Genetic Variation in Circadian Genes and Survival in Patients with CRC

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Abstract

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Disruption of circadian rhythm, characterized by sleep/activity pattern disturbances, is associated with an elevated risk of developing CRC as well as poor prognosis in patients with various cancers. To examine the relationship of single nucleotide polymorphisms (SNPs) in circadian genes and chronotype-associated SNPs with CRC specific survival and overall survival in patients with CRC, we used data from 16 studies participating in the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) (N=17,550 participants). The results identified 8 variants with modest increased hazard ratios (HRs) in analyses of CRC survival overall and one SNP located on RORA (rs1869486 HR = 1.8, CI 1.2–2.7, p = 0.004) that was statistically significantly associated with disease-specific survival in patients with stage 0/1 tumors. None of these associations remained significant after adjusting for multiple comparisons. Overall, our study finds that the underlying germline variation in the circadian clock pathway, captured by the selected SNPs within circadian genes and chronotype variants, is not statistically significantly associated with survival outcomes after CRC diagnosis.

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I. Introduction

Background and Significance

Colorectal cancer (CRC) has the third highest incidence and the second highest mortality rate of any cancer worldwide, accounting for 10.0% of all cancer diagnoses and 9.4% of all cancer-related deaths [1]. Based on data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry network, the 5-year relative survival of patients with CRC in the US ranges drastically from 90% for patients diagnosed with localized disease to 14% for those diagnosed with distant-stage disease [2]. The development and progression of CRC involves numerous risk factors, such as alcohol consumption, smoking, low levels of physical activity, certain dietary factors, and elevated body mass index [3, 4]. Heritable genetic factors are also known to predispose individuals to CRC, as well as affecting the prognosis of the disease [5, 6, 7].

It has long been known that organisms across the spectrum of life, including mammals, have circadian clocks that coordinate behaviors like sleeping, eating, and immune responses [8, 9, 10, 11, 12]. The manifestation of these behaviors also depends on circadian preference, known as chronotype, which is present at the individual level and describes the tendency for earlier or later sleep timing [13]. Studies suggest that disruption of the sleep/activity rhythm is associated with an elevated risk of developing cancer as well as poor prognosis in patients with cancer [8, 9, 10, 11, 12, 13]. Circadian rhythms are directly involved in a wide variety of physiological and metabolic functions that govern cellular processes implicated in cancer development, such as cell cycle regulation, DNA damage response and apoptosis [11, 12, 14].

The connection between circadian cycle and colorectal tumorigenesis is influenced by factors that include inter-individual differences and clock gene polymorphism and/or down regulation [9]. Numerous genetic polymorphisms in clock genes (*Cry1*, *RORA*) have been associated with significantly increased risk in CRC [7, 14, 15], while some have been found to have a notable association with the survival of CRC patients (*Clock*, *RORA*) [7, 16]. However, understanding of the relationship between germline variation in circadian genes and CRC survival is currently limited.

We examined the relationship of single nucleotide polymorphisms (SNPs) in circadian clock pathway genes and chronotype-associated SNPs with colorectal cancer-specific survival and overall survival in patients with CRC from studies participating in an international consortium of CRC studies.

II. Materials and methods

GECCO

The study analysis was conducted with data from the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO). GECCO is an international collaborative effort of researchers across the world, with harmonized information on germline genetic factors, CRC diagnosis information, and demographic and epidemiologic factors for over 130,000 patients with CRC and control participants from 70 epidemiologic studies of CRC from North America, Australia, Asia, and Europe [17, 18].

Study population

The study participants included patients of (self-reported) European descent participating in 16 studies (clinical trials, case-control, and cohort studies) within the consortium, diagnosed with CRC and with available genotyping data and information on survival outcomes after CRC diagnosis. The following GECCO studies were included in the present analysis: the Colon Cancer Family Registry (CCFR) [19], the Cancer Prevention Study-II (CPS-II) [20], the German Darmkrebs: Chancen der Verhutung durch Screening Study (DACHS) [21], the Diet Activity and Lifestyle Study (DALS) [22], the Early Detection Research Network (EDRN) [23], the Swedish population of the European Prospective Investigation into Cancer (EPIC) [24], the Health Professionals Follow-up Study (HPFS) [25], the Melbourne Collaborative Cohort Study (MCCS) [26], the N9741 clinical trial (N9741) [27], the Nurses' Health Study I and II (NHS, NHS-II) [28, 29], the Physician's Health Study (PHS) [30, 31], the Prostate, Lung, Colorectal, and Ovarian Study (PLCO) [32, 33], the UK Biobank (UKB) [34], the VITamins And Lifestyle Study (VITAL) [35], and the Women's Health Initiative (WHI) [36, 37].

In all studies, CRC cases were defined as colorectal adenocarcinoma (International Classification of Disease Code 153–154) confirmed by medical records and/or pathologic reports. The survival outcomes ascertainment process in this study population has been described previously [38]. In brief, vital status was determined through study-specific protocols involving either the National Death Index, state cancer registries, state death records, population registers or, in some studies, via active follow up with cause of death verified by death certificates. All studies were approved by their respective Institutional Review Boards, and participants gave written informed consent for study participation.

SNP Selection

We selected 123 SNPs within 13 core genes known to be fundamentally involved in the circadian rhythm physiology and cell cycle regulation, including *CLOCK*, *ARNTL*, *NPAS2*, *PER1*, *PER2*, *PER3*, *CRY1*, *CRY2*, *NR1D2*, *RORA*, *TIMELESS*, *CSNK1D*, *CSNK1E* [39]. Additionally, we selected another 304 SNPs that were recently identified as being predictive of chronotype in a large-scale genome-wide association study (GWAS) using data from the UK Biobank [40]. We retrieved the minor allele frequency (MAF) for all the SNPs using the Bioconductor package - MafDb.gnomAD.r2.1.GRCh38, which stores MAF data from the Genome Aggregation Database (gnomAD release 2.1) for the human genome version GRCh38 [41] and filtered out the SNPs with a MAF< 0.05. A total of 412 SNPs (120 circadian gene SNPs, 292 chronotype SNPs) met inclusion criteria

Statistical Analysis

Data from individual studies within GECCO were combined for pooled statistical analyses. Prior to conducting data analysis, we performed data interrogation and standard quality control (QC) to eliminate samples with missing survival data and other covariates. Genomic data for the 412 candidate SNPs and data on covariates of interest were available for 17,550 participants after QC, while 8,476 patients were excluded from the original dataset due to missing survival outcome data.

We evaluated the Linkage Disequilibrium (LD) between the selected SNPs by computing the Pearson correlation between the counts of the minor alleles for each pair of SNPs, a common approach when the genotype dosage information is known [42].

The outcome measures used in this study were the overall survival (OS), measured from the date of diagnosis until the date of death from any cause or the date of last contact, whichever came first. For analyses of CRC-specific survival (CRC-S), the outcome of interest was defined as death attributed to CRC; in analyses of CRC-S, individuals who died from causes other than CRC were censored at the date of death. We evaluated the association of each genetic variant with clinical outcome by employing a single SNP Cox proportional hazard regression model to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) and p-values. Separate models were constructed for associations with OS and CRC-S. We adjusted all models for study population, sex, and age at diagnosis; to control for population stratification, we included the first five principal components of genetic ancestry as covariates for each model. We confined our analysis to SNPs with MAF >5%

and used a log-additive approach to model the selected SNPs, relating genotype dosage (i.e. major homozygote allele (reference)/heterozygote/minor homozygote allele) to survival outcomes. The dosage was calculated on a scale from 0 to 2 based on the sequenced data and imputation probabilities for each genotype. The statistical significance threshold was set at 0.05. Additionally, we used a Bonferroni correction for the number of SNPs included in each analysis to evaluate the chance of obtaining false-positive associations due to multiple comparisons. The proportional hazards assumption was tested based on the Schoenfeld residual analysis, using the cox.zph function of the survival package in R. SNPs that violated the PH assumption (i.e., variants with possible time-varying associations) were excluded from the final results. Due to a high number of SNPs that violated the PH assumption, regression models were refitted with follow up truncated at 5 years post-diagnosis. Focusing on the first 5 years of follow up is clinically meaningful time point (i.e. the most cancer deaths occur in the first 5 years of diagnosis) and minimized PH assumption violations.

Exploratory analysis was conducted to examine the association of genetic loci and CRC survival stratified by tumor stage (i.e., 0 - 4) and location (i.e., colon, rectum). All the analyses were carried out in R version 4.1.1.

III. RESULTS

Sample Description

The final survival analysis included 17,550 CRC patients. The distribution of patient's characteristics and clinical outcomes are summarized in Table 1. At the median follow-up time of 1,766 days (58.8 months), a total of 4,846 deaths occurred, of which 3,773 (77.9%) were attributed to CRC. A total of 4907 deaths occurred within the first 5 years follow up time (60 months), of which 3810 (77.6%) were attributed to CRC. The number of cases was split evenly among both sexes, while the majority of participants were aged 65 years and older (40%) at the time of diagnosis. Stage 2 and 3 tumors were the most predominant (40%), however, participants with stage 4 tumors at diagnosis were more likely to die from CRC (of those who died, 37.3% were stage 4, whereas only 11.5% of all included cases were diagnosed with stage 4 disease). The majority of cases were colon cancers (71.2%), but only 12.5% of them died of CRC compared to 22.9% CRC deaths of total rectal tumor cases.

Survival Analysis Results

Among all the candidate SNPs, we identified 20 SNP pairs in high LD (r>0.8) located exclusively on 8 of the circadian genes (*PER3, NPAS2, NR1D2, CLOCK, ARNTL, CRY2, RORA, CSNK1E*), and consequently we excluded from the analysis one variant from each SNP pair. The pairwise Pearson correlation coefficients (r), as proxy measure for LD, are presented in Supplementary Table 1. The distribution of the estimate of the linkage disequilibrium for all the candidate SNPs withing the circadian genes are graphically represented in Figure 1.

Associations of selected circadian clock pathway genes and chronotype-associated SNPs with both overall and CRC-specific survival are presented in Table 2.1. Although multiple chronotype and circadian gene SNPs were nominally associated with survival after CRC diagnosis (P <0.05), none of these associations remained significant after adjusting for multiple comparisons.

The associations between our candidate SNPs and survival outcome (both overall and CRC-specific survival) for the first 5 years of follow up time period are presented in Supplementary Table 2. In the initial 5 years of follow up, although we observed the same nominal level of association, the number of SNPs that yielded a statistically significant result (P <0.05) reduced in half. Notably, there were no significant results after employing Bonferroni correction when adjusting for multiple comparisons.

Next, we evaluated if genetic associations between selected SNPs and survival differed by tumor stage. Table 3.1 presents the association between the genetic loci and the overall survival outcome stratified by cancer stage, and based on the same stratification, the CRC survival outcome association with the SNPs of interest are presented in Table 3.2. The cancer stage stratified survival analysis results suggested nominal associations with overall survival across all tumor stages (P<0.05), with the most significant hazard ratio registered in stage 0/1 for rs2706762 located on *PCYOX1* gene (HR= 0.83, 95% CI: 0.72-0.94), but none of these results remained statistically significant after correction for multiple testing. Further, the same trend was observed for the tumor stage stratified survival analysis when using the CRC survival as the outcome. Therefore, only nominal associations between the selected SNPs and CRC survival (P<0.05) were detected in patients with regional and distant tumor stages, while significantly higher hazard ratios were observed in patients with stage 0/1 CRC.

The associations between the SNPs of interest and overall and CRC-specific survival stratified by tumor stage, at the follow up truncated at 5 years post-diagnosis, are presented in Supplementary Table 3.1 and Table 3.2 respectively. When looking at overall survival, we observed nominal associations, with the highest (rs12808544, HR=1.38, CI:1.10-1.70) and lowest (rs3857599, HR=0.72, CI:0.58-0.90) HR registered for patients with stage 0/1 CRC. When examining the relationship of SNPs and CRC survival at our truncated time point, we identified significantly increased HRs in three SNPs (rs1869486, HR=1.80, CI:1.21-2.70; rs12808544, HR=1.57, CI:1.18-2.10; rs6468316, HR=1.49, CI:1.14-1.95;) located on *RORA*, *ZFP91*, *UNC5D* and one inverse association for a SNP (rs3955311, HR=0.58, CI:0.37-0.90;) on *RBM19*, among patients diagnosed with localized tumor stage. However, none of the associations with SNPs identified to be significantly associated with CRC survival in patients with local stage tumors at the alpha level of 0.05 remained significant after Bonferroni multiple comparison correction.

We then evaluated the relationship of SNPs in circadian genes and chronotype-associated SNPs with survival after CRC according to the anatomical location of the cancer. Tumor location stratified survival analysis results are presented in Table 4.1 and Table 4.2. All the candidate SNPs that yielded a statistically significant P-value (<0.05) in this analysis showed nominal associations with overall and CRC survival. No variants reached alpha level threshold significance ($p < 0.05$) after correction for multiple comparison. Additionally, there were no significant associations detected among the results for survival analysis stratified by tumor location in the first 5 years of follow up, presented in Supplementary Table 4.

IV. DISCUSSION

Description of Findings

In this large survival analysis study of 17,550 colorectal cancer patients, we examined the relationship of 120 candidate SNPs in 13 circadian genes and 292 chronotype SNPs with CRC-specific survival and overall survival in patients with CRC participating in 16 GECCO studies. We found no overall evidence of an association between chronotype and circadian gene variants and survival after CRC diagnosis. For some variants (rs975025, rs2289163, rs2506089, rs11032362, rs11200159, rs7701529, rs12808544, rs6468316) a relatively modest increased HR was observed in patients with stage 0/1 tumors, when doing a stratified analysis for CRC survival. At the same time, rs1869486 showed a relatively significant increase in HR. This could suggest that carrying

minor homozygote allele for these variants slightly decreases your survival time after diagnosis with stage 0/1 CRC; however, we approach these findings with caution, given the high survival associated with stage 1 CRC [2]. Additionally, to the best of our knowledge, these 8 particular SNPs have not previously been linked with other health outcomes or phenotypes, while rs1869486 was formerly reported to be associated with the trait called fractional anisotropy (FA), a measurement for water diffusion in the brain. [43].

While somatic mutations are the main driver for cancer, inherent germline changes may have an impact on cancer outcome. More so, in the CRC model, they shape the tumor somatic alteration landscape [44]. Several studies suggest that carrying common germline variants might be indicative of the overall CRC prognosis and might provide predictive value for survival outcome [44, 45]. The epidemiological evidence for an association between long term circadian disruption and colorectal cancer development [46] served as premises for forming our initial hypothesis of possible association of genetic variation in the circadian rhythm and CRC survival. However, our results do not support this hypothesis.

Study Strengths and Limitations

The limitations of this study include the use of limited number of genes (13) central to the circadian system incorporated in the analysis, and the lack of racial/ethnic diversity among the study participants. Additionally, the study analysis was conducted on purely genetic inputs (circadian genes SNPs and chronotype associated SNPs) without having any (self-reported) phenotypic information on the circadian rhythm, chronotype, or sleep patterns of the participants.

Despite the many enumerated weaknesses of the study, there are several notable strengths to it. A major strength of the study was the sample size, given the availability of genotype data of interest for a large sample of CRC patients. At the same time, the use of multiple study populations led to heterogeneity in participant characteristics and study covariates. Additionally, the analysis was based on high quality data that was pooled from the 16 established studies within GECCO.

V. CONCLUSION

In conclusion, our study finds that the underlying germline variation in the circadian clock pathway captured by the selected SNPs within circadian genes and chronotype variants is not statistically significantly associated with survival outcomes after CRC diagnosis. Further

epidemiological research should seek to investigate the hypothesized, plausible associations of circadian cycle disruption and chronotype with CRC outcomes.

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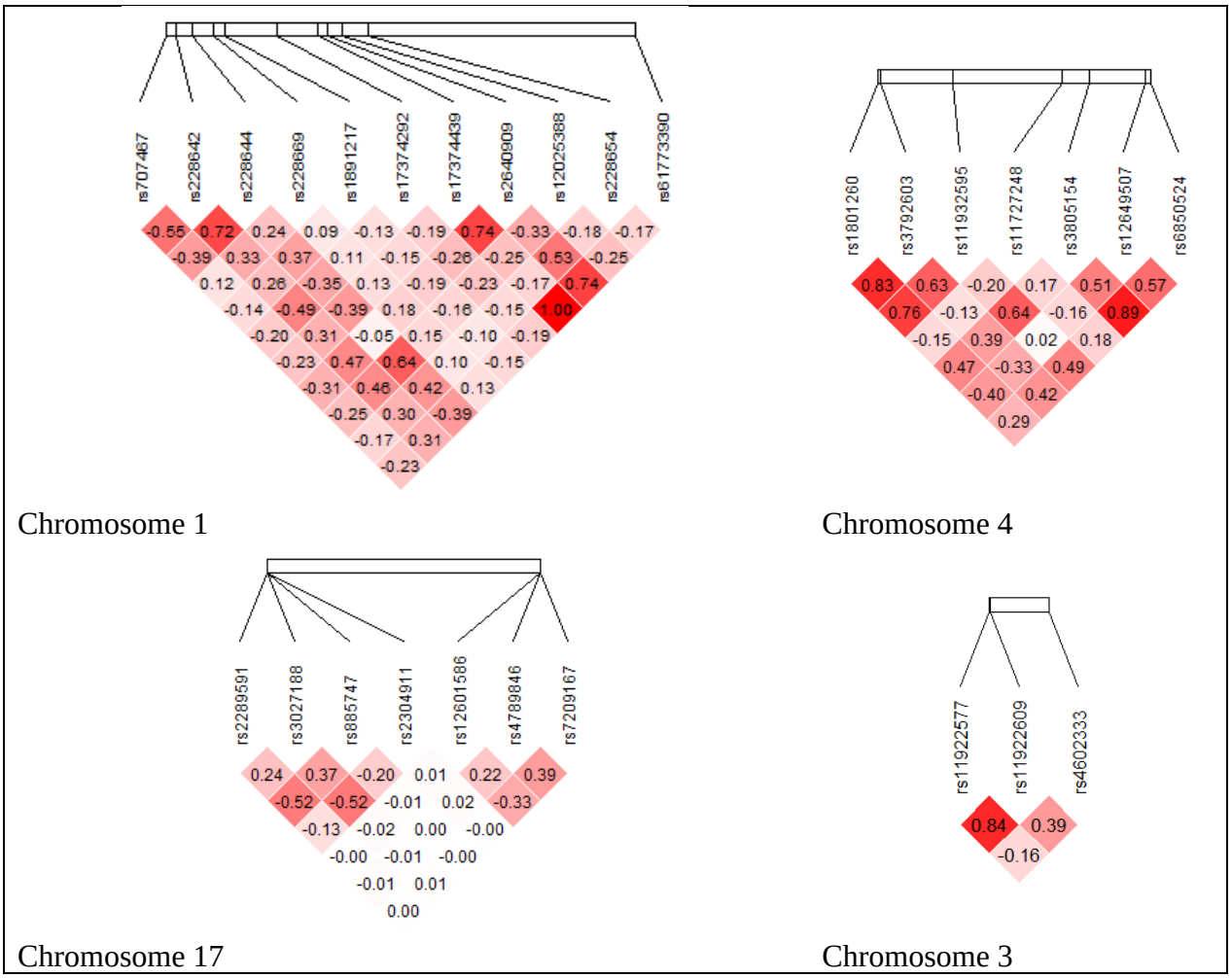
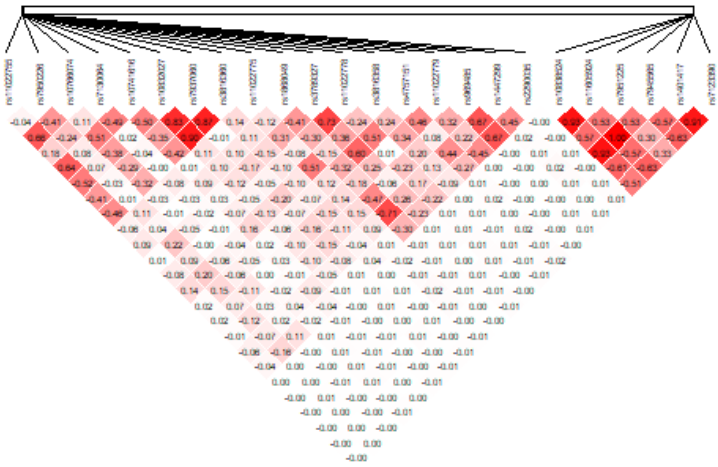
FIGURES AND TABLES

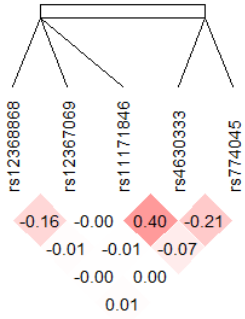
FIGURES

Figure 1. Pairwise LD among the 120 SNPs located withing the 13 circadian genes. In each box are shown the Pearson correlation coefficient (r) values between the counts of the minor alleles for two SNPs, indicating the LD relationships between each SNP pair. The bright red color indicates a high correlation.

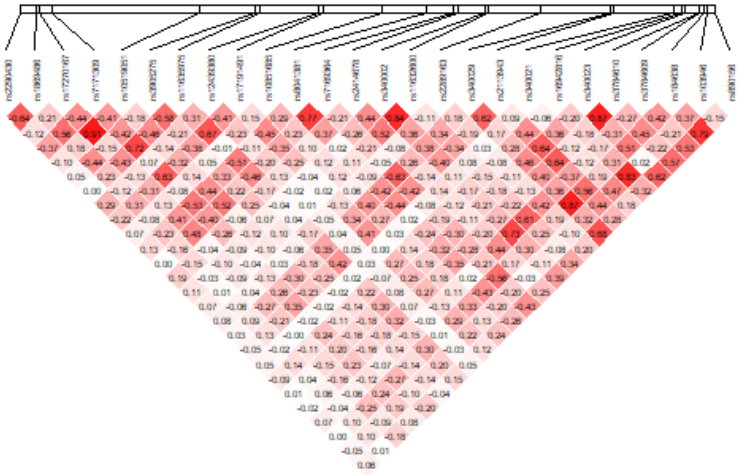




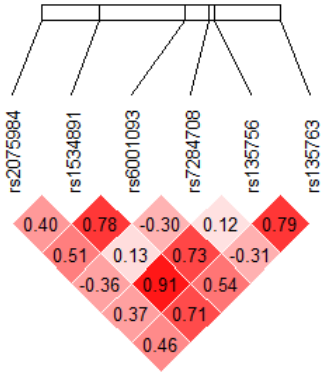
Chromosome 11



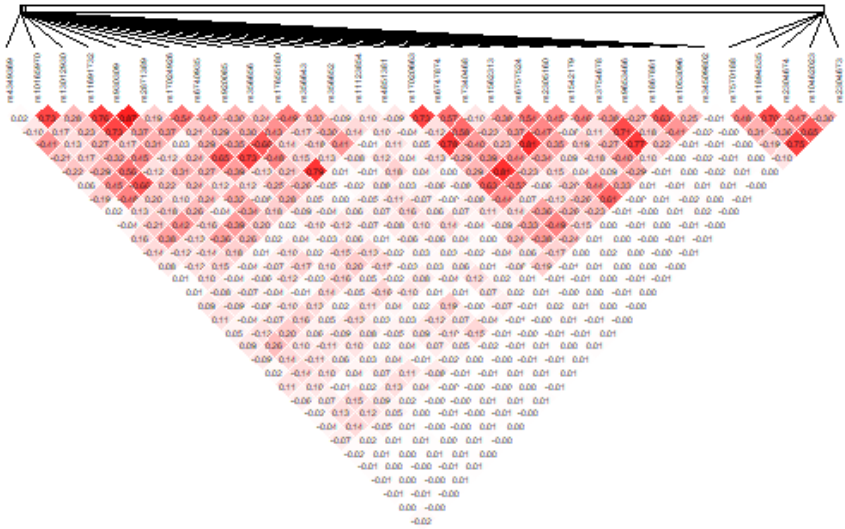
Chromosome 12



Chromosome 15



Chromosome 22



Chromosome 2

TABLES

Table 1. Participant demographic and clinical characteristics

Variable	Total		Deaths, Number (%)	
	N	**%**	**all-cause, N (column %)**	**CRC, N (column %)**
Age				
<65	7015	40.0%	2468 (33.7)	1770 (40.8)
65-69	3168	18.1%	1672 (22.8)	871 (20.1)
70-74	3807	21.7%	1511 (20.6)	860 (19.8)
≥75	3560	20.3%	1671 (22.8)	841 (19.4)
Sex				
Male	8758	49.9%	3504 (47.9)	2155 (49.6)
Female	8792	50.1%	3818 (52.1)	2187 (50.4)
Stage				
0|I or local	3693	21.0%	1098 (15.0)	205 (4.7)
II/III or regional	7016	40.0%	2859 (39.0)	1435 (33.0)
IV or distant	2018	11.5%	1767 (24.1)	1620 (37.3)
Missing	4823	27.5%	1598 (21.8)	1082 (24.9)
Tumor site				
Colon	12496	71.2%	5412 (73.9)	3181 (73.3)
Rectal	4890	27.9%	1817 (24.8)	1118 (25.7)
Missing	164	0.9%	93 (1.3)	43 (1.0)
Study				
CCFR	2508	14.3%	1313 (17.9)	608 (14.0)
CPSII	825	4.7%	321 (4.4)	188 (4.3)
DACHS	2659	15.2%	725 (9.9)	537 (12.4)
DALS	1098	6.3%	351 (4.8)	210 (4.8)
EDRN	207	1.2%	20 (0.3)	14 (0.3)
EPIC	1753	10.0%	555 (7.6)	439 (10.1)
HPFS	585	3.3%	411 (5.6)	122 (2.8)
MCCS	634	3.6%	359 (4.9)	193 (4.4)
N9741	495	2.8%	469 (6.4)	428 (9.9)
NHS	850	4.8%	468 (6.4)	208 (4.8)
NHSII	109	0.6%	22 (0.3)	22 (0.5)
PHS	323	1.8%	199 (2.7)	130 (3.0)
PLCO	976	5.6%	565 (7.7)	232 (5.3)
UKB	2996	17.1%	795 (10.9)	596 (13.7)
VITAL	270	1.5%	109 (1.5)	67 (1.5)
WHI	1262	7.2%	640 (8.7)	348 (8.0)

Table 2. Cox Proportional Hazard Ratios (HR) and 95% CI for the association between selected SNPs and clinical outcome of CRC patients

Outcome	Gene	SNP	Adjusted HR[1] (95% CI)	P-value	MAF
Overall survival	PDE8B	rs7721608	0.95 (0.92 - 0.98)	0.001	0.44
	SNORD37	rs495593	1.06 (1.02 - 1.10)	0.002	0.29
	PER3	rs707467	1.07 (1.02 - 1.11)	0.003	0.21
	HIST1H3PS1	rs766406	0.95 (0.92 - 0.99)	0.005	0.26
	NCEH1	rs3850174	0.95 (0.91 - 0.99)	0.005	0.2
	ZNF536	rs73026775	1.07 (1.02 - 1.13)	0.011	0.07
	ZCCHC2	rs11152350	1.04 (1.01 - 1.08)	0.012	0.41
	NT5C2	rs1163238	0.96 (0.93 - 0.99)	0.013	0.4
	NPAS2	rs356652	1.07 (1.02 - 1.14)	0.013	0.11
	RNU6-1037P	rs34329963	1.07 (1.01 - 1.12)	0.014	0.15
	RP11-613D13.5	rs7111582	0.94 (0.89 - 0.99)	0.029	0.16
	CTD-2568P8.1	rs6573308	1.04 (1.01 - 1.07)	0.029	0.48
	EEF1A1P11	rs11165655	0.96 (0.93 - 1)	0.029	0.37
	NRXN1	rs12470914	1.06 (1.01 - 1.12)	0.031	0.08
	TMCO4	rs10917513	1.04 (1 - 1.07)	0.035	0.47
	TTC28	rs695459	0.97 (0.93 - 1)	0.038	0.39
	YWHAZ	rs3100052	1.04 (1 - 1.07)	0.042	0.35
	PCYOX1	rs2706762	0.95 (0.91 - 1)	0.048	0.09
	DDI2	rs17448682	0.96 (0.93 - 1)	0.049	0.22
CRC survival	TTC28	rs695459	0.93 (0.89 - 0.97)	0.001	0.39
	SNORD37	rs495593	1.07 (1.02 - 1.12)	0.007	0.29
	NCEH1	rs3850174	0.94 (0.89 - 0.99)	0.011	0.2
	ZNF536	rs73026775	1.09 (1.02 - 1.17)	0.012	0.07
	HIST1H3PS1	rs766406	0.95 (0.91 - 0.99)	0.016	0.26
	PER3	rs707467	1.07 (1.01 - 1.13)	0.018	0.21
	RP11-404I7.1	rs17455138	0.94 (0.89 - 1)	0.019	0.16
	RNU6-1037P	rs34329963	1.08 (1.01 - 1.15)	0.019	0.15
	NPAS2	rs9653466	1.10 (1.01 - 1.19)	0.022	0.11
	NRXN1	rs12470914	1.08 (1.01 - 1.16)	0.023	0.08
	RP11-239A17.1	rs12298405	0.95 (0.91 - 1)	0.028	0.45
	PDE8B	rs7721608	0.95 (0.91 - 1)	0.029	0.44
	TMCO4	rs10917513	1.05 (1.01 - 1.10)	0.029	0.47
	PER3	rs10864315	0.95 (0.91 - 1)	0.029	0.28
	LRRTM4	rs10520176	1.05 (1 - 1.09)	0.039	0.34
	ARNTL	rs11022775	0.92 (0.85 - 1)	0.042	0.14

	CTD-2568P8.1	rs6573308	1.04 (1 - 1.09)	0.045	0.48
	EPC2	rs2166559	1.06 (1 - 1.13)	0.047	0.2
	SEMA6D	rs59986227	1.05 (1 - 1.10)	0.049	0.18
	ATE1	rs11200159	1.05 (1 - 1.09)	0.05	0.32

1. Adjusted for study, age at diagnosis and sex.

Table 3.1. Hazard ratios and 95% CI for the association between selected SNPs and ***overall survival*** of CRC patients **stratified by tumor stage**

Tumor stage	Gene	SNP	Adjusted HR[1] (95% CI)	P-value	MAF
Stage 0/1 or local	PCYOX1	rs2706762	0.83 (0.72 - 0.94)	0.005	0.09
	KHDRBS2	rs1931814	1.12 (1.03 - 1.22)	0.006	0.50
	ADH5P2	rs11588913	0.89 (0.82 - 0.97)	0.010	0.29
	MIR548X2	rs9571526	1.13 (1.02 - 1.24)	0.018	0.27
	CSNK1D	rs4789846	0.87 (0.76 - 0.98)	0.023	0.11
	RORA	rs3784609	0.88 (0.79 - 0.98)	0.023	0.14
	RNU6-248P	rs2881955	0.90 (0.81 - 0.99)	0.024	0.26
	MIR100HG	rs3867239	1.11 (1.01 - 1.21)	0.026	0.29
	EHMT2	rs486416	0.90 (0.82 - 0.99)	0.026	0.26
	RP11-189E14.5	rs4785296	0.89 (0.80 - 0.99)	0.028	0.17
	PRR7	rs465670	1.10 (1.01 - 1.20)	0.032	0.42
	DRD3	rs1800828	0.90 (0.81 - 0.99)	0.037	0.20
	CTD-2313J23.1	rs7203707	1.09 (1.00 - 1.19)	0.039	0.39
	U8	rs301218	1.09 (1.00 - 1.19)	0.042	0.36
	RP11-231G15.1	rs1559253	1.10 (1.00 - 1.20)	0.044	0.27
	GNG7	rs10402849	0.90 (0.80 - 1)	0.045	0.23
	BTBD9	rs3923809	0.91 (0.83 - 1)	0.049	0.33
Stage 2/3 or regional	ZCCHC2	rs11152350	1.08 (1.02 - 1.14)	0.006	0.41
	CLOCK	rs11932595	0.93 (0.89 - 0.98)	0.011	0.40
	RP11-700E23.3	rs7006885	1.08 (1.02 - 1.14)	0.012	0.22
	RP11-114G22.1	rs2433634	1.08 (1.02 - 1.14)	0.014	0.21
	PER3	rs707467	1.09 (1.02 - 1.16)	0.015	0.21
	BDNF-AS	rs10742179	0.93 (0.88 - 0.99)	0.015	0.28
	SNORD37	rs495593	1.08 (1.01 - 1.14)	0.017	0.29
	DDI2	rs17448682	0.93 (0.87 - 0.99)	0.017	0.22
	CLOCK	rs3792603	0.92 (0.86 - 0.99)	0.022	0.18
	PTPRD	rs6477309	1.07 (1.01 - 1.13)	0.023	0.31
	ACTG1P9	rs2396004	0.94 (0.90 - 0.99)	0.027	0.46

	AC087477.1	rs12442674	0.93 (0.87 - 0.99)	0.029	0.22
	RORA	rs890156	1.06 (1 - 1.11)	0.036	0.45
	AC009313.2	rs747003	1.06 (1 - 1.12)	0.037	0.35
	NOL4L	rs1737893	1.06 (1 - 1.12)	0.039	0.45
	RORA	rs103946	0.93 (0.86 - 1)	0.043	0.22
	TTC28	rs695459	0.95 (0.90 - 1)	0.044	0.39
	ZBTB16	rs4936290	0.94 (0.89 - 1)	0.046	0.31
Stage 4 or distant	PPP5D1	rs11670534	1.16 (1.06 - 1.27)	0.002	0.13
	RORA	rs12439380	1.14 (1.05 - 1.25)	0.003	0.15
	HIST1H3PS1	rs766406	0.90 (0.84 - 0.97)	0.004	0.26
	ESR2	rs2978382	0.91 (0.85 - 0.98)	0.011	0.42
	RNU7-145P	rs12969848	0.92 (0.86 - 0.98)	0.013	0.50
	AC007381.3	rs359248	0.92 (0.86 - 0.98)	0.015	0.44
	LINC01793	rs10175975	1.11 (1.02 - 1.21)	0.019	0.14
	PDZD8	rs7900191	0.92 (0.86 - 0.99)	0.021	0.49
	HMGN2P39	rs12871550	1.09 (1.01 - 1.17)	0.024	0.32
	CCDC90B	rs1278402	0.92 (0.85 - 0.99)	0.030	0.18
	RP11-282C5.1	rs60616179	0.85 (0.74 - 0.97)	0.031	0.10
	CTA-398F10.1	rs2979139	1.07 (1.00 - 1.14)	0.037	0.47
	MAP3K20	rs13004345	0.93 (0.87 - 1)	0.037	0.49
	TET1	rs2298117	0.93 (0.87 - 1)	0.038	0.49
	TARS2	rs9436119	0.93 (0.87 - 1)	0.046	0.30

1. Adjusted for study, age at diagnosis and sex

Table 3.2. Hazard ratios and 95% CI for the association between selected SNPs and ***CRC survival*** of CRC patients **stratified by tumor stage**

Tumor stage	**Gene**	**SNP**	**Adjusted HR[1] (95% CI)**	**P-value**	**MAF**
Stage 0/1 or local	AXDND1	rs975025	1.59 (1.16 - 2.18)	0.004	0.1
	RP11-4M23.7	rs2506089	1.34 (1.11 - 1.73)	0.004	0.48
	ATE1	rs11200159	1.32 (1.06 - 1.63)	0.012	0.32
	RORA	rs2289163	1.57 (1.09 - 2.24)	0.014	0.05
	RP11-114G22.1	rs2433634	0.74 (0.59 - 0.94)	0.015	0.21
	TMEM161B-AS1	rs4269995	0.75 (0.59 - 0.96)	0.02	0.25
	EIF2AK3	rs11681299	0.76 (0.60 - 0.96)	0.022	0.25
	CSNK1D	rs4789846	0.73 (0.55 - 1)	0.024	0.11
	RP11-958F21.3	rs1013987	0.8 (0.66 - 0.98)	0.027	0.34
	RGS7BP	rs7701529	1.31 (1.03 - 1.68)	0.028	0.2
	CD59	rs11032362	1.39 (1.04 - 1.86)	0.029	0.06

	UNC5D	rs6468316	1.24 (1.02 - 1.51)	0.029	0.48
	PER2	rs2304674	1.26 (1.02 - 1.55)	0.03	0.35
	RP11-775H9.2	rs4241964	0.80 (0.66 - 0.98)	0.032	0.37
	ADCY3	rs6718511	0.81 (0.66 - 0.99)	0.035	0.47
	EIF4G3	rs10916892	1.24 (1.02 - 1.52)	0.035	0.33
	ALG10B	rs1843888	1.23 (1.01 - 1.50)	0.036	0.43
	STUB1	rs72773411	0.71 (0.51 - 0.98)	0.037	0.13
	ZFP91	rs12808544	1.25 (1.01 - 1.55)	0.038	0.21
	C1QL1	rs3760381	0.78 (0.62 - 0.99)	0.039	0.27
	TARS2	rs9436119	1.23 (1 - 1.49)	0.044	0.3
	PER2	rs11894535	1.26 (1 - 1.57)	0.048	0.34
	SPTSSB	rs6440833	0.82 (0.67 - 1)	0.050	0.49
Stage 2/3 or regional	TTC28	rs695459	0.87 (0.81 - 0.94)	0.0004	0.39
	BICC1	rs9416744	1.14 (1.05 - 1.24)	0.003	0.25
	CLOCK	rs3792603	0.87 (0.789 - 0.96)	0.004	0.18
	SUCLA2P2	rs6727752	0.92 (0.85 - 0.99)	0.026	0.29
	RP11-700E23.3	rs7006885	1.09 (1.01 - 1.19)	0.028	0.22
	PHACTR1	rs9381812	0.92 (0.84 - 0.99)	0.030	0.26
	RP11-333O1.1	rs62124718	0.87 (0.76 - 0.99)	0.034	0.06
	AC079807.4	rs17396357	0.92 (0.86 - 1)	0.036	0.31
	CTD-2568P8.1	rs6573308	1.08 (1 - 1.164)	0.042	0.48
	BDNF-AS	rs10742179	0.92 (0.85 - 1)	0.043	0.28
	KAZN	rs12065331	0.92 (0.85 - 1)	0.046	0.27
	AJAP1	rs909757	0.92 (0.86 - 1)	0.048	0.29
	CLOCK	rs12649507	1.08 (1 - 1.17)	0.048	0.3
Stage 4 or distant	PPP5D1	rs11670534	1.17 (1.06 - 1.29)	0.002	0.13
	RORA	rs12439380	1.14 (1.04 - 1.25)	0.007	0.15
	HIST1H3PS1	rs766406	0.91 (0.84 - 0.97)	0.007	0.26
	RP11-282C5.1	rs60616179	0.82 (0.70 - 0.95)	0.010	0.1
	LINC01793	rs10175975	1.12 (1.03 - 1.23)	0.011	0.14
	CCDC90B	rs1278402	0.91 (0.84 - 0.99)	0.022	0.18
	ESR2	rs2978382	0.92 (0.85 - 0.99)	0.022	0.42
	RNU7-145P	rs12969848	0.92 (0.86 - 0.99)	0.027	0.5
	TET1	rs2298117	0.93 (0.86 - 0.99)	0.029	0.49
	AC007381.3	rs359248	0.93 (0.864 - 0.99)	0.029	0.44
	CTA-398F10.1	rs2979139	1.08 (1 - 1.15)	0.030	0.47
	RP11-397A16.1	rs4800998	1.10 (1 - 1.20)	0.037	0.15
	PDZD8	rs7900191	0.93 (0.86 - 1)	0.041	0.49
	RORA	rs2113943	0.93 (0.87 - 1)	0.048	0.43
	RP1-130G2.1	rs9465253	0.93 (0.86 - 1)	0.049	0.33

1. Adjusted for study, age at diagnosis and sex

Table 4.1. Hazard ratios and 95% CI for the association between selected SNPs and ***overall survival*** of CRC patients **stratified by tumor site**

Tumor site	Gene	SNP	Adjusted HR[1] (95% CI)	P-value	MAF
Colon	NCEH1	rs3850174	0.93 (0.89 - 0.97)	0.001	0.20
	HIST1H3PS1	rs766406	0.94 (0.91 - 0.98)	0.003	0.26
	ZCCHC2	rs11152350	1.06 (1.02 - 1.10)	0.005	0.41
	NT5C2	rs1163238	0.95 (0.91 - 0.99)	0.005	0.40
	PER3	rs707467	1.07 (1.02 - 1.12)	0.007	0.21
	RNU6-1037P	rs34329963	1.08 (1.02 - 1.15)	0.009	0.15
	ZNF536	rs73026775	1.08 (1.02 - 1.15)	0.010	0.07
	RORA	rs103946	0.93 (0.89 - 0.99)	0.010	0.22
	RP11-613D13.5	rs7111582	0.93 (0.87 - 0.99)	0.014	0.16
	SEMA6D	rs59986227	1.05 (1.01 - 1.10)	0.025	0.18
	PDE8B	rs7721608	0.96 (0.92 - 1)	0.026	0.44
	NPAS2	rs356652	1.08 (1.01 - 1.15)	0.029	0.11
	PCYOX1	rs2706762	0.94 (0.89 - 1)	0.030	0.09
	TMCO4	rs10917513	1.05 (1 - 1.09)	0.033	0.47
	THOC3	rs7735794	0.95 (0.90 - 1)	0.036	0.28
	SCUBE1	rs28459838	0.95 (0.91 - 1)	0.036	0.32
	SNORD37	rs495593	1.05 (1 - 1.09)	0.043	0.29
	ARNTL	rs11022755	1.04 (1 - 1.09)	0.044	0.27
Rectal	BEGAIN	rs11845599	0.91 (0.85 - 1)	0.009	0.47
	SNORD37	rs495593	1.11 (1.03 - 1.20)	0.009	0.29
	CLOCK	rs6850524	0.92 (0.86 - 0.98)	0.010	0.44
	CNTNAP5	rs76064513	0.88 (0.79 - 0.97)	0.011	0.14
	FAM185A	rs4729854	1.09 (1.02 - 1.17)	0.016	0.35
	ARNTL	rs7130064	1.13 (1.02 - 1.24)	0.017	0.14
	RP11-239A17.1	rs12298405	0.92 (0.86 - 0.99)	0.020	0.45
	NRXN1	rs12470914	1.13 (1.02 - 1.26)	0.020	0.08
	CSNK1D	rs7209167	0.92 (0.85 - 0.99)	0.026	0.31
	RP11-508N12.2	rs10759208	0.93 (0.87 - 0.99)	0.031	0.50
	PER1	rs2304911	1.17 (1.01 - 1.36)	0.032	0.09
	EEF1A1P11	rs11165655	0.93 (0.87 - 1)	0.035	0.37
	ARNTL	rs7950226	0.93 (0.87 - 1)	0.037	0.41
	RP11-189E14.5	rs4785296	0.92 (0.85 - 1)	0.039	0.17
	TET1	rs2298117	1.07 (1 - 1.14)	0.040	0.49

1. Adjusted for study, age at diagnosis and sex.

Table 4.2. Hazard ratios and 95% CI for the association between selected SNPs and ***CRC survival*** of CRC patients **stratified by tumor site**

Tumor site	Gene	SNP	Adjusted HR[1] (95% CI)	P-value	MAF
Colon	TTC28	rs695459	0.93 (0.88 - 0.98)	0.004	0.39
	PER3	rs707467	1.09 (1.02 - 1.16)	0.009	0.21
	TMCO4	rs10917513	1.07 (1.02 - 1.13)	0.011	0.47
	SEMA6D	rs59986227	1.08 (1.02 - 1.14)	0.012	0.18
	RP11-404I7.1	rs17455138	0.93 (0.88 - 0.99)	0.016	0.16
	THOC3	rs7735794	0.92 (0.86 - 0.99)	0.017	0.28
	HIST1H3PS1	rs766406	0.94 (0.89 - 0.99)	0.017	0.26
	RNU6-1037P	rs34329963	1.09 (1.01 - 1.18)	0.020	0.15
	CTD-2568P8.1	rs6573308	1.06 (1.01 - 1.12)	0.024	0.48
	NPAS2	rs9653466	1.11 (1.01 - 1.22)	0.026	0.11
	RORA	rs103946	0.92 (0.86 - 0.99)	0.026	0.22
	PER3	rs10864315	0.94 (0.89 - 0.99)	0.027	0.28
	ARNTL	rs11022775	0.90 (0.82 - 0.99)	0.034	0.14
	PER3	rs228642	0.95 (0.90 - 1)	0.040	0.49
	ZNF536	rs73026775	1.08 (1 - 1.17)	0.048	0.07
	RP11-613D13.5	rs7111582	0.92 (0.85 - 1)	0.049	0.16
Rectal	SNORD37	rs495593	1.14 (1.04 - 1.26)	0.008	0.29
	DUS3L	rs36055559	1.17 (1.04 - 1.32)	0.010	0.12
	RP11-508N12.2	rs10759208	0.90 (0.82 - 0.98)	0.011	0.5
	RP11-239A17.1	rs12298405	0.89 (0.82 - 0.98)	0.015	0.45
	ALG10B	rs1843888	1.11 (1.02 - 1.21)	0.017	0.43
	TIMELESS	rs4630333	1.11 (1.02 - 1.20)	0.019	0.34
	NRXN1	rs12470914	1.17 (1.03 - 1.34)	0.019	0.08
	CNTNAP5	rs76064513	0.86 (0.75 - 0.98)	0.020	0.14
	PABPC1L	rs2072727	1.10 (1.06 - 1.20)	0.021	0.4
	CLOCK	rs6850524	0.91 (0.83 - 0.99)	0.022	0.44
	BEGAIN	rs11845599	0.90 (0.83 - 0.99)	0.024	0.47
	PPP2R2D	rs12771973	1.17 (1.01 - 1.23)	0.025	0.25
	ST18	rs7845620	1.13 (1.01 - 1.26)	0.026	0.2
	DDI2	rs17448682	0.9 (0.82 - 0.99)	0.036	0.22
	AC087477.1	rs12442674	0.89 (0.81 - 0.99)	0.037	0.22
	SPTSSB	rs111867612	0.86 (0.74 - 1)	0.048	0.06

1. Adjusted for study, age at diagnosis and sex.

SUPPLEMENTARY TABLES

Table 1. List of highly correlated (r > 0.8) circadian SNP pairs. The SNP 1 list of variants was excluded from the analysis.

SNP 1	SNP 1 Position	SNP 2	SNP 2 Position	Gene	Chr	Pearson correlation coefficient
rs17374439	7828378	rs61773390	7828378	PER3	1	0.999
rs930309	100868072	rs2871389	100868072	NPAS2	2	0.872
rs6747874	100962027	rs1542179	100962027	NPAS2	2	0.811
rs1562313	100970993	rs1542179	100970993	NPAS2	2	0.807
rs11922577	23948750	rs11922609	23948750	NR1D2	3	0.843
rs1801260	55435202	rs3792603	55435202	CLOCK	4	0.827
rs3805154	55497760	rs6850524	55497760	CLOCK	4	0.894
rs10832027	13335636	rs7937060	13335636	ARNTL	11	0.829
rs10832027	13335636	rs3816360	13335636	ARNTL	11	0.897
rs7937060	13341268	rs3816360	13341268	ARNTL	11	0.869
rs10838524	45848626	rs11605924	45848626	CRY2	11	0.929
rs10838524	45848626	rs7945565	45848626	CRY2	11	0.928
rs11605924	45851540	rs7945565	45851540	CRY2	11	1.000
rs1401417	45858559	rs7123390	45858559	CRY2	11	0.909
rs17270167	60502976	rs10519051	60502976	RORA	15	0.909
rs340002	60580912	rs11632600	60580912	RORA	15	0.838
rs340023	60615883	rs3784610	60615883	RORA	15	0.869
rs340029	60602766	rs184638	60602766	RORA	15	0.869
rs16942816	60615293	rs103946	60615293	RORA	15	0.826
rs1534891	38299094	rs135756	38299094	CSNK1E	22	0.909

Table 2. Cox Proportional Hazard Ratios (HR) and 95% CI for the association between selected SNPs and clinical outcome of 9310 CRC patients ***in the first 5 years of follow up***.

Outcome	Gene	SNP	Adjusted HR[1] (95% CI)	P-value	MAF
Overall survival	HIST1H3PS1	rs766406	0.94 (0.90 - 0.98)	0.002	0.26
	KLF5	rs45597035	1.06 (1.01 - 1.10)	0.011	0.30
	HCRTR2	rs2653349	0.94 (0.90 - 0.99)	0.013	0.16
	TMCO4	rs10917513	1.05 (1.01 - 1.10)	0.014	0.47
	ARNTL	rs2290035	0.95 (0.91 - 0.99)	0.016	0.47
	SNORD37	rs495593	1.05 (1.01 - 1.10)	0.025	0.29
	ARNTL	rs11022755	1.05 (1 - 1.10)	0.038	0.27
	CRY2	rs7951225	0.95 (0.91 - 1)	0.040	0.38
	NCEH1	rs3850174	0.95 (0.91 - 1)	0.046	0.20
CRC survival	HIST1H3PS1	rs766406	0.94 (0.89 - 0.98)	0.006	0.26
	NCEH1	rs3850174	0.93 (0.88 - 0.98)	0.008	0.20
	KLF5	rs45597035	1.06 (1.01 - 1.11)	0.023	0.30
	NPS	rs10830107	0.94 (0.89 - 0.99)	0.028	0.15
	RP11-231G15.1	rs1559253	1.05 (1 - 1.11)	0.030	0.27
	TMCO4	rs10917513	1.05 (1 - 1.10)	0.033	0.47
	ARNTL	rs2290035	0.95 (0.91 - 1)	0.035	0.47
	HCRTR2	rs2653349	0.94 (0.89 - 1)	0.040	0.16
	NOCT	rs938836	0.95 (0.91 - 1)	0.040	0.42
	RNU6-1037P	rs34329963	1.07 (1 - 1.15)	0.042	0.15
	CTD-2015H3.1	rs2580160	0.95 (0.91 - 1)	0.043	0.45
	NPAS2	rs9653466	1.09 (1 - 1.19)	0.045	0.11
	FEZF1	rs6968240	0.95 (0.91 - 1)	0.045	0.33

1. Adjusted for study, age at diagnosis and sex.

Table 3.1. Hazard ratios and 95% CI for the association between selected SNPs and ***overall survival*** of CRC patients **stratified by tumor stage, *in the first 5 years of follow up***.

Tumor site	Gene	SNP	Adjusted HR[1] (95% CI)	P-value	MAF
Stage 0/1 (1163 patients)	ZFP91	rs12808544	1.3 (1.12 - 1.58)	0.001	0.21
	NRXN3	rs12436039	1.37 (1.10 - 1.70)	0.004	0.18
	RP11-228O6.2	rs3857599	0.73 (0.58 - 0.90)	0.004	0.16
	NPAS2	rs3754678	0.81 (0.69 - 0.95)	0.008	0.50
	TFEC	rs17302081	1.23 (1.05 - 1.42)	0.008	0.39
	HCRTR2	rs2653349	0.79 (0.66 - 0.94)	0.010	0.16
	SEMA6D	rs59986227	0.78 (0.65 - 0.94)	0.010	0.18
	ARNTL	rs11022779	1.27 (1.05 - 1.54)	0.016	0.16
	NAA25	rs7298532	0.81 (0.68 - 0.97)	0.019	0.46
	ADCY3	rs6718511	0.84 (0.72 - 0.98)	0.023	0.47
	HNRNPA1P57	rs7602499	0.84 (0.71 - 0.98)	0.027	0.37
	TRIM33	rs11102807	1.20 (1.02 - 1.41)	0.028	0.43
	RP11-415G4.1	rs9597241	0.81 (0.66 - 0.98)	0.028	0.14
	AC087477.1	rs12442674	0.81 (0.67 - 0.98)	0.028	0.22
	PPP3CA	rs2850979	1.22 (1.02 - 1.46)	0.029	0.27
	SLC12A5	rs57236847	1.19 (1.02 - 1.39)	0.031	0.29
	ARNTL	rs3816358	1.29 (1.02 - 1.63)	0.031	0.10
	RORA	rs890156	0.85 (0.73 - 0.99)	0.031	0.45
	RORA	rs3784610	0.82 (0.68 - 0.98)	0.033	0.20
	HDAC4	rs62182135	1.20 (1.01 - 1.41)	0.033	0.24
	USP34	rs812925	0.84 (0.72 - 0.99)	0.034	0.31
	RORA	rs340029	0.85 (0.74 - 0.99)	0.034	0.29
	NPAS2	rs1867861	0.85 (0.73 - 0.99)	0.034	0.37
	RORA	rs184638	0.86 (0.74 - 0.99)	0.035	0.38
	RASD1	rs11545787	1.21 (1.01 - 1.45)	0.036	0.20
	GNG7	rs10402849	0.82 (0.68 - 0.99)	0.038	0.23
	MARK2P10	rs10254050	1.22 (1.01 - 1.47)	0.039	0.26
	PRR7	rs465670	1.18 (1.01 - 1.39)	0.041	0.42
	AC079807.4	rs17396357	0.85 (0.72 - 0.99)	0.042	0.31
Stage 2/3 (3132 patients)	EHMT2	rs486416	1.13 (1.05 - 1.22)	0.002	0.26
	METTL15	rs4923541	0.91 (0.85 - 0.98)	0.010	0.40
	RP11-4M23.7	rs2506089	1.11 (1.08 - 1.20)	0.018	0.48
	SNORD37	rs495593	1.10 (1.01 - 1.19)	0.027	0.29
	AC007381.3	rs359248	0.93 (0.86 - 0.99)	0.033	0.44
	RORA	rs890156	1.08 (1.01 - 1.16)	0.033	0.45
	RNU6-1037P	rs34329963	1.12 (1.01 - 1.25)	0.034	0.15
	PATJ	rs12140153	0.86 (0.75 - 0.99)	0.035	0.06

	NR1D2	rs11922577	1.09 (1.01 - 1.18)	0.037	0.29
	NMD3	rs1599374	1.08 (1 - 1.16)	0.039	0.35
	RP11-775H9.2	rs4241964	0.93 (0.87 - 1)	0.049	0.37
	ARNTL	rs10832027	0.93 (0.86 - 1)	0.049	0.35
Stage 4 (1802 patients)	USP34	rs812925	1.11 (1.03 - 1.20)	0.005	0.31
	RNU7-145P	rs12969848	0.90 (0.84 - 0.97)	0.006	0.50
	PDE4B	rs11208844	1.14 (1.03 - 1.26)	0.009	0.20
	LIN52	rs4903203	0.90 (0.84 - 0.98)	0.010	0.40
	RORA	rs2290430	1.16 (1.03 - 1.31)	0.012	0.08
	KHDRBS2	rs1931814	0.92 (0.86 - 0.98)	0.012	0.50
	NOCT	rs938836	0.91 (0.85 - 0.98)	0.012	0.42
	PPP5D1	rs11670534	1.12 (1.02 - 1.24)	0.017	0.13
	AL354741.1	rs9558942	1.09 (1.01 - 1.18)	0.021	0.25
	CLOCK	rs12649507	1.09 (1.01 - 1.17)	0.022	0.30
	AC133680.1	rs2362775	0.92 (0.86 - 0.99)	0.023	0.35
	HIST1H3PS1	rs766406	0.92 (0.86 - 0.99)	0.023	0.26
	KLF5	rs45597035	1.08 (1.01 - 1.17)	0.029	0.30
	RORA	rs16942816	0.88 (0.79 - 0.99)	0.031	0.14
	CLOCK	rs3805154	1.08 (1.01 - 1.16)	0.032	0.30
	FOXP1	rs7626335	1.09 (1.01 - 1.17)	0.033	0.37
	CYP2A6	rs56113850	0.92 (0.86 - 0.99)	0.033	0.49
	DDI2	rs17448682	1.09 (1.01 - 1.19)	0.034	0.22
	LINC01249	rs13011556	1.10 (1.01 - 1.19)	0.039	0.23
	LINC01793	rs10175975	1.10 (1.01 - 1.20)	0.039	0.14
	RP11-415G4.1	rs9597241	0.91 (0.83 – 1)	0.039	0.14
	BICC1	rs9416744	0.92 (0.86 – 1)	0.041	0.25
	CLOCK	rs11932595	1.07 (1 - 1.15)	0.047	0.40
	LINC01088	rs6816922	1.07 (1 - 1.15)	0.048	0.45

1. Adjusted for study, age at diagnosis and sex.

Table 3.2. Hazard ratios and 95% CI for the association between selected SNPs and ***CRC survival*** of CRC patients **stratified by tumor stage, *in the first 5 years of follow up***.

Tumor site	Gene	SNP	Adjusted HR[1] (95% CI)	P-value	MAF
Stage 0/1 (1163 patients)	ZFP91	rs12808544	1.57 (1.18 - 2.10)	0.002	0.21
	UNC5D	rs6468316	1.49 (1.14 - 1.95)	0.003	0.48
	RORA	rs1869486	1.81 (1.21 - 2.70)	0.004	0.24
	C1QL1	rs3760381	0.64 (0.46 - 0.87)	0.005	0.27
	ADCY3	rs6718511	0.70 (0.52 - 0.91)	0.008	0.47
	NRXN3	rs12436039	1.60 (1.12 - 2.25)	0.009	0.18
	RP11-958F21.3	rs1013987	0.72 (0.55 - 0.94)	0.014	0.34
	HNRNPA1P57	rs7602499	0.69 (0.52 - 0.93)	0.014	0.37
	RP11-114G22.1	rs2433634	0.65 (0.46 - 0.92)	0.015	0.21
	RBM19	rs3955311	0.58 (0.37 - 0.91)	0.016	0.11
	PER2	rs2304674	1.40 (1.06 - 1.85)	0.017	0.35
	RORA	rs3784610	0.67 (0.48 - 0.95)	0.023	0.2
	SEMA6D	rs59986227	0.68 (0.48 - 0.96)	0.029	0.18
	RP11-231G15.1	rs1559253	1.37 (1.03 - 1.81)	0.029	0.27
	PER2	rs11894535	1.39 (1.03 - 1.86)	0.029	0.34
	AC112518.3	rs4860734	0.71 (0.51 - 0.97)	0.033	0.24
	MARK2P10	rs10254050	1.46 (1.03 - 2.08)	0.036	0.26
	TRIM33	rs11102807	1.33 (1.01 - 1.77)	0.045	0.43
	SYT16	rs7143933	0.75 (0.56 – 1)	0.048	0.21
	AXDND1	rs975025	1.57 (1 - 2.44)	0.048	0.1
Stage 2/3 (3132 patients)	EHMT2	rs486416	1.14 (1.04 - 1.25)	0.005	0.26
	AL357932.1	rs4657983	0.89 (0.82 - 0.97)	0.008	0.35
	RP11-4M23.7	rs2506089	1.13 (1.03 - 1.25)	0.013	0.48
	ARNTL	rs10832027	0.90 (0.83 - 0.99)	0.021	0.35
	CNTN4	rs35346733	0.88 (0.79 - 0.98)	0.022	0.13
	NR1D2	rs11922577	1.11 (1.01 - 1.22)	0.026	0.29
	ARNTL	rs3816358	1.16 (1.02 - 1.32)	0.028	0.1
	MAP3K20	rs13004345	0.91 (0.83 - 0.99)	0.03	0.49
	ARNTL	rs10741616	1.10 (1.01 - 1.19)	0.033	0.43
	VAMP2	rs1061032	0.86 (0.75 - 0.99)	0.033	0.16
	ADH5P2	rs11588913	0.91 (0.84 - 0.99)	0.035	0.29
	NPAS2	rs34509802	1.12 (1.01 - 1.25)	0.038	0.13
	NCEH1	rs3850174	0.91 (0.82 – 1)	0.044	0.2
	RORA	rs12439380	0.89 (0.80 – 1)	0.045	0.15
	RP11-333O1.1	rs62124718	0.86 (0.75 – 1)	0.048	0.06

Stage 4 (1802 patients)	KHDRBS2	rs1931814	0.90 (0.84 - 0.97)	0.005	0.5
	NOCT	rs938836	0.90 (0.84 - 0.97)	0.006	0.42
	USP34	rs812925	1.11 (1.03 - 1.20)	0.006	0.31
	PDE4B	rs11208844	1.14 (1.03 - 1.27)	0.009	0.2
	RNU7-145P	rs12969848	0.91 (0.84 - 0.98)	0.01	0.5
	RORA	rs2290430	1.17 (1.04 - 1.32)	0.011	0.08
	LIN52	rs4903203	0.90 (0.83 - 0.98)	0.012	0.4
	FOXP1	rs7626335	1.10 (1.02 - 1.19)	0.015	0.37
	PPP5D1	rs11670534	1.13 (1.02 - 1.25)	0.015	0.13
	HIST1H3PS1	rs766406	0.92 (0.85 - 0.99)	0.02	0.26
	PER1	rs3027188	1.13 (1.02 - 1.25)	0.021	0.24
	RORA	rs16942816	0.88 (0.78 - 0.98)	0.026	0.14
	AC016194.1	rs16939162	0.90 (0.81 - 0.99)	0.026	0.18
	LINC01793	rs10175975	1.11 (1.01 - 1.22)	0.027	0.14
	RP11-282C5.1	rs60616179	0.83 (0.71 - 0.98)	0.028	0.1
	RP11-415G4.1	rs9597241	0.90 (0.82 - 0.99)	0.028	0.14
	CLOCK	rs3805154	1.08 (1.01 - 1.17)	0.03	0.3
	AC133680.1	rs2362775	0.92 (0.86 - 0.99)	0.031	0.35
	AL354741.1	rs9558942	1.09 (1.01 - 1.18)	0.032	0.25
	RORA	rs10851685	1.14 (1.01 - 1.28)	0.035	0.11
	PIGK	rs12040629	1.11 (1.01 - 1.23)	0.036	0.15
	CYP2A6	rs56113850	0.92 (0.85 – 1)	0.037	0.49

1. Adjusted for study, age at diagnosis and sex.

Table 4. Hazard ratios and 95% CI for the association between selected SNPs and clinical outcome of CRC patients **stratified by tumor site*, in the first 5 years of follow up***.

Outcome	Tumor site	Gene	SNP	Adjusted HR[1] (95% CI)	P-value	MAF
Overall survival	Colon (6604 patients)	KLF5	rs45597035	1.08 (1.03 - 1.14)	0.002	0.3
		RP11-282C5.1	rs4535583	1.07 (1.02 - 1.13)	0.007	0.3
		HIST1H3PS1	rs766406	0.94 (0.89 - 0.98)	0.008	0.26
		NR1D2	rs11922577	1.07 (1.02 - 1.13)	0.008	0.29
		TMCO4	rs10917513	1.07 (1.02 - 1.12)	0.009	0.47
		NCEH1	rs3850174	0.94 (0.89 - 0.99)	0.02	0.2
		HCRTR2	rs2653349	0.94 (0.88 - 0.99)	0.02	0.16
		CCDC12	rs78580841	0.89 (0.80 - 0.99)	0.026	0.05
		NR1D2	rs11922609	1.06 (1.01 - 1.11)	0.029	0.42
		METTL15	rs4923541	0.95 (0.91 – 1)	0.029	0.4
		GNAO1	rs2550298	1.05 (1 - 1.1)	0.042	0.43
		ZNF536	rs73026775	1.08 (1 - 1.16)	0.044	0.07
		ZBTB16	rs4936290	0.95 (0.91 – 1)	0.045	0.31
		ZFP91	rs12808544	1.06 (1 - 1.11)	0.045	0.21
		RBM6	rs12636669	0.91 (0.83 – 1)	0.048	0.08
		ARNTL	rs4757151	1.05 (1 - 1.10)	0.049	0.43
		ARNTL	rs2290035	0.95 (0.91 - 1)	0.049	0.47
	Rectal (2642 patients)	BEGAIN	rs11845599	0.89 (0.81 - 0.97)	0.007	0.47
		RBM6	rs12636669	1.23 (1.06 - 1.43)	0.008	0.08
		TET1	rs2298117	1.11 (1.03 - 1.21)	0.01	0.49
		ST18	rs7845620	1.14 (1.03 - 1.27)	0.013	0.2
		GPR26	rs3808964	0.90 (0.83 - 0.98)	0.016	0.48
		U8	rs301218	0.91 (0.84 - 0.99)	0.022	0.36
		ARNTL	rs10832027	0.91 (0.83 - 0.99)	0.025	0.35
		ARHGAP15	rs28380327	1.10 (1.01 - 1.20)	0.029	0.26
		DUS3L	rs36055559	1.13 (1.01 - 1.27)	0.035	0.12
		ARNTL	rs10766074	1.12 (1 - 1.25)	0.043	0.14
		ARNTL	rs7950226	0.92 (0.84 – 1)	0.044	0.41
CRC Survival	Colon (6604 patients)	NCEH1	rs3850174	0.91 (0.86 - 0.97)	0.004	0.2
		KLF5	rs45597035	1.08 (1.02 - 1.14)	0.011	0.3
		TMCO4	rs10917513	1.07 (1.02 - 1.14)	0.011	0.47
		CD200R1L	rs34967119	0.94 (0.89 - 0.99)	0.013	0.45
		SEMA6D	rs59986227	1.07 (1.01 - 1.14)	0.021	0.18
		NPAS2	rs4349369	0.92 (0.85 - 0.99)	0.029	0.3
		CRY2	rs7951225	0.93 (0.88 – 1)	0.035	0.38
		ARNTL	rs969485	0.94 (0.89 – 1)	0.037	0.35
		HIST1H3PS1	rs766406	0.94 (0.89 – 1)	0.038	0.26

		RP11-282C5.1	rs4535583	1.06 (1 - 1.12)	0.04	0.3
		NPS	rs10830107	0.94 (0.88 – 1)	0.045	0.15
		ARNTL	rs2290035	0.95 (0.90 – 1)	0.045	0.47
	Rectal (2642 patients)	ST18	rs7845620	1.19 (1.05 - 1.33)	0.005	0.2
		DUS3L	rs36055559	1.17 (1.03 - 1.34)	0.015	0.12
		RBM6	rs12636669	1.23 (1.03 - 1.46)	0.019	0.08
		BEGAIN	rs11845599	0.89 (0.80 - 0.98)	0.019	0.47
		TET1	rs2298117	1.10 (1.01 - 1.21)	0.036	0.49
		PATJ	rs12140153	0.83 (0.70 - 0.99)	0.038	0.06
		RP11-415G4.1	rs9597241	0.88 (0.78 – 1)	0.044	0.14
		HIST1H3PS1	rs766406	0.91 (0.82 – 1)	0.048	0.26
		GPR26	rs3808964	0.91 (0.83 - 1)	0.049	0.48

1. Adjusted for study, age at diagnosis and sex.