,79**
RAN binding protein 1	Ranbp1	**0,54**
RAN binding protein 3	Ranbp3	**1,29**

RAN binding protein 5	Ranbp5	**1,20**
receptor (calcitonin) activity modifying protein 1	Ramp1	**0,65**
receptor (calcitonin) activity modifying protein 3	Ramp3	**1,17**
regulating synaptic membrane exocytosis 1	Rims1	**1,61**
reticulon 3	Rtn3	**1,34**
retinaldehyde binding protein 1	Rlbp1	**0,82**
retinol binding protein 3, interstitial	Rbp3	**1,29**
retinol binding protein 4, plasma	Rbp4	**0,63**
retinol binding protein 7, cellular	Rbp7	**0,80**
Rho GTPase activating protein 17	Arhgap17	**1,27**
ribosome binding protein 1	Rrbp1	**0,71**
RIKEN cDNA 1110001D15 gene	1110001D15Rik	**0,84**
ring finger and FYVE like domain containing protein	Rffl	**1,25**
RPA interacting protein	Rpain	**0,84**
SAP30-like	Sap30l	**1,39**
SAR1 gene homolog A (S. cerevisiae)	Sar1a	**0,80**
SAR1 gene homolog B (S. cerevisiae)	Sar1b	**0,58**
scavenger receptor class B, member 1	Scarb1	**0,86**
SEC13 homolog (S. cerevisiae)	Sec13	**0,72**
SEC22 vesicle trafficking protein-like A (S. cerevisiae)	Sec22a	**0,83**
SEC23A (S. cerevisiae)	Sec23a	**1,23**
Sec61 alpha 1 subunit (S. cerevisiae)	Sec61a1	**0,69**
Sec61, alpha subunit 2 (S. cerevisiae)	Sec61a2	**0,85**
secernin 1	Scrn1	**1,21**
secretory carrier membrane protein 2	Scamp2	**1,32**
selenium binding protein 1	Selenbp1	**0,88**
serine/threonine kinase 38 like	Stk38l	**0,80**
SFT2 domain containing 2	Sft2d2	**1,19**
SH3-domain GRB2-like 2	Sh3gl2	**0,86**
signal recognition particle 14	Srp14	**0,77**
signal recognition particle 19	Srp19	**0,75**
signal recognition particle 9	Srp9	**0,72**
signal sequence receptor, beta	Ssr2	**0,60**
signal transducing adaptor molecule (SH3 domain and ITAM motif) 2	Stam2	**0,81**
sine oculis-related homeobox 2 homolog (Drosophila)	Six2	**1,20**
sirtuin 4 (silent mating type information regulation 2 homolog) 4 (S. cerevisiae)	Sirt4	**0,84**
six transmembrane epithelial antigen of prostate 2	Steap2	**0,86**
six transmembrane epithelial antigen of the prostate 1	Steap1	**0,78**
sodium channel, nonvoltage-gated 1 beta	Scnn1b	**1,14**
sodium channel, nonvoltage-gated, type I, alpha	Scnn1a	**1,25**
sodium channel, voltage-gated, type I, alpha	Scn1a	**1,43**
sodium channel, voltage-gated, type I, beta	Scn1b	**1,45**
sodium channel, voltage-gated, type II, beta	Scn2b	**1,35**
solute carrier family 1 (glutamate transporter), member 7	Slc1a7	**1,23**
solute carrier family 1 (glutamate/neutral amino acid transporter), member 4	Slc1a4	**0,78**
solute carrier family 10, member 2	Slc10a2	**1,70**
solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1	Slc11a1	**0,82**
solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	Slc11a2	**0,80**
solute carrier family 12 (potassium/chloride transporters), member 8	Slc12a8	**0,62**
solute carrier family 12 (potassium/chloride transporters), member 9	Slc12a9	**1,19**
solute carrier family 12, member 7	Slc12a7	**1,40**
solute carrier family 13 (sodium/sulphate symporters), member 1	Slc13a1	**1,77**
solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 2	Slc13a2	**1,56**
solute carrier family 15 (H+/peptide transporter), member 2	Slc15a2	**1,77**
solute carrier family 15 (oligopeptide transporter), member 1	Slc15a1	**1,35**
solute carrier family 15, member 4	Slc15a4	**0,87**
solute carrier family 16 (monocarboxylic acid transporters), member 7	Slc16a7	**0,82**
solute carrier family 17 (anion/sugar transporter), member 5	Slc17a5	**1,39**
solute carrier family 18 (vesicular monoamine), member 1	Slc18a1	**0,83**
solute carrier family 19 (sodium/hydrogen exchanger), member 1	Slc19a1	**1,15**
solute carrier family 19 (thiamine transporter), member 2	Slc19a2	**1,21**
solute carrier family 2 (facilitated glucose transporter), member 5	Slc2a5	**1,22**
solute carrier family 2 (facilitated glucose transporter), member 9	Slc2a9	**1,25**
solute carrier family 22 (organic cation transporter), member 17	Slc22a17	**1,29**
solute carrier family 22, member 23	Slc22a23	**1,56**
solute carrier family 24 (sodium/potassium/calcium exchanger), member 3	Slc24a3	**1,49**
solute carrier family 25 (mitochondrial carnitine/acylcarnitine translocase), member 20	Slc25a20	**1,41**
solute carrier family 25 (mitochondrial carrier, peroxisomal membrane protein), member 17	Slc25a17	**0,80**
solute carrier family 25 (mitochondrial carrier, phosphate carrier), member 3	Slc25a3	**0,87**
solute carrier family 25 (mitochondrial thiamine pyrophosphate carrier), member 19	Slc25a19	**0,83**
solute carrier family 25, member 32	Slc25a32	**0,83**
solute carrier family 25, member 37	Slc25a37	**1,51**
solute carrier family 25, member 38	Slc25a38	**0,84**
solute carrier family 25, member 42	Slc25a42	**1,24**
solute carrier family 25, member 45	Slc25a45	**0,87**
solute carrier family 25, member 46	Slc25a46	**0,78**
solute carrier family 26 (sulfate transporter), member 2	Slc26a2	**2,36**

solute carrier family 27 (fatty acid transporter), member 4	Slc27a4	**1,48**
solute carrier family 3, member 1	Slc3a1	**1,32**
solute carrier family 30 (zinc transporter), member 3	Slc30a3	**1,26**
solute carrier family 30 (zinc transporter), member 4	Slc30a4	**1,39**
solute carrier family 34 (sodium phosphate), member 2	Slc34a2	**0,82**
solute carrier family 35 (UDP-galactose transporter), member A2	Slc35a2	**0,78**
solute carrier family 35, member C1	Slc35c1	**0,69**
solute carrier family 35, member D3	Slc35d3	**1,35**
solute carrier family 35, member F2	Slc35f2	**0,84**
solute carrier family 35, member F5	Slc35f5	**0,83**
solute carrier family 38, member 10	Slc38a10	**0,75**
solute carrier family 38, member 2	Slc38a2	**1,49**
solute carrier family 38, member 7	Slc38a7	**1,20**
solute carrier family 39 (metal ion transporter), member 6	Slc39a6	**1,24**
solute carrier family 39 (metal ion transporter), member 8	Slc39a8	**0,81**
solute carrier family 4 (anion exchanger), member 2	Slc4a2	**1,44**
solute carrier family 40 (iron-regulated transporter), member 1	Slc40a1	**1,46**
solute carrier family 43, member 1	Slc43a1	**0,87**
solute carrier family 5 (choline transporter), member 7	Slc5a7	**0,85**
solute carrier family 5 (inositol transporters), member 3	Slc5a3	**0,71**
solute carrier family 5 (sodium/glucose cotransporter), member 1	Slc5a1	**1,44**
solute carrier family 6 (neurotransmitter transporter, betaine/GABA), member 12	Slc6a12	**1,33**
solute carrier family 6 (neurotransmitter transporter, taurine), member 6	Slc6a6	**1,55**
solute carrier family 7 (cationic amino acid transporter, y+ system), member 1	Slc7a1	**1,36**
solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	Slc7a5	**1,25**
solute carrier family 7 (cationic amino acid transporter, y+ system), member 9	Slc7a9	**1,29**
solute carrier family 9 (sodium/hydrogen exchanger), member 1	Slc9a1	**1,30**
solute carrier family 9 (sodium/hydrogen exchanger), member 2	Slc9a2	**1,48**
solute carrier family 9 (sodium/hydrogen exchanger), member 3	Slc9a3	**1,41**
solute carrier family 9 (sodium/hydrogen exchanger), member 6	Slc9a6	**1,31**
solute carrier organic anion transporter family, member 2a1	Slco2a1	**1,37**
solute carrier organic anion transporter family, member 4a1	Slco4a1	**1,18**
sonic hedgehog	Shh	**1,20**
sorbin and SH3 domain containing 1	Sorbs1	**1,92**
sortilin 1	Sort1	**1,19**
sortilin-related receptor, LDLR class A repeats-containing	Sorl1	**1,51**
sorting nexin 12	Snx12	**1,29**
sorting nexin 14	Snx14	**0,75**
sorting nexin 15	Snx15	**1,26**
sorting nexin 17	Snx17	**1,23**
sorting nexin 5	Snx5	**0,74**
sorting nexin 6	Snx6	**0,78**
spectrin beta 2	Spnb2	**1,32**
spinster homolog 3 (Drosophila)	Spns3	**1,22**
START domain containing 3	Stard3	**0,74**
stromal interaction molecule 1	Stim1	**0,80**
stromal interaction molecule 2	Stim2	**1,35**
succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	Sdhb	**0,59**
succinate dehydrogenase complex, subunit D, integral membrane protein	Sdhd	**0,57**
SUMO/sentrin specific peptidase 2	Senp2	**1,30**
suppressor of fused homolog (Drosophila)	Sufu	**1,30**
synapsin I	Syn1	**1,27**
synapsin II	Syn2	**1,31**
synapsin III	Syn3	**1,30**
synaptic vesicle glycoprotein 2 a	Sv2a	**1,46**
synaptogyrin 1	Syngr1	**1,35**
synaptojanin 1	Synj1	**1,44**
synaptojanin 2 binding protein	Synj2bp	**0,79**
synaptosomal-associated protein 25	Snap25	**1,53**
synaptosomal-associated protein 91	Snap91	**1,36**
synaptotagmin I	Syt1	**1,47**
synaptotagmin V	Syt5	**1,23**
synaptotagmin VIII	Syt8	**1,23**
synaptotagmin XI	Syt11	**1,24**
synaptotagmin XVII	Syt17	**1,26**
synaptotagmin-like 1	Sytl1	**0,79**
synaptotagmin-like 4	Sytl4	**0,76**
syntaxin 12	Stx12	**0,77**
syntaxin 17	Stx17	**0,77**
syntaxin 18	Stx18	**0,81**
syntaxin 2	Stx2	**1,25**
syntaxin 3	Stx3	**0,68**
syntaxin 5A	Stx5a	**0,77**
syntaxin 6	Stx6	**0,87**
syntaxin binding protein 1	Stxbp1	**1,33**
syntaxin binding protein 5 (tomosyn)	Stxbp5	**1,21**
target of myb1-like 2 (chicken)	Tom1l2	**1,85**

taxilin alpha	Txlna	**0,86**
T-cell, immune regulator 1, ATPase, H+ transporting, lysosomal V0 protein A3	Tcirg1	**1,32**
thioredoxin reductase 3	Txnrd3	**1,35**
thioredoxin-like 1	Txnl1	**1,36**
THO complex 1	Thoc1	**0,82**
Tnf receptor-associated factor 6	Traf6	**1,30**
toll-like receptor 2	Tlr2	**0,80**
Traf3 interacting protein 2	Traf3ip2	**0,78**
trafficking protein particle complex 1	Trappc1	**0,74**
trafficking protein particle complex 4	Trappc4	**0,74**
transducer of ErbB-2.1	Tob1	**1,63**
transferrin receptor	Tfrc	**0,61**
transforming growth factor beta regulated gene 1	Tbrg1	**0,57**
transient receptor potential cation channel, subfamily A, member 1	Trpa1	**0,85**
transient receptor potential cation channel, subfamily C, member 2	Trpc2	**1,28**
transient receptor potential cation channel, subfamily C, member 5	Trpc5	**0,82**
transient receptor potential cation channel, subfamily M, member 2	Trpm2	**1,17**
transient receptor potential cation channel, subfamily M, member 3	Trpm3	**1,20**
transient receptor potential cation channel, subfamily M, member 6	Trpm6	**1,55**
transient receptor potential cation channel, subfamily V, member 1	Trpv1	**0,85**
transient receptor potential cation channel, subfamily V, member 5	Trpv5	**0,80**
translocase of inner mitochondrial membrane 13 homolog (yeast)	Timm13	**0,60**
translocase of inner mitochondrial membrane 22 homolog (yeast)	Timm22	**0,77**
translocase of inner mitochondrial membrane 44	Timm44	**0,79**
translocase of inner mitochondrial membrane 8 homolog b (yeast)	Timm8b	**0,62**
transmembrane emp24 domain containing 3	Tmed3	**0,69**
transmembrane emp24 protein transport domain containing 7	Tmed7	**0,75**
transmembrane protease, serine 8 (intestinal)	Tmprss8	**0,62**
transmembrane protein 48	Tmem48	**0,86**
transmembrane protein 9	Tmem9	**0,83**
trinucleotide repeat containing 6a	Tnrc6a	**1,67**
tripartite motif-containing 36	Trim36	**1,54**
tuberous sclerosis 2	Tsc2	**0,85**
tumor necrosis factor, alpha-induced protein 1 (endothelial)	Tnfaip1	**1,47**
tweety homolog 2 (Drosophila)	Ttyh2	**1,17**
tweety homolog 3 (Drosophila)	Ttyh3	**1,72**
two pore channel 1	Tpcn1	**1,88**
ubiquinol cytochrome c reductase core protein 2	Uqcrc2	**1,29**
ubiquinol-cytochrome c reductase core protein 1	Uqcrc1	**0,57**
ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1	Uqcrfs1	**0,64**
ubiquitin carboxy-terminal hydrolase L1	Uchl1	**1,41**
unconventional SNARE in the ER 1 homolog (S. cerevisiae)	Use1	**0,50**
vacuolar protein sorting 16 (yeast)	Vps16	**0,85**
vacuolar protein sorting 26 homolog B (yeast)	Vps26b	**1,25**
vacuolar protein sorting 28 (yeast)	Vps28	**0,60**
vacuolar protein sorting 35	Vps35	**0,70**
vacuolar protein sorting 37C (yeast)	Vps37c	**1,59**
vacuolar protein sorting 39 (yeast)	Vps39	**1,40**
vacuolar protein sorting 41 (yeast)	Vps41	**0,83**
vav 3 oncogene	Vav3	**0,84**
vesicle transport through interaction with t-SNAREs homolog 1A (yeast)	Vti1a	**1,30**
vesicle-associated membrane protein 1	Vamp1	**1,28**
vesicle-associated membrane protein 4	Vamp4	**1,30**
vesicle-associated membrane protein 7	Vamp7	**0,81**
vesicle-associated membrane protein 8	Vamp8	**0,62**
vitamin D receptor	Vdr	**1,64**
Yip1 interacting factor homolog A (S. cerevisiae)	Yif1a	**0,61**
zinc binding alcohol dehydrogenase, domain containing 2	Zadh2	**1,34**
zinc finger protein 282	Zfp282	**0,84**
zinc finger, FYVE domain containing 20	Zfyve20	**0,90**

Table 28: Gene targets in the therapy group (high dose flavone) filtered according to GO "cell cycle"

gene name	gene symbol	**reg. fac.**
A kinase (PRKA) anchor protein 8	Akap8	**1,52**
amyloid beta (A4) precursor protein-binding, family B, member 2	Apbb2	**1,28**
amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 2 (human)	Als2cr2	**1,44**
anaphase promoting complex subunit 4	Anapc4	**0,83**
aurora kinase A	Aurka	**0,76**
aurora kinase B	Aurkb	**0,78**
baculoviral IAP repeat-containing 5	Birc5	**0,70**
BR serine/threonine kinase 1	Brsk1	**1,36**
BRCA2 and CDKN1A interacting protein	Bccip	**0,73**
breakpoint cluster region homolog	Bcr	**0,83**
budding uninhibited by benzimidazoles 3 homolog (S. cerevisiae)	Bub3	**1,28**

c-abl oncogene 1, receptor tyrosine kinase	Abl1	**1,45**
calcium/calmodulin-dependent protein kinase II gamma	Camk2g	**1,30**
calmegin	Clgn	**1,20**
calmodulin 3	Calm3	**0,47**
caspase 3	Casp3	**0,70**
caspase 8 associated protein 2	Casp8ap2	**1,42**
CDC14 cell division cycle 14 homolog A (S. cerevisiae)	Cdc14a	**1,41**
CDC16 cell division cycle 16 homolog (S. cerevisiae)	Cdc16	**0,78**
CDC23 (cell division cycle 23, yeast, homolog)	Cdc23	**0,81**
CDK2 (cyclin-dependent kinase 2)-associated protein 1	Cdk2ap1	**0,81**
cell adhesion molecule 4	Cadm4	**1,21**
cell division cycle 123 homolog (S. cerevisiae)	Cdc123	**0,73**
cell division cycle 2 homolog A (S. pombe)	Cdc2a	**0,64**
cell division cycle 25 homolog A (S. pombe)	Cdc25a	**1,56**
cell division cycle 25 homolog B (S. pombe)	Cdc25b	**0,87**
cell division cycle 27 homolog (S. cerevisiae)	Cdc27	**1,23**
cell division cycle 45 homolog (S. cerevisiae)-like	Cdc45l	**0,83**
cell division cycle 6 homolog (S. cerevisiae)	Cdc6	**1,64**
centrin 2	Cetn2	**0,71**
centromere protein H	Cenph	**0,85**
centrosomal protein 55	Cep55	**0,82**
checkpoint with forkhead and ring finger domains	Chfr	**1,32**
CHK2 checkpoint homolog (S. pombe)	Chek2	**0,84**
chromatin assembly factor 1, subunit A (p150)	Chaf1a	**0,81**
chromatin licensing and DNA replication factor 1	Cdt1	**0,77**
CLIP associating protein 1	Clasp1	**1,39**
CLIP associating protein 2	Clasp2	**1,91**
COP9 (constitutive photomorphogenic) homolog, subunit 5 (Arabidopsis thaliana)	Cops5	**0,68**
cyclin A2	Ccna2	**0,74**
cyclin B2	Ccnb2	**0,65**
cyclin D binding myb-like transcription factor 1	Dmtf1	**0,74**
cyclin D2	Ccnd2	**0,69**
cyclin D3	Ccnd3	**0,84**
cyclin G1	Ccng1	**0,68**
cyclin G2	Ccng2	**1,43**
cyclin I	Ccni	**1,76**
cyclin T2	Ccnt2	**0,82**
cyclin-dependent kinase 4	Cdk4	**0,69**
cyclin-dependent kinase 7 (homolog of Xenopus MO15 cdk-activating kinase)	Cdk7	**0,77**
cyclin-dependent kinase 9 (CDC2-related kinase)	Cdk9	**1,42**
cyclin-dependent kinase inhibitor 1A (P21)	Cdkn1a	**1,32**
cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4)	Cdkn2b	**1,25**
cyclin-dependent kinase inhibitor 3	Cdkn3	**0,71**
defective in sister chromatid cohesion 1 homolog (S. cerevisiae)	Dscc1	**0,84**
discs, large homolog 7 (Drosophila)	Dlg7	**0,81**
dynactin 3	Dctn3	**0,54**
dystrophia myotonica-containing WD repeat motif	Dmwd	**1,23**
E2F transcription factor 3	E2f3	**1,54**
endoplasmic reticulum (ER) to nucleus signalling 1	Ern1	**1,44**
EP300 interacting inhibitor of differentiation 1	Eid1	**1,27**
establishment of cohesion 1 homolog 2 (S. cerevisiae)	Esco2	**0,77**
extra spindle poles-like 1 (S. cerevisiae)	Espl1	**0,84**
Fanconi anemia, complementation group I	Fanci	**1,20**
folliculin	Flcn	**0,85**
formin 2	Fmn2	**1,26**
fyn-related kinase	Frk	**1,50**
germ cell-specific gene 2	Gsg2	**0,84**
glucocorticoid induced transcript 1	Glcci1	**1,25**
growth arrest and DNA-damage-inducible 45 alpha	Gadd45a	**1,24**
growth arrest and DNA-damage-inducible, gamma interacting protein 1	Gadd45gip1	**0,70**
growth arrest specific 1	Gas1	**1,56**
growth arrest specific 2	Gas2	**1,32**
high mobility group AT-hook 2	Hmga2	**0,85**
HRAS like suppressor 3	Hrasls3	**0,57**
inhibitor of DNA binding 4	Id4	**1,40**
Jun oncogene	Jun	**1,35**
kelch domain containing 3	Klhdc3	**1,31**
kinesin family member 11	Kif11	**0,81**
lethal giant larvae homolog 2 (Drosophila)	Llgl2	**1,55**
MAD2L1 binding protein	Mad2l1bp	**1,34**
max binding protein	Mnt	**1,46**
microtubule-actin crosslinking factor 1	Macf1	**1,45**
microtubule-associated protein, RP/EB family, member 3	Mapre3	**1,30**
minichromosome maintenance deficient 2 mitotin (S. cerevisiae)	Mcm2	**0,75**
minichromosome maintenance deficient 7 (S. cerevisiae)	Mcm7	**0,72**
mitogen-activated protein kinase 6	Mapk6	**1,43**
mutL homolog 1 (E. coli)	Mlh1	**0,85**

mutS homolog 2 (E. coli)	Msh2	**0,79**
neuroblastoma ras oncogene	Nras	**0,82**
nibrin	Nbn	**0,81**
NIMA (never in mitosis gene a)-related expressed kinase 3	Nek3	**1,32**
NIMA (never in mitosis gene a)-related expressed kinase 4	Nek4	**0,86**
NIMA (never in mitosis gene a)-related expressed kinase 6	Nek6	**0,76**
NUF2, NDC80 kinetochore complex component, homolog (S. cerevisiae)	Nuf2	**0,80**
OVO homolog-like 1 (Drosophila)	Ovol1	**1,28**
par-3 (partitioning defective 3) homolog (C. elegans)	Pard3	**1,26**
PDS5, regulator of cohesion maintenance, homolog A (S. cerevisiae)	Pds5a	**1,55**
peripheral myelin protein	Pmp22	**1,50**
pleckstrin homology domain containing, family O member 1	Plekho1	**1,41**
podoplanin	Pdpn	**1,35**
polo-like kinase 2 (Drosophila)	Plk2	**0,78**
polycystic kidney disease 1 homolog	Pkd1	**1,25**
protamine 3	Prm3	**1,18**
protein (peptidyl-prolyl cis/trans isomerase) NIMA-interacting 1	Pin1	**0,65**
protein phosphatase 1, catalytic subunit, alpha isoform	Ppp1ca	**0,49**
protein phosphatase 1, catalytic subunit, beta isoform	Ppp1cb	**1,29**
protein phosphatase 3, catalytic subunit, alpha isoform	Ppp3ca	**1,27**
protein regulator of cytokinesis 1	Prc1	**0,83**
PYD and CARD domain containing	Pycard	**0,47**
Rac GTPase-activating protein 1	Racgap1	**0,79**
RAD50 homolog (S. cerevisiae)	Rad50	**0,81**
RAD51 homolog (S. cerevisiae)	Rad51	**0,76**
Rad51 homolog c (S. cerevisiae)	Rad51c	**0,83**
RAN binding protein 1	Ranbp1	**0,54**
Ras association (RalGDS/AF-6) domain family member 4	Rassf4	**0,86**
Ras association (RalGDS/AF-6) domain family member 5	Rassf5	**0,82**
retinoblastoma 1	Rb1	**1,47**
retinoblastoma binding protein 4	Rbbp4	**1,79**
retinoblastoma-like 2	Rbl2	**0,82**
reversion-inducing-cysteine-rich protein with kazal motifs	Reck	**1,34**
Rho GTPase activating protein 8	Arhgap8	**0,86**
RIKEN cDNA 1190002H23 gene	1190002H23Rik	**0,77**
ring finger protein 2	Rnf2	**1,37**
ring finger protein 8	Rnf8	**1,31**
RNA binding motif protein 5	Rbm5	**1,41**
S100 calcium binding protein A6 (calcyclin)	S100a6	**0,66**
SAC3 domain containing 1	Sac3d1	**0,80**
SAM and SH3 domain containing 1	Sash1	**1,58**
septin 11	Sept11	**1,23**
septin 3	Sept3	**1,34**
septin 4	Sept4	**0,84**
serine/threonine kinase 11	Stk11	**0,74**
sestrin 3	Sesn3	**1,40**
shugoshin-like 1 (S. pombe)	Sgol1	**0,83**
stromal antigen 2	Stag2	**0,76**
telomeric repeat binding factor 2	Terf2	**1,39**
topoisomerase (DNA) II beta binding protein	Topbp1	**0,80**
transcription factor 3	Tcf3	**1,46**
transcription factor Dp 2	Tfdp2	**1,40**
transformation related protein 53 binding protein 2	Trp53bp2	**1,25**
transformation related protein 53 inducible nuclear protein 1	Trp53inp1	**1,44**
transformation/transcription domain-associated protein	Trrap	**1,43**
transforming growth factor beta regulated gene 1	Tbrg1	**0,57**
transforming growth factor, beta 2	Tgfb2	**1,37**
transforming, acidic coiled-coil containing protein 2	Tacc2	**1,60**
tuberous sclerosis 2	Tsc2	**0,85**
tumor suppressor candidate 4	Tusc4	**0,80**
ubiquitin protein ligase E3 component n-recognin 2	Ubr2	**1,81**
ubiquitin-like modifier activating enzyme 3	Uba3	**0,63**
von Hippel-Lindau syndrome homolog	Vhlh	**1,37**
zinc finger protein 318	Zfp318	**1,24**

Table 29: Gene targets in the therapy group (high dose flavone) filtered according to GO "induction of apoptosis"

gene name	gene symbol	**reg. fac.**
Bcl-2 binding component 3	Bbc3	**1,30**
Bcl2-interacting killer	Bik	**1,27**
Bcl-2-related ovarian killer protein	Bok	**1,23**
Bcl-associated death promoter	Bad	**0,69**
caspase 1	Casp1	**0,64**
caspase 3	Casp3	**0,70**

caspase 4, apoptosis-related cysteine peptidase	Casp4	**0,79**
caspase 6	Casp6	**0,67**
caspase 8 associated protein 2	Casp8ap2	**1,42**
catenin, beta like 1	Ctnnbl1	**0,77**
CCAAT/enhancer binding protein (C/EBP), beta	Cebpb	**1,53**
CCAAT/enhancer binding protein (C/EBP), gamma	Cebpg	**0,82**
death associated protein kinase 1	Dapk1	**1,29**
death effector domain-containing	Dedd	**1,22**
endoplasmic reticulum (ER) to nucleus signalling 1	Ern1	**1,44**
excision repair cross-complementing rodent repair deficiency, complementation group 6	Ercc6	**1,25**
Fas (TNF receptor superfamily member 6)	Fas	**0,84**
Fc receptor, IgG, high affinity I	Fcgr1	**0,82**
forkhead box O3a	Foxo3a	**1,35**
glutathione peroxidase 1	Gpx1	**0,62**
granzyme B	Gzmb	**0,81**
immunoglobulin heavy constant gamma 1 (G1m marker)	Ighg1	**0,62**
integral membrane protein 2B	Itm2b	**1,22**
interferon activated gene 204	Ifi204	**0,82**
junction-mediating and regulatory protein	Jmy	**1,32**
methyl-CpG binding domain protein 4	Mbd4	**1,29**
mucin 2	Muc2	**0,58**
mutL homolog 1 (E. coli)	Mlh1	**0,85**
mutS homolog 6 (E. coli)	Msh6	**0,80**
myelin and lymphocyte protein, T-cell differentiation protein	Mal	**1,56**
myelocytomatosis oncogene	Myc	**0,81**
nucleotide-binding oligomerization domain containing 1	Nod1	**1,30**
peroxiredoxin 1	Prdx1	**0,67**
PERP, TP53 apoptosis effector	Perp	**1,48**
purine-nucleoside phosphorylase	Pnp	**0,63**
PYD and CARD domain containing	Pycard	**0,47**
RAB27A, member RAS oncogene family	Rab27a	**0,85**
receptor-interacting serine-threonine kinase 3	Ripk3	**0,79**
ribonucleotide reductase M2 B (TP53 inducible)	Rrm2b	**0,89**
RIKEN cDNA 1200009F10 gene	1200009F10Rik	**0,83**
RIKEN cDNA 5730403B10 gene	5730403B10Rik	**1,18**
serine/threonine kinase 17b (apoptosis-inducing)	Stk17b	**1,38**
SH3-domain GRB2-like B1 (endophilin)	Sh3glb1	**1,28**
TCF3 (E2A) fusion partner	Tfpt	**0,85**
TNFRSF1A-associated via death domain	Tradd	**0,73**
transformation related protein 53 inducible nuclear protein 1	Trp53inp1	**1,44**
transforming growth factor, beta 2	Tgfb2	**1,37**

9.2. Chemicals

Chemicals	Company
1,2-dimethylhydrazine (DMH)	Sigma-Aldrich, Steinheim
5-Bromo-2'deoxyuridine	Sigma-Aldrich, Steinheim
Acetic acid	Carl Roth GmbH & Co., Karlsruhe
Acetone	Merck, Darmstadt
Acetonitrile	Merck, Darmstadt
Acrylamide and Bisacrylamide stock solution (Rotiphorese Gel 30)	Carl Roth GmbH & Co., Karlsruhe
Agarose	Merck, Darmstadt
Agarose MP	Roche Diagnostics, Mannheim
Ammonium hydrogen carbonate	Merck, Darmstadt
Ammonium persulphate (APS)	Merck, Darmstadt
Ammonium sulphate	Merck, Darmstadt
Animal diet (V1534, Ssniff)	Soest, Germany
Anti-rabbit IgG	Vector Laboratories, Wertheim
Biorad Protein Assay	BioRad Laboratories GmbH, München
Bovine serum albumin	Sigma-Aldrich, Steinheim
Bromphenol blue	Carl Roth GmbH & Co., Karlsruhe
Camptothecin	Sigma-Aldrich, Steinheim
CHAPS	Merck, Darmstadt
Chloroform	Merck, Darmstadt
Coomassie Brilliant Blue G250	Serva Electrophoresis GmbH, Heidelberg
DeStreak	Amersham Bioscience, Freiburg
Diaminobenzidine	Sigma-Aldrich, Steinheim
Diethyl pyrocarbonate	Merck, Darmstadt
Dimethylsulfoxid (DMSO)	Sigma, Deisenhofen
Dithiothreitol (DTT)	Sigma, Deisenhofen
DMEM/HEPES	Gibco BRL, Karlsruhe
DulbeccosModEM/ 25mM Hepes	Gibco BRL, Karlsruhe
Entellan	Merck, Darmstadt
Ethanol	J.T. Baker, Devender

Ethanol	Carl Roth GmbH & Co., Karlsruhe
Ethidiumbromide	Merck, Darmstadt
Ethylendiamintetraacid (EDTA/Na_2)	Sigma, Deisenhofen
Flavone	Sigma-Aldrich, Steinheim
Foetal calf serum (FCS)	PAA Laboratories GmbH, Pasching
Formaldehyde	Merck, Darmstadt
Formaldehyde loading dye	Ambion, Austin, Texas, USA
Formaline	Merck, Darmstadt
Fungizone	Gibco BRL, Karlsruhe
Gentamycin	Gibco BRL, Karlsruhe
Glutardialdehyde	Amersham Pharmacia Biotech, Freiburg
Glycerol	Merck, Darmstadt
Glycine	Merck, Darmstadt
Hematoxylin	Merck, Darmstadt
HEPES	Biochrom AG, Berlin
Hydrochloric acid	Merck, Darmstadt
Hydrogen peroxide	Merck, Darmstadt
IgG from mouse	Sigma-Aldrich, Steinheim
Immobiline II	Amersham Pharmacia Biotech, Freiburg
Iodacetamide	Merck, Darmstadt
IPG Puffer	Amersham Pharmacia Biotech, Freiburg
IPG-Puffer pH 4-7	Amersham Bioscience, Freiburg
IPG-Puffer pH 6-11	Amersham Bioscience, Freiburg
Isobutanol	Carl Roth GmbH & Co., Karlsruhe
Isopropanol	Carl Roth GmbH & Co., Karlsruhe
Jodacetamide	Merck, Darmstadt
L-Glutamine	Gibco BRL, Karlsruhe
MEM amino acids (50X)	Gibco BRL, Karlsruhe
MEM Vitamin Solution	Gibco BRL, Karlsruhe
Methanol	Carl Roth GmbH & Co., Karlsruhe
MOPS	Merck, Darmstadt
Mouse-anti-BrdU monoclonal antibody	Sigma-Aldrich, Steinheim
Myrj 53	Sigma-Aldrich, Steinheim
Ortho-phosphoric acid	Merck, Darmstadt
Paraffin	Merck, Darmstadt
PBS	Merck, Darmstadt
Penicillin/Streptomycin (Lyophilisat)	Sigma, Deisenhofen
PenStrep	PAA Laboratories GmbH, Pasching
Pharmalyte pH 3-10	Amersham Pharmacia Biotech, Freiburg
Potassium chloride	Carl Roth GmbH & Co., Karlsruhe
Potassium hydroxide	Carl Roth GmbH & Co., Karlsruhe
Protease Inhibitor Cocktail Tablets (CompleteMini)	Roche Diagnostic GmbH, Mannheim
Quercetin	Sigma-Aldrich, Steinheim
Rabbit polyclonal cleaved caspase-3 (Asp175) antibody	Cell Signalling, Frankfurt
RhEGF	Promega, Madison, WI USA
RNAse Inhibitor	MBI Fermentas GmbH, St. Leon-Rot
RNA-Wiz Lösung	Ambion, Austin, Texas, USA
RPMI Medium 1640	Biochrom AG, Berlin
Saccharose	Merck, Darmstadt
Serdolite	Serva Electrophoresis GmbH, Heidelberg
Silicone oil	Serva Electrophoresis GmbH, Heidelberg
Sodium acetate	Merck, Darmstadt
Sodium carbonate	Merck, Darmstadt
Sodium dodecyl sulfat (SDS)	Merck, Darmstadt
Sodium thiosulfat	Merck, Darmstadt
Sodium thiosulfat pentahydrate	Merck, Darmstadt
Starter Kit for MALDI-TOF MS	Bruker Daltonics GmbH, Leipzig
t-Butanol	Merck, Darmstadt
Tetramethylenethylendiamine (TEMED)	Merck, Darmstadt
Thiourea	Merck, Darmstadt
Trichloroacetic acid	Merck, Darmstadt
Trifluoroacetic acid	Merck, Darmstadt
Tris(hydroxymethyl)aminomethan (Tris)	Carl Roth GmbH & Co., Karlsruhe
Trizol	Invitrogen, Karlsruhe
Trypan blue solution	Sigma, Deisenhofen
Trypsin, sequencing grade for MS	Promega, Madison, WI USA
Trypsin/EDTA	PAA Laboratories GmbH, Pasching
Urea	Merck, Darmstadt
Xylene	Merck, Darmstadt
α-cyano-4-hydroxy-cinnamic acid	Sigma-Aldrich, Steinheim

9.3. Equipment and Consumables

Device	Company
Agarosegel Scanner	Amersham Pharmacia Biotech, Freiburg
Autoclave steam sterilizer	Webecco, Fridolfing
Balance	Scaltec, Göttingen
Bio Photometer	Eppendorf, Hamburg
Cell culture flasks ($25cm^2$, $75cm^2$)	TPP Laboratories, Schweiz
Cell scraper	TPP Laboratories, Schweiz
Centrifugal Evaporator	Jouan, Saint-Herblain, France
CO_2 incubator Stericult 200	Forma Scientific, Frankfurt
Ettan Dalt II System Gel Caster	Amersham Pharmacia Biotech, Freiburg
Ettan Dalt II System Seperation Unit	Amersham Pharmacia Biotech, Freiburg
Ettan IPGPhor Cup Loading Manifold	Amersham Pharmacia Biotech, Freiburg
Falcon-Tubes	Greiner Bio-one,
Fluidics Station 450	Affymetrix, Santa Clara, CA, USA
Gene Chip® 3' Expression Arrays	Affymetrix, Santa Clara, CA, USA
Glasplatte mit 0,5 mm U-frame (200 x 260 mm^2)	Amersham Pharmacia Biotech, Freiburg
Hautstanze, Ø 3mm	Stiefel Laboratorium GmbH, Offenbach
Heizkammer	Juan, Frankreich
Hybridization Oven 640	Affymetrix, Santa Clara, CA, USA
Image Scanner	Amersham Pharmacia Biotech, Freiburg
Immobiline Dry Strips (pH 4-7, pH 6-11, pH 3-10)	Amersham Pharmacia Biotech, Freiburg
Incubator	Binder, Tuttlingen
IPG cup loading strip holder	Amersham Pharmacia Biotech, Freiburg
Laminar flow HeraSafe	Heraeus, Hanau
Light Microscope	Leica, Wetzlar
MALDI TOF Autoflex mass spectrometer	Bruker Daltonics GmbH, Leipzig
Microcentrifuge	Eppendorf, Hamburg
Microcentrifuge tubes (1,5 ml, 2 ml, 0,2 ml safe lock)	Eppendorf, Hamburg
Milliporeanlage MilliQ Biocel A10	Millipore GmbH, Schwalbach
Mini Dialysis Kit	Amersham Bioscience
PCR (Personal Cycler)	Biometra, Göttingen
pipette tips	Eppendorf, Hamburg
Potter	MAGV GmbH, Rabenau-Londorf
precision balance	Sartorius GmbH, Göttingen
prespotted AnchorChip target PAC384	Bruker Daltonics GmbH, Leipzig
Prespotted AnchorChip target PAC384	Bruker Daltonics GmbH, Leipzig
Proteineer dp digester/workstation	Bruker Daltonics GmbH, Leipzig
Proteineer Kits SP and DP	Bruker Daltonics GmbH, Leipzig
Proteineer spII spot picker	Bruker Daltonics GmbH, Leipzig
Reswelling Tray	Amersham Pharmacia Biotech, Freiburg
RNeasy spin columns	Qiagen, Hilden
Scanner 3000 with Autoloader	Affymetrix, Santa Clara, CA, USA
Shaker HS 250 basic	Kika Labortechnik
Speed vacuum centrifuge RC 10.10	Jouan, Saint-Herblain, France
Ultrasonic bath	MAGV GmbH, Rabenau-Landorf
Ultrasonic homogenizer	Dr.Hielscher GmbH, Stuttgart
Umax Scanner Power Look III	Amersham Pharmacia Biotech, Freiburg

9.4. Composition of buffers and solutions

Prepared medium for HT 29

500 ml	RPMI 1640 standard medium
10%	FCS
2.5 mM	HEPES
100 U/ml	penicillin
100 µg/ml	streptomycin

Lysis buffer

7 M	urea
2 M	thiourea
2%	CHAPS
1%	DTT
2%	pharmalyte
0.3%	proteinase inhibitor

Polyacrylamide gel solution (12.5%)

12.5%	acrylamide
0.375 M	TrisHCl, pH 8.8
0.1%	APS
0.1%	SDS (20%)
0.01%	TEMED

Sealing Solution

25 mM	Tris
192 mM	glycine
0.1%	SDS
0.5%	agarose
	bromphenolblue

Rehydration buffer

8 M	urea
2%	CHAPS
2%	pharmalyte pH 3-10
1%	DTT

Equilibration buffer I

6 M	urea
1,5 M	TrisHCl, pH 8.8
26%	glycerol (87% v/v)
2%	SDS
1%	DTT

Equilibration buffer II

6 M	urea
1.5 M	TrisHCl, pH 8.8
26%	glycerol (87% v/v)
2%	SDS
4%	iodacetamide

Elektrophoresis running buffer

25 mM	Tris
192 mM	glycine
0.1%	SDS

Fixation solution

40%	ethanol
10%	acetic acid (conc.)

Coomassie staining solution

0.625%	coomassie brilliant blue G250
25%	methanol
10%	ammoniumsulfate
2%	ortho-phosphoric acid

9.5. Abbreviations

°C	degree centigrade
2D	two dimensional
ACF	aberrant crypt foci
ACN	acetonitrile
AIF	apoptosis inducing factor
APC	adenomatous polyposis coli
APS	ammonium persulfate
ATCC	American Type Culture Collection
ATP	adenosine 5'-triphosphate
Bax	BCL-2 associated protein x
BCL-2	B-Cell-Lymphoma-2
BrdU	5-Bromo-2'deoxyuridine
BSA	bovine serum albumin
Caspase	calcium-dependent cysteine protease
CDK	Cyclin-dependent-kinases
cDNA	complementary DNA
CHAPS	3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate
cm	centimeter
CO_2	carbon dioxide
COX	cyclooxygenase
CRC	colorectal cancer
Da	dalton
DCA	dichloroacetate
DEPC	diethyl pyrocarbonate
DMEM	dulbeco's modified eagle medium
DMH	1,2-dimethylhydrazine
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dNTP	deoxyribonucleotide triphosphate (dATP, dCTP, dGTP, dTTP)
DTT	dithiothreitol, 1,4-dithiothreit
EDTA	ethylenediamine-tetraacetic acid
ER	endoplasmic reticulum
FAP	familial adenomatous polyposis
FAST	fragment analysis and structural time-of-flight
FCS	fetal calf serum
Fig.	figure
g	gram(s)
g	acceleration of gravity
h	hour(s)
HCCA	α-cyano-4-hydroxy-cinnamic acid
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HNPCC	hereditary nonpolyposis colorectal cancer
HSP	heat shock protein
i.p.	intraperitoneal
IEF	isoelectric focusing
IPG	immobilized pH gradient
kDa	kilodalton
kg	kilogram(s)
M	molar (mol/l)
mA	milliampère
MALDI	matrix assisted laser desorption ionization
mg	milligram(s)
min	minute(s)
ml	milliliter(s)
mRNA	messenger RNA

Addendum

MS	mass spectrometry
MSDB	Mascot Search Database
n	number (of samples, replicates, experiments)
NCBI	National Center for Biotechnology Information
PAGE	polyacrylamide gel electrophoresis
PBS	phosphate buffered saline
PCR	polymerase chain reaction
pI	isoelectric point
PMF	peptide mass fingerprint
PMSF	phenylmethanesulfonyl fluoride
PSD	post source decay
RNA	ribonucleic acid
ROS	reactive oxygen species
rpm	rounds per minute
s	second(s)
SDS	sodium dodecyl sulfate
Tab.	table
TEMED	N,N,N',N'- tetramethylethylenediamine
TFA	trifluor acetic acid
TOF	time-of-flight
Tris	tris-(hydroxymethyl)-aminomethane
UV	ultraviolet
V	volt
WHO	World Health Organisation
µg	microgram(s)
µl	microliter(s)
µM	micromolar

9.6. Table index

9.7. Figure index

9.8. Acknowledgment

Herzlich bedanken möchte ich mich an dieser Stelle bei allen, die zum Gelingen der vorliegenden Doktorarbeit beigetragen haben. Mein besonderer Dank gilt:

Frau Prof. Dr. Hannelore Daniel für die Überlassung des interessanten Themas und die Bereitstellung der Laborausstattungen sowie für ihr entgegengebrachtes Vertrauen und ihre Begleitung der Arbeit.

Herrn Prof. Dr. Uwe Wenzel für seine vielseitige Unterstützung und Diskussionsbereitschaft, seinen auflockernden, witzig-schrägen Humor sowie seine bereichernden Anregungen bei der Durchsicht der Publikationen und der Arbeit. Außerdem für seine amüsanten Kicker-Einlagen zusammen mit Kai im Keller des alten Institutes.

Frau Dr. Daniela Diehl für die Einführung in die Techniken bei den *in vivo* Experimenten, ihre Unterstützung und ihr gutes Auge bei den Mikroskop-Arbeiten.

Prof. Dr. Edwin Mariman für die Erstellung eines externen Gutachtens und Prof Dr. Dirk Haller für die Übernahme des Prüfungsvorsitzes und die Organisation des Prüfungsverfahrens.

Anne Näßl, die bei der Erstellung ihrer Diplomarbeit wichtige Ergebnisse zu meinen Projekten beigesteuert hat und zusammen mit Ronny für eine abwechslungsreiche und gute Atmosphäre im Proteomiklabor gesorgt hat.

Jacki und Katrin, für die kleinen Pausen zwischendurch und diverse Ansporn-Wetten.

Beate Rauscher, die mich sehr bei den *in vivo* Experimenten unterstützt hat, außerdem Frau Spiller und Frau Berauer, die auch die Versorgung der Tiere übernommen haben. Barbara Gelhaus für die Unterstützung bei den Microarray-Arbeiten.

Helene Prunkl als gute Seele der Arbeitsgruppe und Kaffeemaschinen-Instandhaltungsdame sowie Elmar Jocham für innovative Ansätze bei Reparaturarbeiten an meinem Auto.

Ladi für seine Eiskreationen, Tanja, Gabi, Daniel, Alex, Didi, Annika, Kai und Rainer sowie allen Mitarbeitern der Arbeitsgruppe für die angenehme Zusammenarbeit und allen, die ich an dieser Stelle nicht namentlich erwähnt habe. Meinen Korrekturlesern, vor allem Julia.

Meinen Freunden für ihre Aufmunterungen und ihre Geduld, allen voran Silvia Reichenwallner und Gabi Martin, die mir vor allem in der Endphase dieser Arbeit in allen Lebenslagen zur Seite standen, und äußerst wichtig für mich waren.

Meiner Familie, besonders meinen Eltern, die immer an mich geglaubt und mich unterstützt haben und mir die Gabe des positiven Denkens vermittelt haben.

9.9. List of publications

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