XCyting

FISH Probes

1st Edition

CATALOG

MetaSystems
Probes

Dear Customer,

As a globally operating company, we stand for trust in reason, global cooperation and the desire for peace and unity. We are following the current events in Ukraine and the associated suffering of the people with great concern. We would like to express our loyalty to Ukraine and have therefore decided to suspend our business relations with Russia until further notice.

On May 26, 2022, the Regulation (EU) 2017/746 of the European parliament and of the council of 5 April 2017 on in vitro medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (IVDR) entered into force as scheduled. However, the EU has extended the transition period to give manufacturers the opportunity to implement the high requirements and to avoid that certain IVDs are no longer available to the diagnostic market. For us as manufacturers and for you as users of in vitro diagnostics, the IVDR has far-reaching consequences. As we have already informed you, it could unfortunately not be avoided that we can now offer some products only labeled as Research Use Only. However, we are in the process of bringing the majority of our portfolio in line with the requirements of IVDR, so that we can provide you with our products as CE-IVD under the new certificate by the end of the transition period at the latest. This will ensure that you can continue to use our products in diagnostics without any worries in the future. We expect to be able to offer part of our portfolio compliant with IVDR as early as 2023, as we are registering products in groups sequentially.

We thank you for your loyalty and look forward to further years of good cooperation.

Altlussheim, Germany, 2023

Disclaimer
All our CE-IVD labeled MetaSystems Human FISH probe products were lawfully placed on the market before the date of application of the IVDR (Regulation (EU) 2017/746) in May 2022 on the basis of a valid certificate according to the IVDD (Directive 98/79/EC). They are still available on the market according to their IVDD classification. We assure you that the delivered products for in-vitro diagnostics always comply with the respective applicable requirements of the IVDR. The specified transition periods are applied (Article 110 of the IVDR).

CE-IVD products may not be available in all markets outside the EU due to varying regulatory requirements.

Note

Probe maps are created in accordance with the intended purpose of the product. Solid colored bars do not necessarily indicate that the probe fully covers the indicated genomic region. Therefore, caution is advised when interpreting results generated through off-label use. Further information is available on request. Probe map details based on UCSC Genome Browser GRCh37/hg19. Map components not to scale.

Notes

Order No:
D-5138-100-OG

Size: **100 µl**

XL ABL2 BA IVD

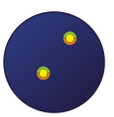
XL ABL2 BA consists of an orange-labeled probe hybridizing proximal to the breakpoint in the ABL2 gene region at 1q25.2 and a green-labeled probe hybridizing distal to the break point in the ABL2 gene region at 1q25.2.

Acute lymphoblastic leukemia (ALL) is a rare disease with approximately 1:100.000 new diagnoses per year. Around 3-5% of pediatric ALL and 25% of adult ALL are characterized by t(9;22), resulting in the BCR-ABL1 fusion gene, a constitutively active tyrosine kinase. Furthermore, BCR-ABL1 is genetically characterizing chronic myelogenous leukemia. Tyrosine kinase inhibitor treatment of BCR-ABL1-positive cases, which initially have a poor prognosis, dramatically improves the outcome. A novel high risk subtype called BCR-ABL1-like ALL or Philadelphia-like ALL was discovered based on similar gene expression profiles to BCR-ABL1-positive ALL and is characterized by aberrations resulting in activation of tyrosine kinase signaling pathways. Prominent genes in the JAK/STAT activating group are CRLF2, EPOR and JAK2, while members of the ABL-class fusions are ABL1, ABL2, CSF1R and PDGFRB. ´The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia´ specifies B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like as a provisional entity.

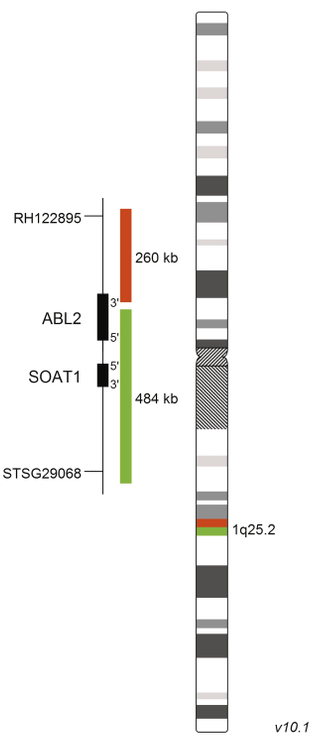
The ABL2 gene has been initially identified as a novel fusion partner of ETV6. ABL2 belongs to the Abelson family of non-receptor tyrosine kinases and is highly similar to ABL1. t(1;12)(q25;p13) results in a chimeric ETV6-ABL2 protein with a constitutive active tyrosine kinase.

Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).



Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.



Literature

- Iijima et al (2000) Blood 95:2126-2131
- Arber et al (2016) Blood 127:2391-2405
- Tasian et al (2017) Blood 130:2064-2072

Order No:
D-6021-100-OG

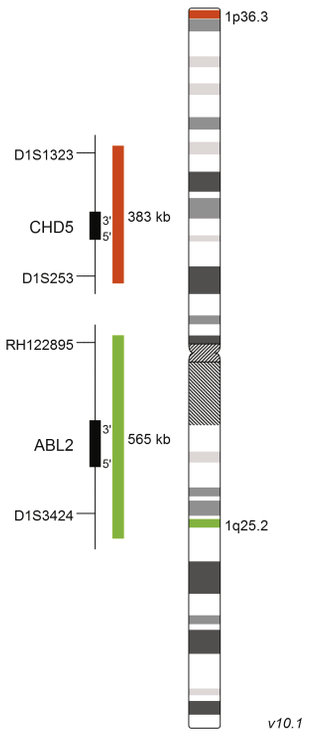
Size: **100 µl**

XCyting Locus-Specific Probes
Deletion Probe **XL**

IVD XL 1p36/1q25 del

XL 1p36/1q25 del consists of an orange-labeled probe hybridizing to the CHD5 gene region at 1p36.3 and a green-labeled probe hybridizing to the ABL2 gene region at 1q25.2.

The 2016 ´World Health Organization Classification of Tumors of the Central Nervous System´ (WHO 2016) combines, for the first time, histological features and molecular signatures for the definition of many tumor entities. Gliomas are a category of tumors of the brain and spinal cord starting in glia cells. Oligodendrogliomas are a subtype of gliomas accounting for up to 18% of all cases. According to the WHO 2016, the classification of an oligodendroglioma requires information about the isocitrate dehydrogenase mutation status and 1p/19q loss of heterozygosity (LOH). LOH of 1p can be detected in about 67% of oligodendroglial tumors and has also been identified in neuroblastomas and other tumor entities. Co-deletion of 1p/19q is a well-accepted prognostic biomarker in neuro-oncology. Patients suffering from anaplastic oligodendroglioma harboring 1p/19q deletion generally have a good prognosis. Co-deletion of 1p/19q also has predictive character, the molecular status of 1p/19q is relevant for therapy decisions.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal resulting from loss of one orange signal.

Literature

- Reifenberger et al (1994) Am J Pathol 145:1175-1190
- Louis et al (2016) Acta Neuropathol 131:803-820
- Staedtke et al (2016) Trends Cancer 2:338-349

Order No:
D-5099-100-OG

Size: **100 µl**

XL CDKN2C/CKS1B IVD

XL CDKN2C/CKS1B consists of a green-labeled probe hybridizing to the CDKN2C (p18) gene region at 1p32.3 and an orange-labeled probe hybridizing to the CKS1B gene region at 1q21-22.

Multiple myeloma (MM) is a plasma cell malignancy characterized by very complex cytogenetic and molecular genetic aberrations. Hyperdiploid karyotypes are characterized mainly by trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21, non-hyperdiploid karytoypes typically have translocations involving the IGH locus at 14q32. The most frequent deletions are 13q, 17p and 1p32.

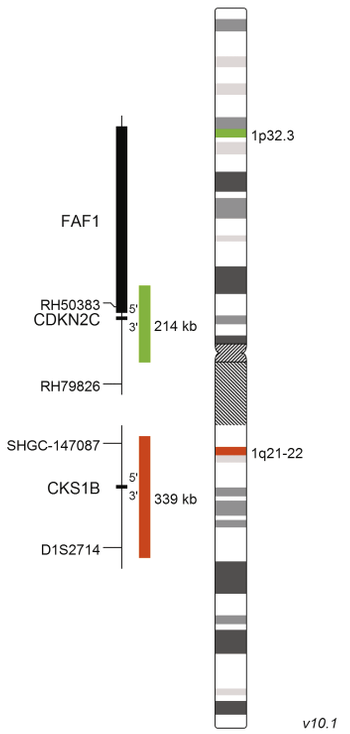
Deletions of chromosome 1p have been described in 7-15% of cases of myeloma with inconsistent clinical consequences. CDKN2C at 1p32.3 has been identified in myeloma cell lines as the potential target of the deletion. Gain of 1q is one of the most recurrent chromosomal aberrations in MM. Amplification and overexpression of the CKS1B gene in chromosome band 1q21 has been associated with an aggressive clinical course in MM.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and three orange (3O) signals, indicating a gain of the CKS1B locus.

Aberrant Cell (typical results)
One green (1G) and two orange (2O) signals, indicating a loss of the CDKN2C locus.



Literature

- Hanamura et al (2006) Blood 108:1724-1732
- Leone et al (2008) Clin Cancer Res 14:6033-6041
- Jian et al (2016) Medicine 95:1-7

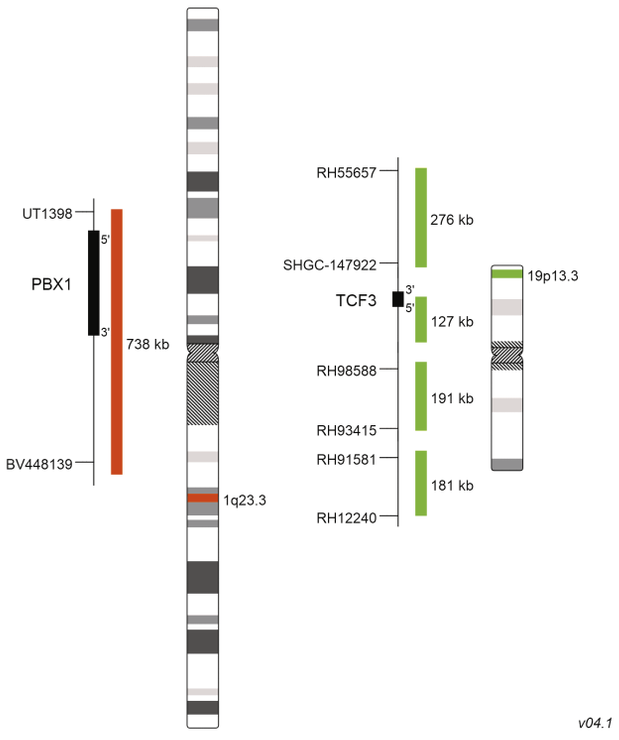
Order No:
D-5153-100-OG

Size: **100 µl**

RUO XL t(1;19) PBX1/TCF3 DF

XL t(1;19) PBX1/TCF3 DF consists of an orange-labeled probe hybridizing to the PBX1 gene region at 1q23.3 and a green-labeled probe hybridizing to the TCF3 (E2A) gene region at 19p13.

Please note that this product is not classified as an IVD product in the EU according to the REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. It is marked as for ´Research Use Only´ (RUO).



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange fusion (2GO) (adjacent green and orange) signals.

Order No:
D-5116-100-OG

Size: **100 µl**

XL 2p11 IGK BA IVD

XL 2p11 IGK BA probe consists of an orange-labeled probe hybridizing to the ´IGKV distal´ region at 2p11.2, and a green-labeled probe hybridizing distal to the ´IGKV proximal´, IGKJ and IGKC region at 2p11.2.

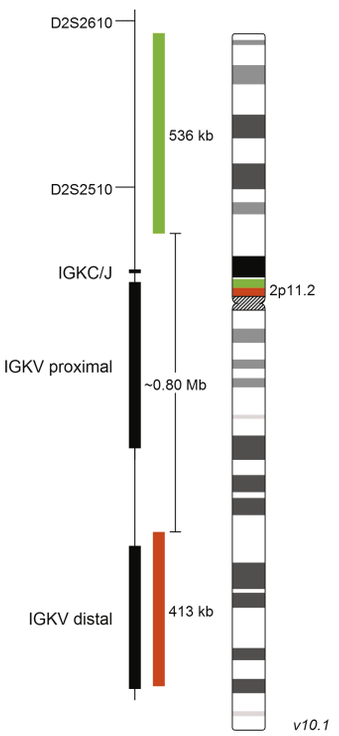
The immunoglobulin (IG) genes for the kappa light chain at 2p11 (IGK), the lambda light chain at 22q11 (IGL) and the heavy chain at 14q32 (IGH) are recurrently involved in the development of non-Hodgkin lymphomas (NHL). By far most frequently involved is IGH with more than 30 partner genes, less frequently IGK and IGL. IG-translocations are leading to juxtaposition of proto-oncogenes with IG enhancer sequences resulting in overexpression of the respective oncogene. Chromosomal translocations involving MYC at 8q24 and IG genes frequently occur in Burkitt lymphoma (BL). BL is a rare but fast growing type of NHL which is rapidly fatal if left untreated. About 75% of BL patients are carrying the MYC rearrangement t(8;14) while the remainder show a translocation between MYC and IGK or IGL. MYC-IG rearrangements are also involved in other B-cell malignancies such as atypical Burkitt/Burkitt-like lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma and multiple myeloma. Besides 8q24 (MYC), other translocation partners for IGK, such as chromosomal regions 1p13, 3q27 (BCL6), 7q21, 16q24 and 18q21 (BCL2), are known.

FISH break apart assays are valuable tools for the detection of IG light chain rearrangements independent of the translocation partner. Furthermore, double translocations have been described which are difficult to detect by PCR-based methods.

Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.



Literature

- Martin-Subero et al (2002) Int J Cancer 98:470-474
- Einerson et al (2006) Leukemia 10:1790-1799
- Fujimoto et al (2008) Eur J Haematol 80:143-150

Order No:
D-6001-100-OG

Size: **100 µl**

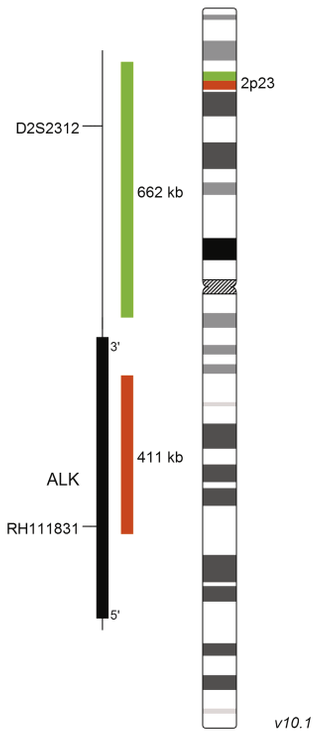
XCyting Locus-Specific Probes
Break Apart Probe
XL

IVD **XL ALK BA**

XL ALK BA consists of an orange-labeled probe hybridizing to a region within the ALK gene at 2p23 and a green-labeled probe hybridizing distal to the ALK gene region at 2p23.

The EML4/ALK fusion gene is responsible for approximately 3-5% of non-small-cell lung cancer (NSCLC). The vast majority of cases are adenocarcinomas. Two other fusion partners of ALK have been reported in lung cancer - TFG and KIF5B. Up to 12 other translocation partners have been described in anaplastic large-cell lymphomas (ALCL), renal cancer, esophageal squamous cell, colon, and breast carcinoma. Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase which was discovered in anaplastic large-cell lymphoma (ALCL).

The formation of a fusion protein with a partner through chromosomal translocations is the most common mechanism of ALK overexpression and ALK kinase domain activation. The ALK inhibitor crizotinib has increased the significance of detecting ALK rearrangements in lung cancer and ALCL.



Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal resulting from loss of one orange signal.

Literature

- Kutok et al (2002) J Clin Oncol 20:3691-3702
- Perner et al (2008) Neoplasia 10:298-302
- Shaw et al (2009) J Clin Oncol 27:4247-4253

Order No:
D-6031-100-OG

Size: **100 µl**

XL MYCN amp IVD

XL MYCN amp consists of a green-labeled probe hybridizing to the MYCN gene region at 2p24 and an orange-labeled probe hybridizing to the NMI gene region at 2q23.

The MYCN gene is a member of the MYC transcription factor family consisting of c-MYC, MYCN and MYCL. It is crucial for embryonic development, especially in the nervous system. The expression is tightly regulated in a spatial and timely manner and high levels are found in the developing brain, retina, neuroepithelial cells, lung and kidney. MYCN expression is associated with the maintenance of self-renewal capacity and the pluripotent status of stem cells. Dysregulation of MYCN contributes to the development of different kinds of childhood tumors including neuroblastoma, medulloblastoma, rhabdomyosarcoma and Wilms tumor. MYCN is also involved in the development of some adulthood neoplasms such as prostate and lung cancer.

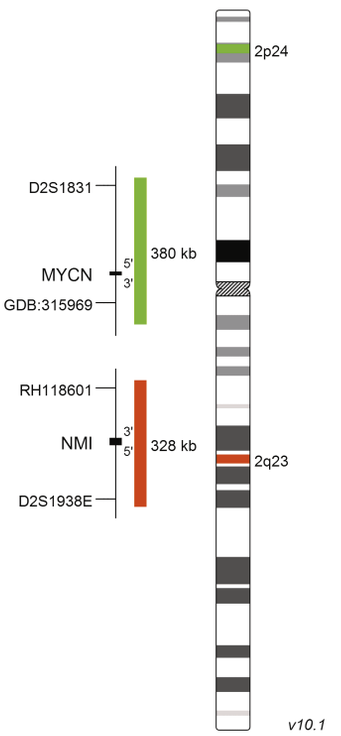
Neuroblastoma is the most common extracranial solid tumor in infants. About 6% of all cancers in children are caused by neuroblastomas and 20-25% of neuroblastoma patients are showing an amplification of the MYCN gene. MYCN amplification is an important prognostic marker for risk stratification in neuroblastoma. Generally, patients with MYCN amplification have a poor prognosis. FISH is a valuable tool for the analysis of the MYCN amplification status. It detects MYCN amplification on single-cell level and allows the correlation with morphological cell features.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two orange (2O), one green (1G) and green signal clusters resulting from an amplification of the green signal (homogenously staining region).

Aberrant Cell (typical results)
Two orange (2O) and multiple green (mG) signals resulting from amplification of the green signal (double minutes).



Literature

- Theissen et al (2009) Clin Cancer Res 15:2085-2090
- Huang and Weiss (2013) Cold Spring Harb Perspect Med 2013;3(10):a014415
- Ruiz-Pérez et al (2017) Genes 8(4):113

Order No:
D-6016-100-OG

Size: **100 µl**

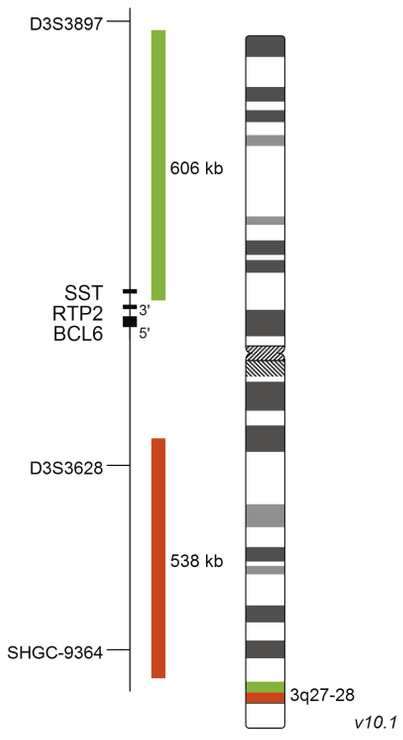
XCyting Locus-Specific Probes
Break Apart Probe
XL

IVD XL BCL6 BA

XL BCL6 BA consists of a green-labeled probe hybridizing proximal to the BCL6 gene region at 3q27 and an orange-labeled probe hybridizing distal to the BCL6 gene region at 3q27-28.

Follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBL) represent the two most common entities of non-Hodgkin lymphoma (NHL) worldwide with up to 22% and 31% of tumors, respectively. FLs have been classically associated with the translocation t(14;18)(q32;q21) in 70% to 95% of reported tumors, whereas translocations involving the BCL6 proto-oncogene locus in chromosomal band 3q27 are encountered in 6% to 14%. In DLBLs, a BCL6 translocation can be found in up to 40% of cases, while BCL2 translocations occur in 20% to 30%.

The relatively wide separation of the probe binding sites allows for the detection of translocations in the MBR (major breakpoint cluster region) as well as in the ABR (alternative breakpoint cluster region).



Expected Patterns

Normal Cell
Two green-orange (2GO, may appear yellow 2Y) fusion signals.

Aberrant Cell (typical results)
One green-orange (1GO, may appear as yellow) fusion signal and one green (1G), one orange (1O) indicating a chromosome break in the BCL6 locus.

Literature

- Butler et al (2002) Cancer Res 62:4089-4094
- Katzenberger et al (2004) Am J Pathol 165:481-490
- Iqbal et al (2007) Leukemia 21:2332-2343

Order No:
D-5059-100-OG

Size: **100 µl**

XL MECOM 3q26 IVD

XL MECOM 3q26 consists of an orange-labeled probe hybridizing proximal to the MECOM gene region at 3q26.2 and a green-labeled probe hybridizing distal to the MECOM gene region also spanning a distal part of the gene region at 3q26.2.

Myelodysplastic neoplasms (MDS) and myeloproliferative neoplasms (MPN) are associated with deregulated production of myeloid cells. According to WHO classification (2008), cytogenetic aberrations are observed in about 50% of MDS cases. The most common aberrations are 5q-, 7/7q-, trisomy 8, del(20q), and inv(3) or t(3;3).

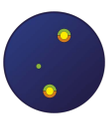
Chromosomal translocations involving the EVI1 locus are a recurrent finding in myeloid leukemia and are associated with poor prognosis. EVI1 is, together with MDS1, located in the ´MDS1 and EVI1 complex locus´ (MECOM) and is the major player in this subtype of AML. Two common recurrent rearrangements affect the 3q26 locus. One is the inv(3)(q21q26) and the translocation t(3;3)(q21;q26), in which EVI1 overexpression is caused by juxtaposition of the EVI1 gene to enhancer elements of the Ribophorin gene at 3q21. EVI1 activation is also observed in the translocations t(3;12)(q26;p13) and t(3;21)(q26;q22) and is due to generation of the fusion genes ETV6/EVI1 and RUNX1/EVI1, respectively.

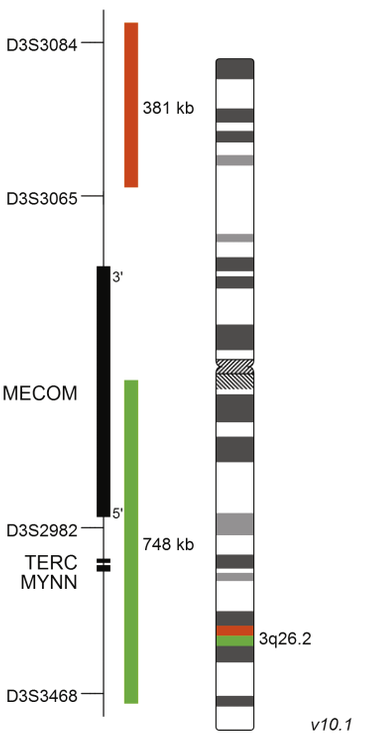
Expected Patterns

Normal Cell
Two green-orange (2GO) fusion signals representing the two normal MECOM loci.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and one green-orange (1GO) fusion signal, indicating a chromosome break in the MECOM locus.

Aberrant Cell (typical results)
One green (1G) and two green-orange (2GO) fusion signals, indicating a variant chromosome break at a more distal region of the MECOM locus.





Literature

- Lugthart et al (2008) Blood 111:4329-4337
- De Melo et al (2008) Leukemia 22:434-437
- De Braekeleer et al (2011) Anticancer Res 31:3441-3448

Order No:
D-5124-100-OG

Size: **100 µl**

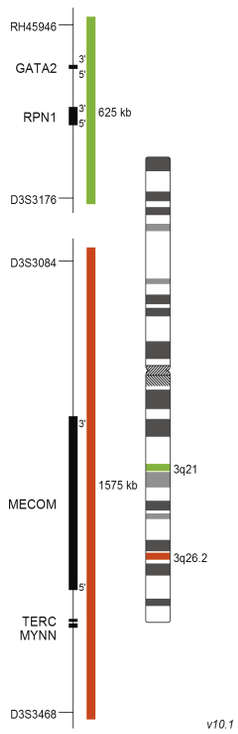
IVD XL t(3;3) GATA2/MECOM DF

XL t(3;3) GATA2/MECOM DF consists of a green-labeled probe hybridizing to the GATA2 gene region at 3q21 and an orange-labeled probe hybridizing to the MECOM gene region at 3q26.2.

The chromosomal aberrations inv(3)(q21q26.2) and t(3;3)(q21;q26.2) characterize a distinct entity within patients with acute myeloid leukemia (AML). Their incidence in AML is about 1-2.5% and patients have an unfavorable prognosis and low response to chemotherapy.

Inv(3)/t(3;3) juxtapose the GATA2 enhancer with the MECOM locus which results in overexpression of EVI1. The EVI1 gene is located in 3q26 and is involved in hematopoietic stem cell maintenance. EVI1 is, together with MDS1, located in the ´MDS1 and EVI1 complex locus´ (MECOM) and is the major player in this subtype of AML.

Furthermore, structural rearrangements caused by inv(3)/t(3;3) result in reduced GATA2 expression which may contribute to the oncogenic potential of this aberration. GATA2 is located in chromosomal region 3q21 and is involved in development and proliferation of hematopoietic stem cells. Several other recurrent 3q26 rearrangements such as t(3;21)(q26;q22), t(3;12)(q26;p13) and t(2;3)(p15-23;q26) are known and many more rearrangements may occur.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from an inversion or reciprocal translocation with breakpoints in the respective loci.

Aberrant Cell (typical results)
Two green (2G) and three orange (3O) signals resulting from a translocation with breakpoints in the orange labeled gene region and another unknown chromosome.

Literature

- Gröschel et al (2014) Cell 157:369-381
- De Braekeleer et al (2015) Fut Oncol 11:1675-1686
- Arber et al (2016) Blood 19:2391-2405

Order No:
D-5063-100-TC

Size: **100 µl**

XL 4q12 IVD

XL 4q12 consists of a green-labeled probe hybridizing proximal to the FIP1L1 gene region at 4q12, an orange-labeled probe hybridizing to the CHIC2 gene region at 4q12 and an aqua-labeled probe hybridizing to the PDGFRA gene region at 4q12.

The category ´myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB or FGFR1, or with PCM1/JAK2´ of the revised 4th edition of the WHO classification defines three particular groups with rearrangements in PDGFRA, PDGFRB or FGFR1 and a provisional entity with PCM1/JAK2 rearrangement. The clinical manifestations within this category are numerous and heterogeneous and include myeloproliferative neoplasms, myelodysplastic neoplasms (MDS) as well as de novo or secondary mixed phenotype acute leukemia and lymphomas. Neoplasms with eosinophilia are associated with dysregulated tyrosine kinases, usually as a result of gene fusions. It is of great importance to identify the genes involved because aberrant tyrosine kinases react with varying sensitivity to tyrosine kinase inhibitors. Patients with PDGFRA and PDGFRB rearrangements are responsive to imatinib whereas FGFR1-related diseases are non-responsive. PDGFRA rearrangements are usually associated with chronic eosinophilic leukemia (CEL).

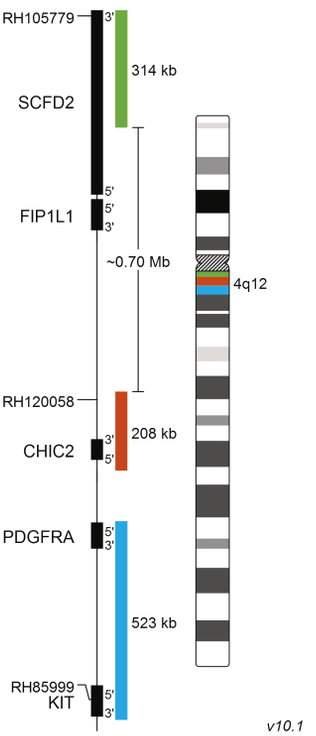
The most frequent PDGFRA-related aberration is the interstitial deletion of the CHIC2 gene with breakpoints in the FIP1L1 and PDGFRA genes. The deletion of a fragment of about 800kb is resulting in the FIP1L1-PDGFRA fusion gene, a constitutively activated tyrosine kinase transforming hematopoietic cells.

In FISH assays, the detection of CHIC2 deletion at 4q12 is a surrogate for the direct detection of the FIP1L1-PDGFRA fusion gene. Translocations with other partner genes, resulting in aberrant tyrosine kinase activity, are known. Involvement of PDGFRA can be detected by break apart FISH strategies.

Expected Patterns

Normal Cell
Two blue-green-orange fusion signals (2BGO).

Aberrant Cell (typical results)
One blue-green-orange (1BGO) and one blue-green (1BG) fusion signal indicating a deletion of CHIC2.



Literature

- Cools et al (2003) N Engl J Med 348:1201-1214
- Pardanani et al (2003) Blood 102:3093-3096
- Swerdlow et al (2017) WHO classification of tumors of haematopoietic and lymphoid tissues (revised 4th edition)

Order No:
D-5123-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Translocation/Deletion Probe **XL**

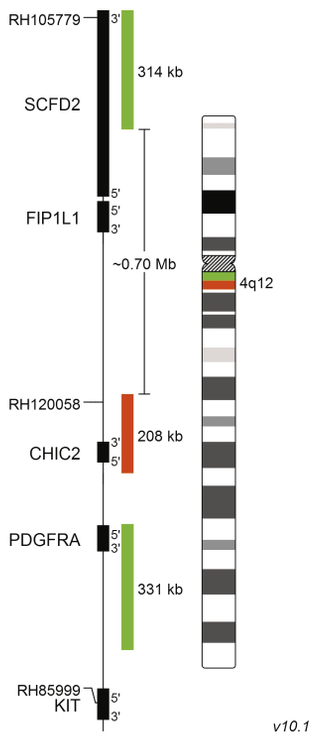
IVD XL 4q12 DC

XL 4q12 DC consists of a green-labeled probe hybridizing proximal to the FIP1L1 gene region at 4q12, an orange-labeled probe hybridizing to the CHIC2 gene region at 4q12 and another green-labeled probe hybridizing to the PDGFRA gene region at 4q12.

The category ´myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB or FGFR1, or with PCM1/JAK2´ of the revised 4th edition of the WHO classification defines three particular groups with rearrangements in PDGFRA, PDGFRB or FGFR1 and a provisional entity with PCM1/JAK2 rearrangement. The clinical manifestations within this category are numerous and heterogeneous and include myeloproliferative neoplasms, myelodysplastic neoplasms (MDS) as well as de novo or secondary mixed phenotype acute leukemias and lymphomas. Neoplasms with eosinophilia are associated with dysregulated tyrosine kinases, usually as a result of gene fusions. It is of great importance to identify the genes involved because aberrant tyrosine kinases react to tyrosine kinase inhibitors with varying sensitivity. Patients with PDGFRA and PDGFRB rearrangements are responsive to imatinib, whereas FGFR1-related diseases are non-responsive. PDGFRA rearrangements are usually associated with chronic eosinophilic leukemia (CEL).

The most frequent PDGFRA-related aberration is the interstitial deletion of the CHIC2 gene with breakpoints in the FIP1L1 and PDGFRA genes. The deletion of a fragment of about 800kb is resulting in the FIP1L1-PDGFRA fusion gene, a constitutively activated tyrosine kinase transforming hematopoietic cells.

In FISH assays, the detection of CHIC2 deletion at 4q12 is a surrogate for the direct detection of the FIP1L1-PDGFRA fusion gene. Translocations with other partner genes, resulting in aberrant tyrosine kinase activity, are known. Involvement of PDGFRA can be detected by FISH using break apart strategies.



Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO) and one green (1G) signal indicating a deletion of CHIC2.

Aberrant Cell (typical results)
One green (1G) and two green-orange colocalization/fusion signals (2GO) signals resulting from a translocation between the green labeled PDGFRA gene region and an unknown chromosome.

Literature

- Cools et al (2003) N Engl J Med 348:1201-1214
- Pardanani et al (2003) Blood 102:3093-3096
- Swerdlow et al (2017) WHO classification of tumors of haematopoietic and lymphoid tissues (revised 4th edition)

Order No:
D-5137-100-OG

Size: **100 µl**

XL PDGFRA BA IVD

XL PDGFRA BA consists of a green-labeled probe hybridizing proximal to the PDGFRA gene region at 4q12 and an orange-labeled probe hybridizing distal to the PDGFRA gene region at 4q12.

The category ´myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB or FGFR1, or with PCM1/JAK2´ of the revised 4th edition of the WHO classification defines three particular groups with rearrangements in PDGFRA, PDGFRB or FGFR1 and a provisional entity with PCM1/JAK2 rearrangement. The clinical manifestations within this category are numerous and heterogeneous and include myeloproliferative neoplasms, myelodysplastic neoplasms (MDS) as well as de novo or secondary mixed phenotype acute leukemia and lymphomas. Neoplasms with eosinophilia are associated with dysregulated tyrosine kinases, usually as a result of gene fusions. It is of great importance to identify the genes involved because aberrant tyrosine kinases react to tyrosine kinase inhibitors with varying sensitivity. Patients with PDGFRA and PDGFRB rearrangements are responsive to imatinib whereas FGFR1-related diseases are non-responsive. PDGFRA rearrangements are usually associated with chronic eosinophilic leukemia (CEL).

The most frequent PDGFRA-related aberration is the interstitial deletion of the CHIC2 gene with breakpoints in the FIP1L1 and PDGFRA genes. The deletion of a fragment of about 800kb results in the FIP1L1-PDGFRA fusion gene, a constitutively activated tyrosine kinase transforming hematopoietic cells.

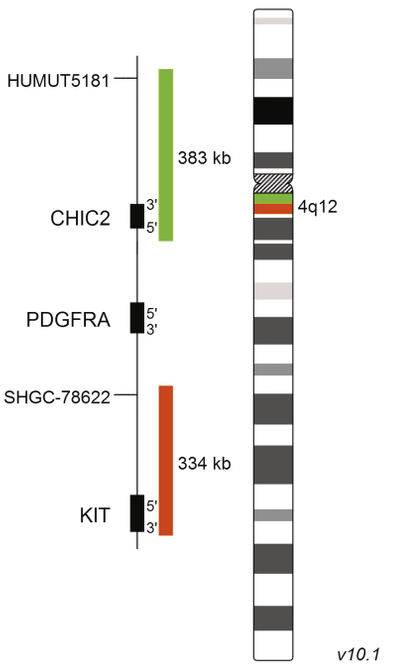
In FISH assays, the detection of CHIC2 deletion at 4q12 is a surrogate for the direct detection of the FIP1L1-PDGFRA fusion gene. Translocations with other partner genes, resulting in aberrant tyrosine kinase activity, are known. Involvement of PDGFRA can be detected by FISH break apart strategies.

Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.

Aberrant Cell (typical results)
One green-orange (1GO) colocalization/fusion signal and one orange (1O) signal resulting from the loss of one green signal.



Literature

- Cools et al (2003) N Engl J Med 348:1201-1214
- Pardanani et al (2003) Blood 102:3093-3096
- Swerdlow et al (2017) WHO classification of tumors of haematopoietic and lymphoid tissues (revised 4th edition)

Order No:
D-5038-100-OG

Size: **100 µl**

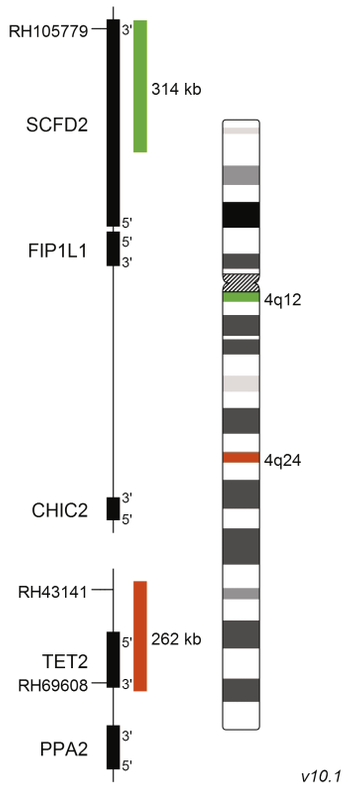
XCyting Locus-Specific Probes
Deletion Probe XL

IVD **XL TET2**

XL TET2 consists of an orange-labeled probe hybridizing to the TET2 gene region at 4q24 and a green-labeled probe hybridizing to 4q12.

Myelodysplastic neoplasms (MDS) and myeloproliferative neoplasms (MPN) are associated with deregulated production of myeloid cells. According to WHO classification (2008), cytogenetic aberrations are observed in about 50% of MDS cases. The most common aberrations are 5q-, 7/7q-, trisomy 8, del(20q), and inv(3) or t(3;3).

A minimally deleted region on chromosome 4q24 is described in subgroups of patients with myelodysplastic neoplasms (MDS) and acute myeloid leukemia (AML). The region encompasses the TET2 gene. The frequency of TET2 mutations in unselected patients was 19% (15 of 81 patients) with myelodysplastic neoplasms (MDS), 12% (24 of 198 patients) with myeloproliferative neoplasms (MPN), 24% (5 of 21 patients) with secondary AML, and 22% (2 of 9 patients) with chronic myelomonocytic leukemia.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal, indicating a deletion of TET2 (4q24).

Literature

- Jankowska et al (2009) Blood 113:6403-6410
- Delhommeau et al (2009) N Engl J Med 360:2289-2301
- Flach et al (2010) Haematologica 95:518-519

Order No:
D-5131-100-OG

Size: **100 µl**

XL t(4;11) AFF1/KMT2A DF IVD

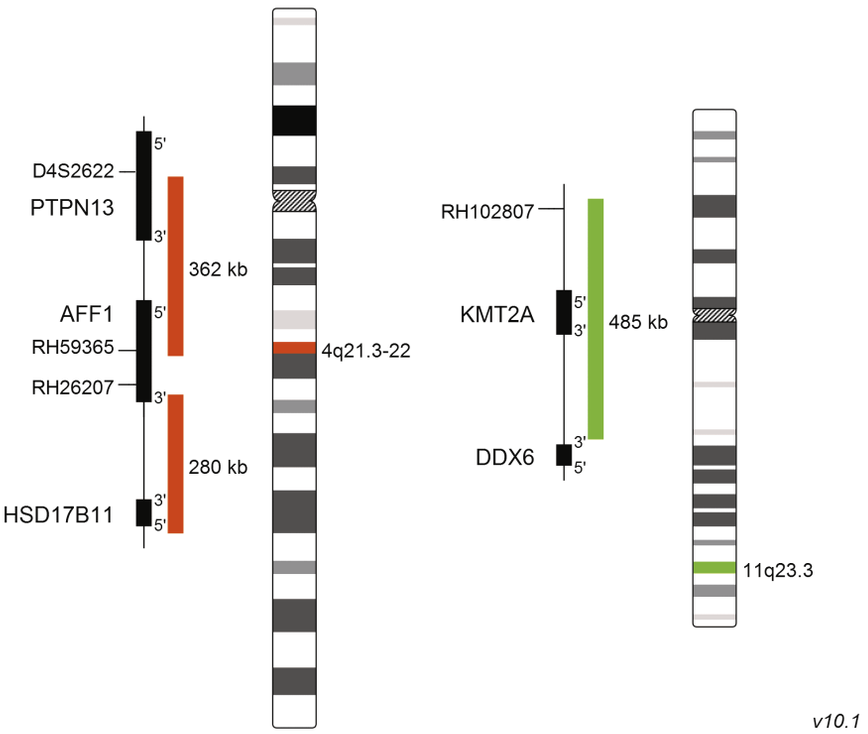
XL t(4;11) AFF1/KMT2A DF consists of an orange-labeled probe hybridizing to the AFF1 gene region at 4q21.3-22 and a green-labeled probe hybridizing to the KMT2A gene region at 11q23.3.

Chromosomal rearrangements of the KMT2A (lysine methyltransferase 2A) gene, formerly MLL (mixed lineage leukemia), are associated with various hematological disorders. Most patients suffer from acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), while only a minority develops mixed lineage leukemia (MLL). Several chromosomal aberrations involving the KMT2A gene have been identified. However, the majority of leukemias result from translocations leading to KMT2A fusions. More than 90 KMT2A translocation partner genes fused to the 5´- KMT2A portion have been identified. The most common translocation partners in KMT2A associated leukemia are AFF1, MLLT3, MLLT1, MLLT10, ELL and AFDN, described here in the order of their frequency. The fusion of KMT2A and AFF1 (AF4/FMR2 family member 1) is the most frequent KMT2A translocation observed in ALL cases. About 60% of ALL patients carrying KMT2A rearrangements are characterized by the KMT2A-AFF1 fusion gene. Infant patients mainly have breakpoints in intron 11 of KMT2A, whereas adult patients have a tendency for breakpoints within intron 9. Oncogenic KMT2A-AFF1 fusions have been implicated in the DOT1L and SEC transcriptional complexes. AFF1 plays an important role in the regulation of RNA polymerase II-dependent transcription, elongation and chromatin remodeling mediated by histone methylation. AFF1 is the docking platform for several components of the DOT1L complex consisting of DOT1L, a H3K79 methyltransferase, MLLT3, MLLT1, and MLLT10, whose genes are also common translocation partners of KMT2A. Mouse studies revealed increased and extended histone methylation signatures in the presence of KMT2A-AFF1 and reciprocal AFF1-KMT2A fusions. DOT1L inhibitors are promising candidates for clinical treatment which are currently being evaluated.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the respective loci.



v10.1

Literature

- De Braekeleer et al (2011) Mol Oncol 5:555-563
- Meyer et al (2013) Leukemia 27:2165-2176
- Burns et al (2018) Hematology (7th ed) Ch 64: Pathobiology of acute lymphoblastic leukemia:1005–1019.e11

Order No:
D-5108-100-OG

Size: **100 µl**

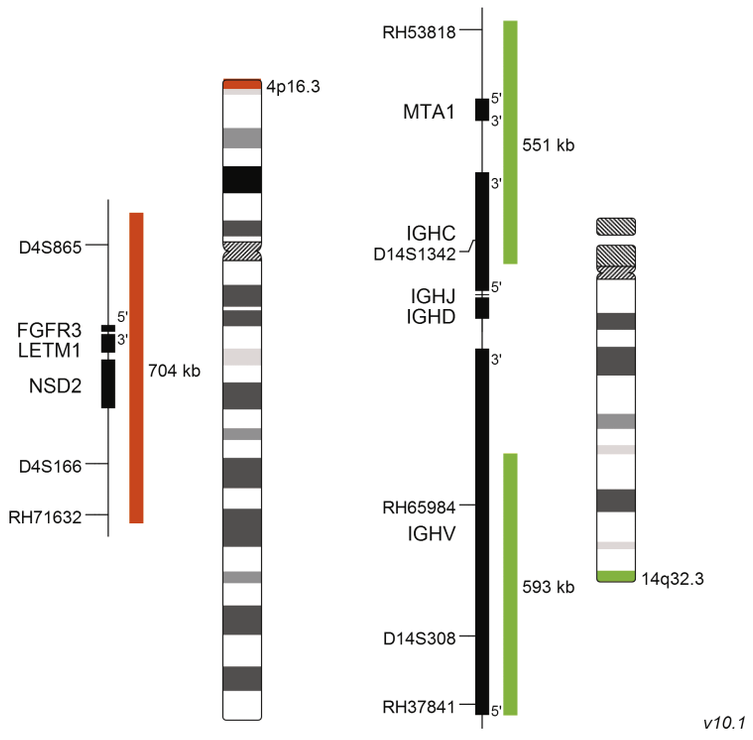
XCyting Locus-Specific Probes
Translocation/Dual Fusion Probe
XL

IVD XL t(4;14) FGFR3/IGH DF

XL t(4;14) FGFR3/IGH DF consists of an orange-labeled probe hybridizing to the FGFR3 gene region at 4p16.3 and a green-labeled probe hybridizing to the IGH gene region at 14q32.3.

The most frequent primary abnormalities in multiple myeloma (MM) are trisomies of odd-numbered chromosomes or translocations involving the immunglobulin heavy chain (IGH) gene locus. The most common MM-associated IGH translocations are t(11;14), t(4;14), t(6;14), t(14;16) and t(14;20) in the order of their occurrence. The consequence of these rearrangements is the dysregulation of genes juxtaposed to transcriptional enhancers in the IGH locus. Prognosis and risk stratification strongly depend on the detection and interpretation of cytogenetic primary abnormalities. t(14;16) and t(14;20) are considered as high risk, t(4;14) as intermediate risk and t(6;14) and t(11;14) as standard risk cytogenetic aberrations in patients with MM based on FISH testing. Secondary aberrations are also influencing the outcome.

The recurrent translocation t(4;14)(p16;q32) is juxtaposing FGFR3 with the 3' alpha IgH enhancer on der(14), whereas expression of NSD2 is controlled by the Eμ enhancer on der(4). FGFR3 overexpression is detectable in about 70% of t(4;14) positive MM patients, suggesting that FGFR3 dysregulation is not the crucial oncogenic event. The poor outcome of patients lacking FGFR3 expression due to the loss of der(14) is supporting this conclusion. Transcripts from the NSD2 locus on the other hand are found to be overexpressed in all t(4;14) positive MM cases, suggesting that this gene region plays a major role in the manifestation of MM.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci.

Literature

- Chesi et al (1998) Blood 92:3025-3034
- Keats et al (2003) Blood 15:4060-4069
- Rajan and Rajkumar (2015) Blood Cancer J 5:e365

XL XCyting Locus-Specific Probes
Break Apart Probe

Order No:
D-5104-100-OG

Size: **100 µl**

XL 5q32 PDGFRB BA IVD

XL 5q32 PDGFRB BA consists of an orange-labeled probe hybridizing proximal to the PDGFRB gene region at 5q32 and a green-labeled probe hybridizing distal to the PDGFRB gene region at 5q32-33.1.

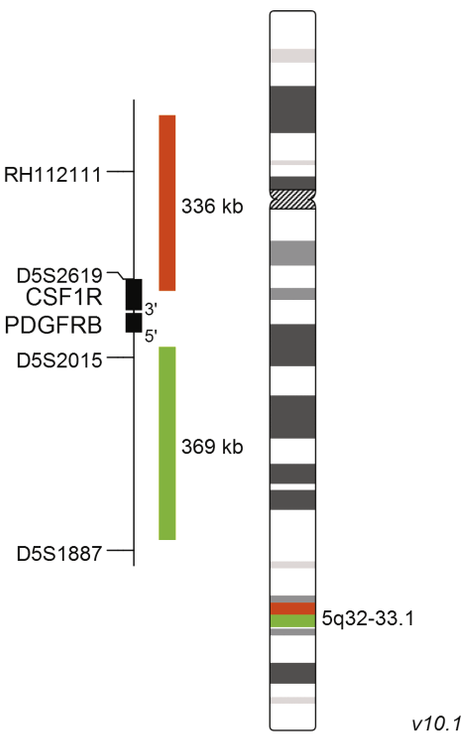
The updated (2016) World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues indicates the category myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, FGFR1, or with PCM1-JAK2.

Myeloid neoplasms (MPNs) with rearrangement of PDGFRB are phenotypically and genotypically diverse. The fusion genes involving PDGFRB described to date have been associated with cytogenetically detectable translocations. MPNs associated with rearrangement of PDGFRB are responsive to imatinib.

Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.



Literature

- Wlodarska et al (1997) Blood 89:1716-1722
- Apperley et al (2002) N Engl J Med 347:481-487
- Wilkinson et al (2003) Blood 102:4187-4190

Order No:
D-5152-100-OG

Size: **100 µl**

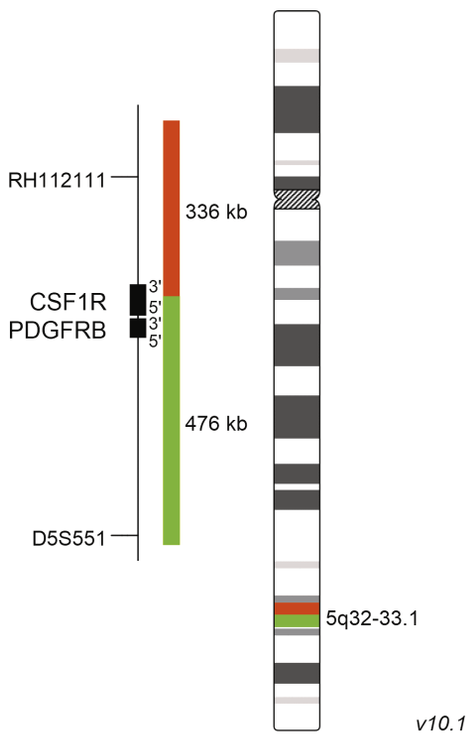
XCyting Locus-Specific Probes
Break Apart Probe **XL**

IVD XL CSF1R BA

XL CSF1R BA consists of an orange-labeled probe hybridizing proximal to the CSF1R gene region at 5q32 extending into the gene up to intron 5 and a green-labeled probe hybridizing distal to the CSF1R gene region at 5q32-33.1 extending into the gene up to intron 5 (GRCh37/hg19).

In the 2016 World Health Organization classification of myeloid neoplasms and acute leukemia, the B-lymphoblastic leukemia/lymphoma subtype 'BCR-ABL1-like acute lymphoblastic leukemia' (BCR-ABL1-like ALL), also called 'Philadelphia chromosome (Ph)-like ALL', was recognized as a provisional entity. BCR-ABL1-like ALL is a high-risk subset of B-cell precursor ALL disorders characterized by a highly similar gene expression profile compared to Ph+ ALL in the absence of BCR-ABL1 fusions. Altered genes involved in the development and maintenance of Ph-like ALL are ABL1, ABL2, BLNK, CRLF2, CSF1R, DGKH, EPOR, FGFR1, IL-2RB, JAK2, LYN, NTRK3, PDGFRA, PDGFRB, PTK2B and TYK2.

CSF1R (colony stimulating factor 1 receptor) is a membrane-integrated tyrosine kinase receptor expressed by monocytes, macrophages, and other cells of the myeloid lineage. Binding of its ligands interleukin 34 or colony stimulating factor 1, respectively, leads to receptor homodimerization and auto-phosphorylation of the intracellular tyrosine kinase domains, subsequent signaling, and gene transcription. CSF1R-mediated signaling plays an important role in the differentiation and survival of monocytes and macrophages. In addition, CSF1R is a key factor in the tumorpermissive and immunosuppressive behavior of 'tumor associated macrophages' by promoting tumor progression and survival via suppressing effector T-cell functions. Known translocation partner genes involved in CSF1R rearrangements, identified in Ph-like cases, are SSBP2, MEF2D and TBL1XR1. The most intensively characterized CSF1R fusion is SSBP2-CSF1R resulting from the translocation t(5;5)(q14;q32). The ABL1 inhibitors Imatinib and Dasatinib are known to have anti-survival and proapoptotic capacities on cells expressing the SSBP2-CSF1R fusion.



Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.

Literature

- Cannarile et al (2017) J Immunother Cancer 5:doi:10.1186/s40425-017-0257-y
- Roberts et al (2017) Blood Adv 1:1657- 1671
- Tasian et al (2017) Blood 130:2064-2072

Clinical Applications
ALL

Chromosome **5** | Page **25**

Order No:
D-5129-100-OG

Size: **100 µl**

XL TLX3 BA IVD

XL TLX3 BA consists of an orange-labeled probe hybridizing proximal to the TLX3 gene region at 5q35.1 and a green-labeled probe hybridizing distal to the TLX3 gene region at 5q35.1.

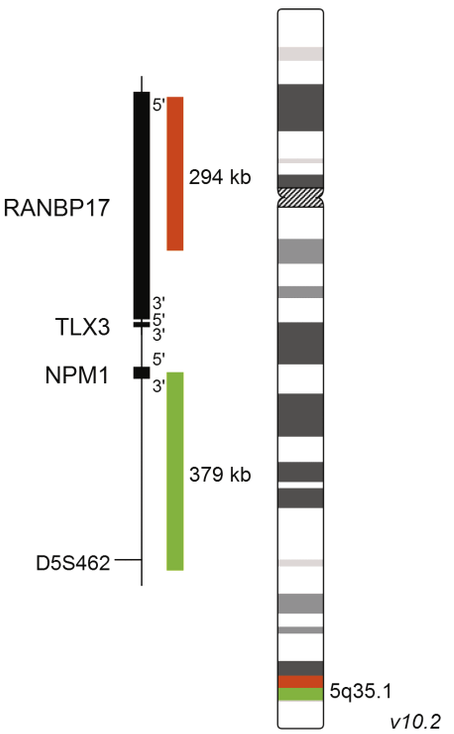
Acute lymphoblastic leukemia (ALL) is the most common childhood cancer type. T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive and quickly progressing type of ALL affecting T-lymphocytes. Genomic data suggests that more than 10 functional aberrations are contributing to the development of this disease. T-ALL cases can be grouped by distinct genetic profiles and the aberrant expression of a characteristic transcription factor. Major subgroups are characterized by ectopic expression of TAL1, TLX1, TLX3, HOXA9/10, LMO2 or NKX2-1 and others as a result of chromosomal rearrangements or mutations. About 20% of childhood T-ALL cases are characterized by aberrant expression of TLX3 as a result of t(5;14)(q35;q32). This cryptic translocation juxtaposes TLX3, normally not expressed in T-cells, with the BCL11B gene, which is active in T-cells, resulting in ectopic expression of TLX3.

Fluorescence in situ hybridization is a valuable method for the detection of t(5;14)(q35;q32) since cryptic translocations may escape during classical cytogenetic analysis. Furthermore, the broad range of breakpoints in the chromosomal region 14q32 makes the development of efficient PCR-based methods difficult.

Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.



Literature

- Van Zutven et al (2004) Haematologica 89:671-678
- Su et al (2006) Blood 108:4198-4201
- Girardi et al (2017) Blood 129:1113-1123

Order No:
D-5042-100-OG

Size: **100 µl**

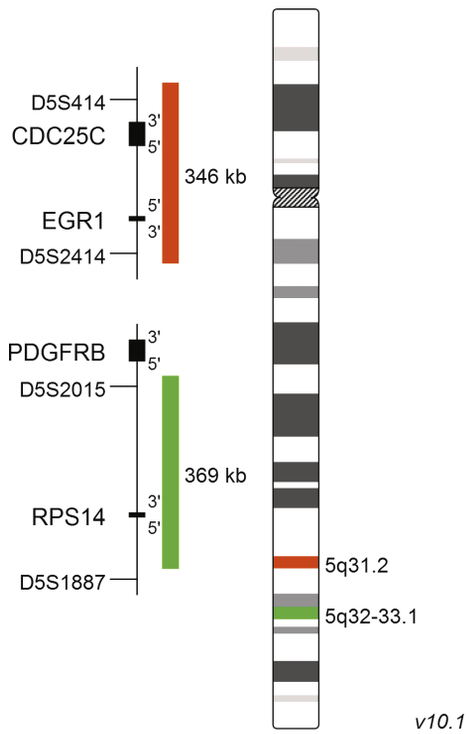
XCyting Locus-Specific Probes
Deletion Probe **XL**

IVD XL 5q31/5q33

XL 5q31/5q33 consists of an orange-labeled probe hybridizing to the EGR1 gene region at 5q31.2 and a green-labeled probe hybridizing to the RPS14 gene region at 5q32-33.1.

Myelodysplastic neoplasms (MDS) and myeloproliferative neoplasms (MPN) are associated with deregulated production of myeloid cells. According to WHO classification (2008), cytogenetic aberrations are observed in about 50% of MDS cases. The most common aberrations are 5q-, 7/7q-, trisomy 8, del(20q), and inv(3) or t(3;3).

The 5q syndrome is defined as a primary MDS with del(5q) as the sole karyotypic abnormality. Two different critical regions are described; one is located at 5q31 and contains the EGR1 and CDC25C genes; a more distal region at 5q32-q33 contains RPS14 which has been identified as a causal gene for the 5q syndrome.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal, indicating a deletion in 5q31.2.

Aberrant Cell (typical results)
One green (1G) and two orange (2O) signals, indicating a deletion in 5q33.

Aberrant Cell (typical results)
One green (1G) and one orange (1O) signal, indicating deletions of both loci in 5q31.2 and 5q33.

Literature

- Horrigan et al (2000) Blood 95:2372-2377
- Wei et al (2009) Proc Natl Acad Sci USA 106:12974-12979
- Boultwood et al (2010) Blood 16:5803-5811

Order No:
D-5085-100-OG

Size: **100 µl**

XL del(5)(q31) IVD

XL del(5)(q31) consists of a green-labeled probe hybridizing to a region at 5p15.2-15.3 and an orange-labeled probe hybridizing to the EGR1 gene region at 5q31.2.

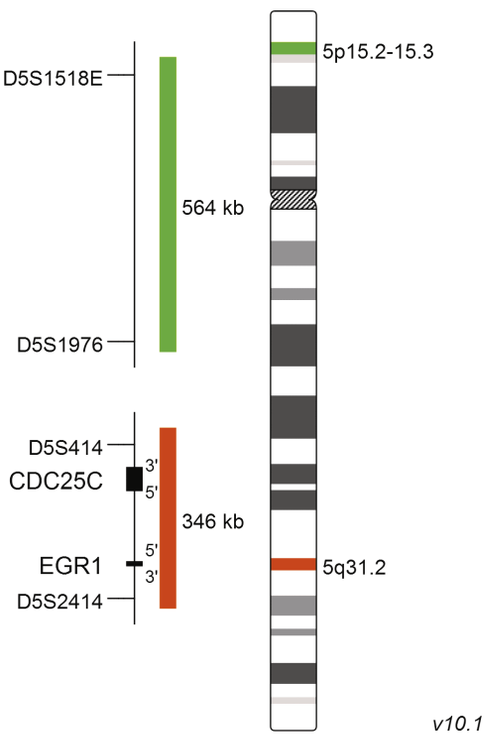
Myelodysplastic neoplasms (MDS) and myeloproliferative neoplasms (MPN) are associated with deregulated production of myeloid cells. According to WHO classification (2008), cytogenetic aberrations are observed in about 50% of MDS cases. The most common aberrations are 5q-, 7/7q-, trisomy 8, del(20q), and inv(3) or t(3,3).

5q syndrome is defined as primary MDS with del(5q) as the sole karyotypic abnormality. Two different critical regions are described, one is located at 5q31 and contains the EGR1 and CDC25C genes. A more distal region at 5q32-q33 containing RPS14 has been identified as a causal region for 5q syndrome.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal, indicating the deletion of the EGR1 at 5q31.



Literature

- Horrigan et al (2000) Blood 95:2372-2377
- Ebert et al (2008) Nature 451:335-339
- Mallo et al (2008) Heamatologica 93:1001-1007

Order No:
D-5091-100-OG

Size: **100 µl**

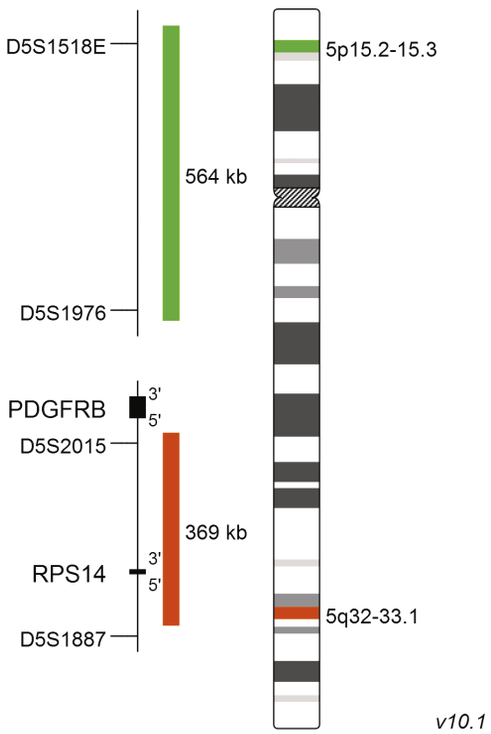
XCyting Locus-Specific Probes
Deletion Probe **XL**

IVD XL del(5)(q33)

XL del(5)(q33) consists of a green-labeled probe hybridizing to a region at 5p15.2-15.3 and an orange-labeled probe hybridizing to the RPS14 locus at 5q32-33.1.

Myelodysplastic neoplasms (MDS) and myeloproliferative neoplasms (MPN) are associated with deregulated production of myeloid cells. According to WHO classification (2008), cytogenetic aberrations are observed in about 50% of MDS cases. The most common aberrations are 5q-, 7/7q-, trisomy 8, del(20q), and inv(3) or t(3,3).

5q syndrome is defined as primary MDS with del(5q) as the sole karyotypic abnormality. Two different critical regions are described, one is located at 5q31 and contains the EGR1 and CDC25C genes. A more distal region at 5q32-q33 containing RPS14 has been identified as a causal region for 5q syndrome.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal, indicating the deletion of the RPS14 at 5q33.

Literature

- Horrigan et al (2000) Blood 95:2372-2377
- Boultwood et al (2002) Blood 99:4638-4641
- Ebert et al (2008) Nature 451:335-339

Order No:
D-5081-100-TC

Size: **100 µl**

XL 5q31/5q33/5p15 IVD

XL 5q31/5q33/5p15 consists of an aqua-labeled probe hybridizing to a region at 5p15.2-15.3, an orange-labeled probe hybridizing to the EGR1 gene region at 5q31.2 and a green-labeled probe hybridizing to the RPS14 gene region at 5q32-33.1.

Myelodysplastic neoplasms (MDS) and myeloproliferative neoplasms (MPN) are associated with deregulated production of myeloid cells. According to WHO classification (2008), cytogenetic aberrations are observed in about 50% of MDS cases. The most common aberrations are 5q-, 7/7q-, trisomy 8, del(20q), and inv(3) or t(3,3).

5q syndrome is defined as a primary MDS with del(5q) as the sole karyotypic abnormality. Two different critical regions are described, one is located at 5q31 and contains the EGR1 and CDC25C genes. A more distal region at 5q32-q33 containing RPS14 has been identified as a causal region for 5q syndrome.

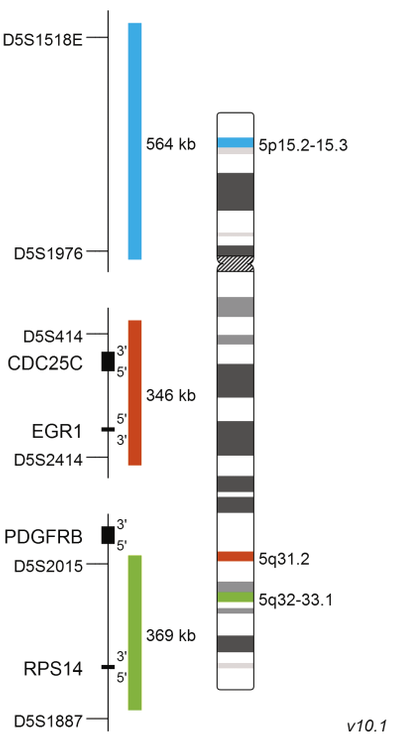
Expected Patterns

Normal Cell
Two green (2G), two orange (2O) and two blue (2B) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two blue (2B) signals indicating the deletion of a 5q33 locus and of a 5q31 locus.

Aberrant Cell (typical results)
Two green (2G), one orange (1O), and two blue (2B) signals indicating the deletion of a 5q31 locus or one green (1G), two orange (2O), and 2 blue (2B) signals, indicating the deletion of a 5q33 locus.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and one blue (1B) signal indicating a monosomy 5.



Literature

- Horrigan et al (2009) Blood 95:2372-2377
- Wei et al (2009) PNAS 106:12974-12979
- Boultwood et al (2010) Blood 16:5803-5811

Order No:
D-5095-100-TC

Size: **100 µl**

XCyting Locus-Specific Probes
Enumeration Probe **XL**

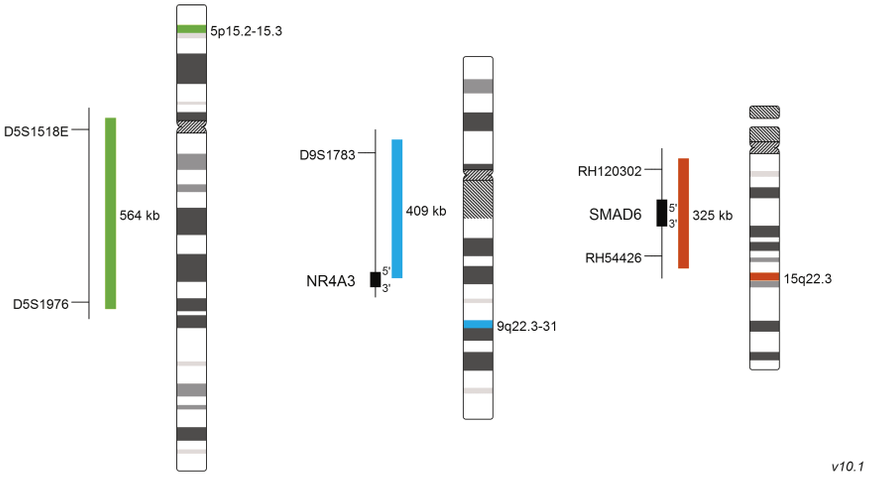
IVD

XL 5p15/9q22/15q22 Hyperdiploidy

XL 5p15/9q22/15q22 Hyperdiploidy consists of a green-labeled probe hybridizing to a region at 5p15.2-15.3, an aqua-labeled probe hybridizing to a region at 9q22.3-31 and an orange-labeled probe hybridizing to the SMAD6 gene region at 15q22.3.

In multiple myeloma (MM) pathogenesis, hyperdiploidy and non-hyperdiploidy are recognized as two major cytogenetic pathways. The hyperdiploid group is characterized by gains of the odd chromosomes 3, 5, 7, 9, 11, 15, 19, and 21. Hyperdiploidy has been internationally defined and requires trisomy for at least 2 of the 3 chromosomes 5, 9, and 15.

Patients with hyperdiploid MM, which can be observed in 50-60% of MM patients, tend to have a better prognosis than those with a non-hyperdiploid subtype.



Expected Patterns

Normal Cell
Two green (2G), two orange (2O), and two blue (2B) signals.

Aberrant Cell
Three green (3G), two blue (2B) and three orange (3O) signals, indicating hyperdiploidy.

Aberrant Cell
Three orange (3O), two green (2G) and three blue (3B) signals, indicating hyperdiploidy.

Aberrant Cell
Three green (3G), three blue (3B) and two orange (2O) signals, indicating hyperdiploidy.

Literature

- Wuilleme et al (2005) Leukemia 19:275-278
- Kumar et al (2009) Mayo Clin Proc 84:1095-1110
- Bochtler et al (2011) Blood 117:3809-3815

Order No:
D-5141-100-OG

Size: **100 µl**

XL t(5;11) NSD1/NUP98 DF IVD

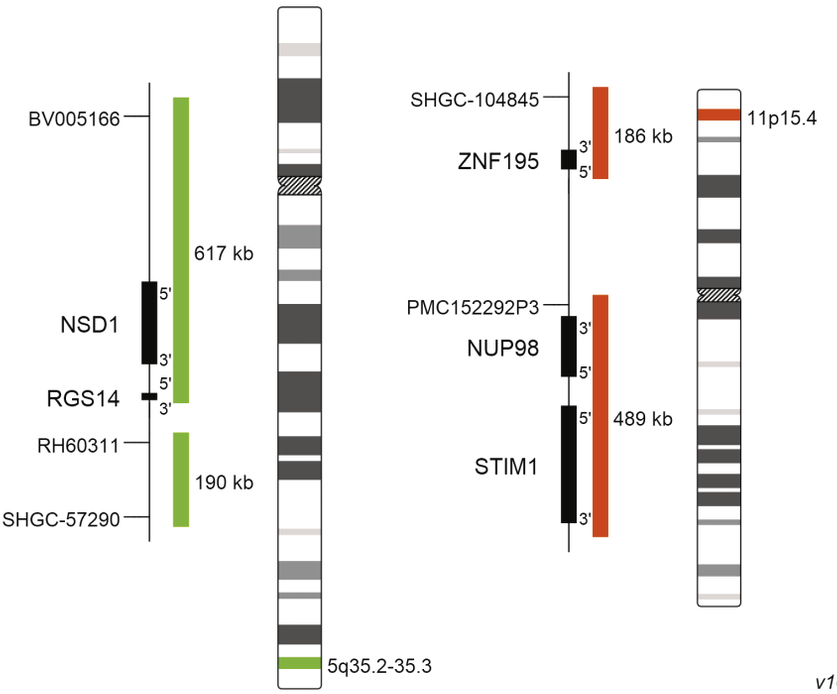
XL t(5;11) NSD1/NUP98 DF consists of a green-labeled probe hybridizing to the NSD1 gene region at 5q35.2-35.3 and an orange-labeled probe hybridizing to the NUP98 gene region at 11p15.4.

Acute myeloid leukemia (AML) is a rare, heterogenic disease whose prognosis varies widely, depending on several factors such as chromosomal abnormalities. Conventional cytogenetics can detect structural and numerical cytogenetic abnormalities in about 50% patients with AML. However, products from cryptic translocations, loss of chromosome material or certain fusion genes, such as t(5;11)(q35;p15) NUP98::NSD1, can only be reliably detected using FISH or molecular genetic approaches as RT-PCR technique. NUP98 (Nucleoporin 98) located at 11p15.4 encodes a protein of the nucleopore complex. So far, more than 30 different fusion partner genes of NUP98 have been identified in various leukemias. The leukemogenesis seems to be mediated by changes in chromatin structure and gene expression. NSD1 (nuclear receptor binding SET domain protein 1) located at 5q35.3 was shown to be the most frequent NUP98 fusion partner gene in pediatric AML. NSD1 is discussed to function as a transcriptional coactivator and also as a corepressor. The chimeric protein, resulting from the fusion between the N-terminal part of NUP98 including phenylalanine-glycine (FG) repeats and the C-terminal part of NSD1 induces AML in vivo and enhances the expression of HOXA and HOXB. The frequency of NUP98::NSD1 translocations in AML is low and age-dependent, with a higher frequency in younger ages than in adults. For both, pediatric and adult NUP98::NSD1-positive AML patients, the prognosis is poor and often associated with primary resistance to chemotherapy. An association with FLT3 -ITD (internal tandem duplications), and/or WT1 mutations is reported in NUP98::NSD1 positive cases, supporting the hypothesis of a multistep AML pathogenesis.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O) and two green-orange fusion (2GO) (adjacent green and orange) signals.



v10.1

Literature

- Jaju et al (2001) Blood 98:1264-1267
- Wang et al (2007) Nat Cell Biol 9:804-812
- Hollink et al (2011) Blood 118:3645-3656
- Fasan et al Leukemia (2013) 27:245–248
- Struski et al (2017) Leukemia 31:565-572

Order No:
D-5155-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Deletion/Enumeration Probe **XL**

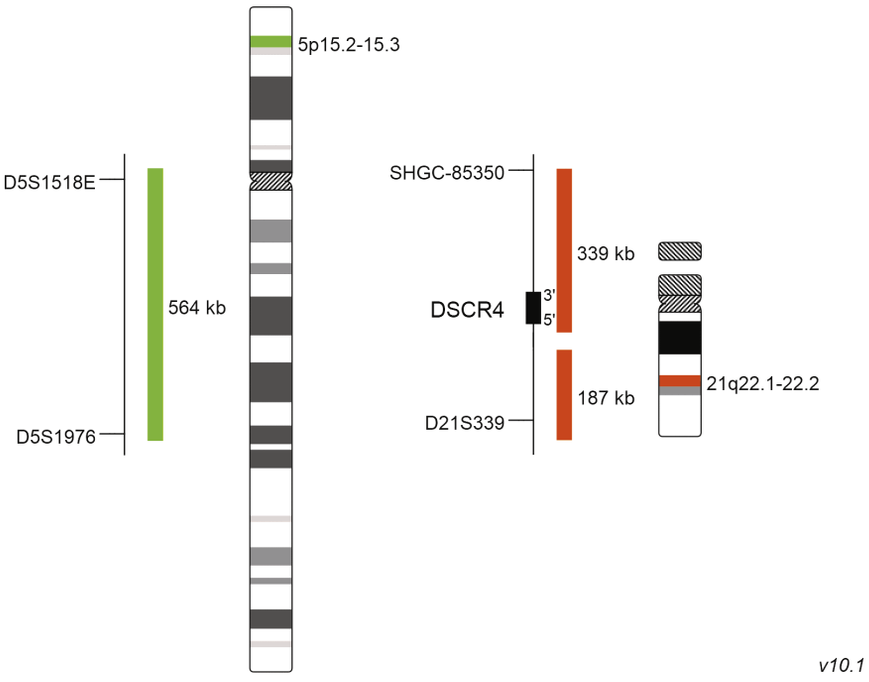
IVD XL 5p15/21q22

XL 5p15/21q22 consists of a green-labeled probe hybridizing to a region at 5p15.2-15.3 and an orange-labeled probe hybridizing to the DSCR4 gene region at 21q22.1-22.2.

Multiple myeloma (MM) is a malignant disorder of plasma cells representing the second most prevalent hematologic malignancy, which is characterized by a wide heterogeneity of disease progression. While some of the MM patients stay alive more than 10 years after first diagnosis, others die within a few months. Chromosomal abnormalities in tumor plasma cells are of great significance among all prognostic factors analyzed in MM. To address the significant role of the different factors, the International Myeloma Working Group has recommended the implementation of these well studied chromosomal aberrations in the revised International Staging System (R-ISS) for MM. While del(17p), t(4;14), and t(14;16) are known to be among the high-risk factors in MM, trisomic MM is generally associated with a favorable outcome. More than half of MM cases diagnosed have a hyperdiploid karyotype, characterized by gains of the odd chromosomes.

While trisomy 3 or 5 significantly improves overall survival in MM patients, trisomy 21 has the adverse effect. The study of Perrot et al analyzed the combination frequency and prognostic impact of the factors del(17p), t(4;14), del(1p32), 1q21 gain, and trisomies 3, 5, and 21 within a big cohort and found out that the most frequent combination was the one between trisomy 5 and 21 among the aberrations examined.

The combined XL 5p15/21q22 fluorescence in situ hybridization (FISH) probe is a helpful aid for diagnosis to rapidly detect trisomy 5 and, or 21 in suspected or confirmed MM cases.



v10.1

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Three green (3G) and two orange (2O) signals resulting from gain of one green signal.

Aberrant Cell (typical results)
Two green (2G) and three orange (3O) signals resulting from gain of one orange signal.

Aberrant Cell (typical results)
Three green (3G) and three orange (3O) signals each resulting from a gain of one green signal and one orange signal.

Literature

- Chretien et al (2015) Blood 126:2713-2719
- Perrot et al (2019) J Clin Oncol 37:1657-1665
- Barilà et al (2020) Blood Cancer J 10:18

Order No:
D-5039-100-OG

Size: **100 µl**

XL 6q21/6q23 IVD

XL 6q21/6q23 consists of a green-labeled probe hybridizing to the SEC63 gene region at 6q21 and an orange-labeled probe hybridizing to the MYB gene region at 6q23.3.

The prognosis and clinical course of chronic lymphocytic leukemia (CLL) are heterogeneous. Conventional banding techniques in CLL are hampered by the low mitotic index of the neoplastic cells. The introduction of interphase cytogenetics using fluorescent *in situ* hybridization (FISH) has greatly increased the sensitivity of cytogenetic analyses. With FISH, abnormalities can be detected in more than 80% of patients by using a 4-probe panel for the detection of trisomy 12q13-15 and deletions 13q14, 17p13, and 11q22-23. An additional 10% of patients can be shown to carry a 6q21 deletion, 14q32 translocation, and partial trisomy 3q or 8q.

Deletions involving the long arm of chromosome 6 (6q) are among the most common structural aberrations leading to a loss of chromosomal material in lymphoproliferative disorders and non-Hodgkin lymphoma (NHL). Two distinct regions, one at 6q21-22.1, the other at 6q23.3-25, have been found as minimal deleted regions in 6q- patients. A 6q deletion has also been found in a variety of other human malignancies, including breast carcinoma, malignant melanoma, renal cell carcinoma, salivary gland adenocarcinoma, ovarian carcinoma, acute lymphoblastic leukemia, and nodal non-Hodgkin lymphomas.

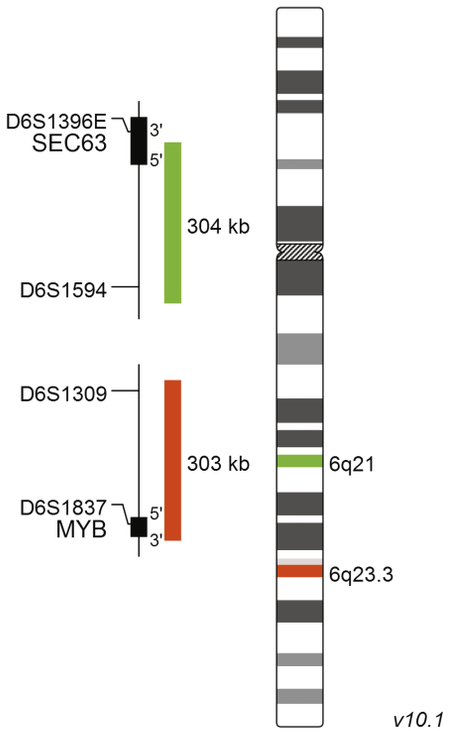
Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal, indicating a deletion in 6q23 (MYB).

Aberrant Cell (typical results)
One green (1G) and two orange (2O) signals, indicating a deletion in 6q21.

Aberrant Cell (typical results)
One green (1G) and one orange (1O) signal, indicating deletions of both loci in 6q21 and 6q23.



Literature

- Stilgenbauer et al (1999) Leukemia 13:1331-1334
- Zhang et al (2000) Genes Chrom Canc 27:52-58
- Starostik et al (2000) Blood 95:1180-1187

Order No:
D-5088-100-TC

Size: **100 µl**

XCyting Locus-Specific Probes
Deletion Probe
XL

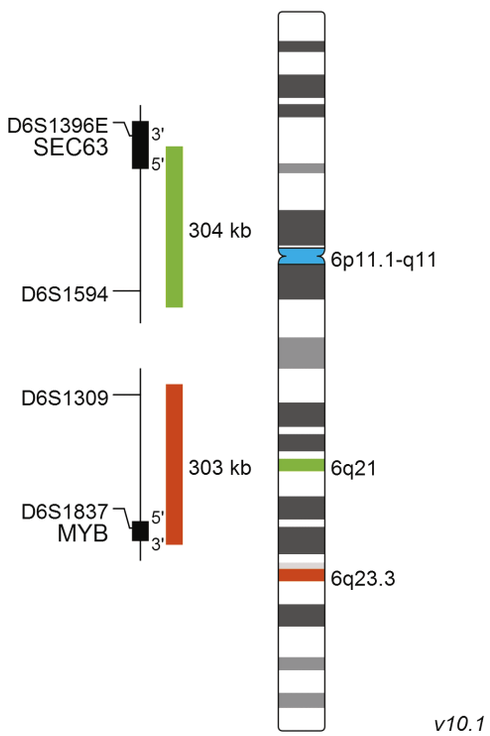
IVD

XL 6q21/6q23/6cen

XL 6q21/6q23/6cen consists of a green-labeled probe hybridizing to the SEC63 gene region at 6q21, an orange-labeled probe hybridizing to the MYB gene region at 6q23.3 and an aqua-labeled probe hybridizing to the centromere of chromosome 6.

The prognosis and clinical course of chronic lymphocytic leukemia (CLL) is heterogeneous. Conventional banding techniques in CLL are hampered by the low mitotic index of the neoplastic cells. The introduction of interphase cytogenetics using fluorescent *in situ* hybridization (FISH) has greatly increased the sensitivity of cytogenetic analyses. With FISH, abnormalities can be detected in more than 80% of patients by using a 4-probe panel for the detection of trisomy 12q13-15 and deletions 13q14, 17p13, and 11q22-23. An additional 10% of patients can be shown to carry a 6q21 deletion, 14q32 translocation, and partial trisomy 3q or 8q.

Deletions involving the long arm of chromosome 6 (6q) are among the most common structural aberrations leading to a loss of chromosomal material in lymphoproliferative disorders and non-Hodgkin lymphoma (NHL). Two distinct regions, one at 6q21-22.1, the other at 6q23.3-25, have been found as minimal deleted regions in 6q- patients. A 6q deletion has been found in a variety of other human malignancies as well, including breast carcinoma, malignant melanoma, renal cell carcinoma, salivary gland adenocarcinoma, ovarian carcinoma, acute lymphoblastic leukemia, and nodal NHL.



Expected Patterns

Normal Cell
Two green (2G), two orange (2O), and two blue (2B) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two blue (2B) signals indicating the deletion of a 6q23 locus and of a 6q21 locus.

Aberrant Cell (typical results)
Two green (2G), one orange (1O), and two blue (2B) signals indicating the deletion of a 6q23 locus or one green (1G), two orange (2O), and two blue (2B) signals, indicating the deletion of a 6q21 locus.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and one blue (1B) signal indicating a monosomy 6.

Literature

- Stilgenbauer et al (1999) Leukemia 13:1331-1334
- Zhang et al (2000) Genes Chrom Canc 27:52-58
- Starostik et al (2000) Blood 95:1180-1187

Clinical Applications
ALL | CLL | NHL

Chromosome **6** | Page **35**

Order No:
D-6040-100-OG

Size: **100 µl**

XL IRF4 BA IVD

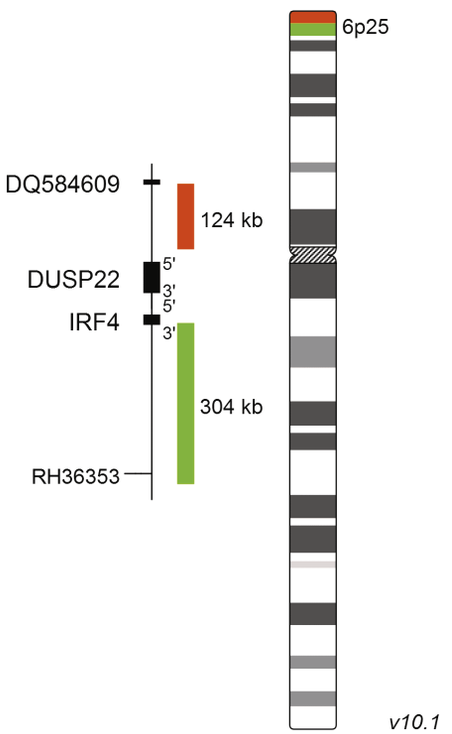
XL IRF4 BA consists of a green-labeled probe hybridizing proximal to the IRF4 gene region at 6p25 and an orange-labeled probe hybridizing distal to the IRF4 gene region at 6p25.

The updated (2016) revision of the World Health Organization (WHO) classification of tumors of lymphoid neoplasms considers the large B-cell lymphoma with IRF4 rearrangement as a new provisional entity. Head and neck regions including the Waldeyer ring are particularly affected. Chromosomal translocations involving the IRF4 gene and the immunoglobulin loci IGH, IGL and IGK (IG) result in dysregulation of IRF4 expression; other translocation partners may occur. Since t(6;14)(p25;q32) is cytogenetically cryptic, FISH is a valuable tool in detecting this recurrent aberration. IG/IRF4 positive lymphomas normally lack t(14;18), which is observed in about 85% of adult patients with follicular lymphoma, and are commonly associated with young age and a good course. IRF4 rearrangements have also been identified in peripheral T-cell lymphomas (PTCL). PTCL are defined as a diverse group of aggressive lymphomas of mature-stage T-cells accounting for about 10% of non-Hodgkin lymphomas. Recent data suggests that IRF4 translocations detected by FISH have a predictive value for primary cutaneous CD30(+) anaplastic large cell lymphoma.

Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the respective locus.



Literature

- Feldman et al (2009) Leukemia 23:574-580
- Salaverria et al (2011) Blood 7:139-147
- Kiran et al (2013) Leukemia Research 37:396-400

Order No:
D-6029-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe
XL

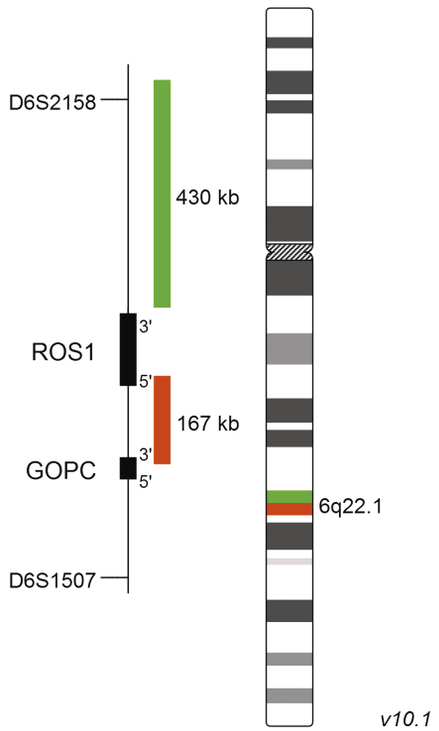
IVD

XL ROS1-GOPC BA

XL ROS1-GOPC BA consists of a green-labeled probe hybridizing proximal to the ROS1 gene region at 6q22.1 and an orange-labeled probe hybridizing distal to the ROS1 gene region at 6q22.1.

Translocations involving the ROS1 receptor tyrosine kinase gene have recently been described in a subset of non-small-cell lung cancers (NSCLCs). Chromosomal rearrangements involving the ROS1 gene were originally described in glioblastomas, where ROS1 is fused to the GOPC gene by an interstitial deletion.

Fusions of ROS1 with other genes lead to constitutive kinase activity and are associated with *in vitro* sensitivity to tyrosine kinase inhibitors such as crizotinib.



Expected Patterns

Normal Cell
Two green-orange (2GO) fusion signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and one green-orange (1GO) fusion signal.

Aberrant Cell (typical results)
One green (1G) and one green-orange (1GO) fusion signal.

Literature

- Charest et al (2003) Genes Chrom Cancer 37:58-71
- Takeuchi et al (2011) Nat Med 18:378-381
- Bergethon et al (2012) J Clin Oncol 30:863-870

Order No:
D-5097-100-OG

Size: **100 µl**

XL t(6;9) DEK/NUP214 IVD

XL t(6;9) DEK/NUP214 consists of a green-labeled probe hybridizing to the DEK gene region at 6p22.3 and an orange-labeled probe hybridizing to the NUP214 gene region at 9q34.1.

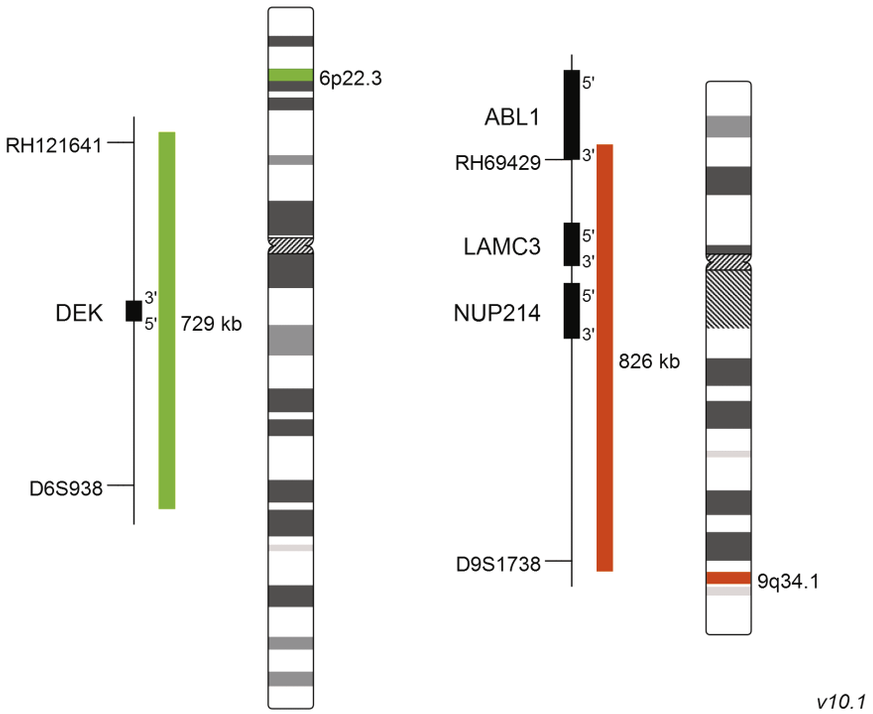
Several recurrent balanced translocations and inversions, and their variants, are recognized in the WHO category acute myelogenous leukemia (AML) with recurrent genetic abnormalities. Three new cytogenetically defined entities were recently incorporated: AML with t(6;9)(p23;q34) DEK/NUP214; AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2) RPN1/EVI1 and AML (megakaryoblastic) with t(1;22)(p13;q13) RBM15/MKL1, a rare leukemia most commonly occurring in infants.

The t(6;9)(p23;q34) DEK/NUP214 fusion occurs with an incidence of 1–5% in adult patients with AML. This translocation tends to occur in younger adults and is associated with an unfavorable prognosis at diagnosis. Although the t(6;9) is usually the sole cytogenetic aberration at diagnosis, additional karyotypic abnormalities are frequently identified during disease progression.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange fusion (2GO) (adjacent green and orange) signals.



v10.1

Literature

- Shearer et al (2005) Leukemia 19:126-131
- Doehner et al (2010) Blood 115:453-474
- Sandahl et al (2014) Haematologica 99:865-872

Order No:
D-5132-100-OG

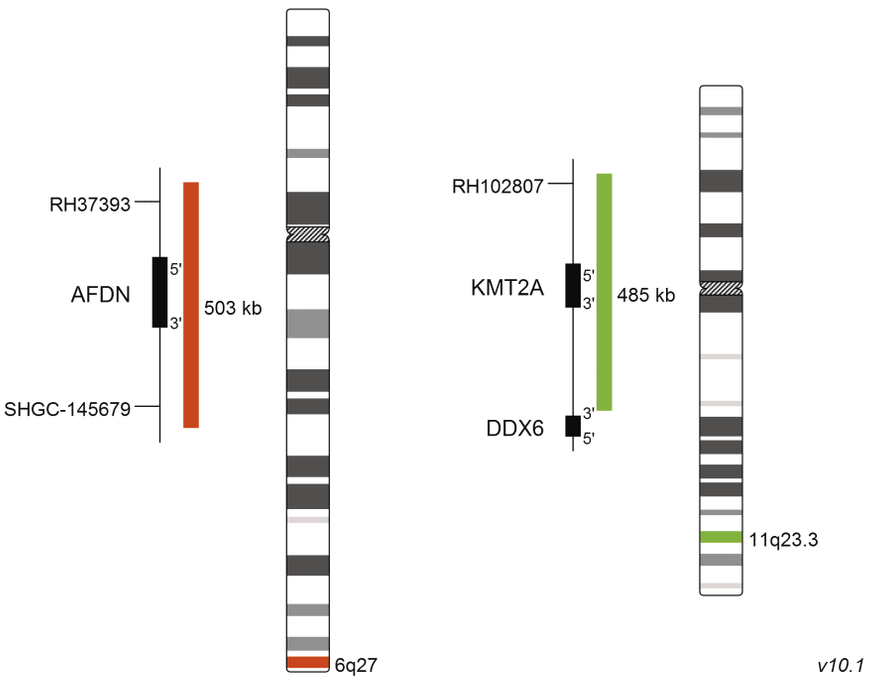
Size: **100 µl**

XCyting Locus-Specific Probes
Translocation/Dual Fusion Probe **XL**

IVD XL t(6;11) AFDN/KMT2A DF

XL t(6;11) AFDN/KMT2A DF consists of an orange-labeled probe hybridizing to the AFDN gene region at 6q27 and a green-labeled probe hybridizing to the KMT2A gene region at 11q23.3.

Chromosomal rearrangements of the KMT2A (lysine methyltransferase 2A) gene, formerly MLL (mixed lineage leukemia) gene, are associated with various hematological disorders. Most patients suffer from acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), while only a minority develops mixed lineage leukemia (MLL). Several chromosomal aberrations involving the KMT2A gene have been identified. However, the majority of leukemias result from translocations leading to KMT2A fusions. More than 90 KMT2A translocation partner genes fused to the 5´- KMT2A portion have been identified. The most common translocation partners in KMT2A associated leukemia are AFF1, MLLT3, MLLT1, MLLT10, ELL and AFDN, described here in the order of their frequency. The AFDN (afadin) gene, formerly known as MLLT4 and AF6, is located on chromosome 6 (6q27). KMT2A-AFDN fusions result from translocations of the type t(6;11)(q27;q23). The most frequent breakpoint in the KMT2A gene leading to this translocation is positioned in intron 9. The majority of ALL patients have breakpoints in exon 1 or 2 of the AFDN gene. Intriguingly, T-cell ALL patients show a significantly higher percentage of KMT2A-AFDN and KMT2A-MLLT1 fusions than other ALL subgroup patients. However, within the cohort of patients with KMT2A-AFDN rearrangements, unusual KMT2A breakpoints in intron 21 and 23 have been detected, in a minority of cases. One cellular consequence of the KMT2A-AFDN fusion is an increased and extended DOT1L mediated H3K79 methylation signature, which is also being observed in the presence of KMT2A-AFF1, AFF1-KMT2A, KMT2A-MLLT3, KMT2A-MLLT1, and KMT2A-MLLT10 fusions. Therefore, DOT1L inhibitors are promising candidates for clinical treatment which are currently being evaluated.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the respective loci.

Literature

- De Braekeleer et al (2011) Mol Oncol 5:555-563
- Meyer et al (2013) Leukemia 27:2165-2176
- Meyer et al (2017) Leukemia 32:273–284

Order No:
D-5109-100-OG

Size: **100 µl**

XL t(6;14) CCND3/IGH DF IVD

XL t(6;14) CCND3/IGH DF consists of an orange-labeled probe hybridizing to the CCND3 gene region at 6p21.1 and a green-labeled probe hybridizing to the IGH gene region at 14q32.3.

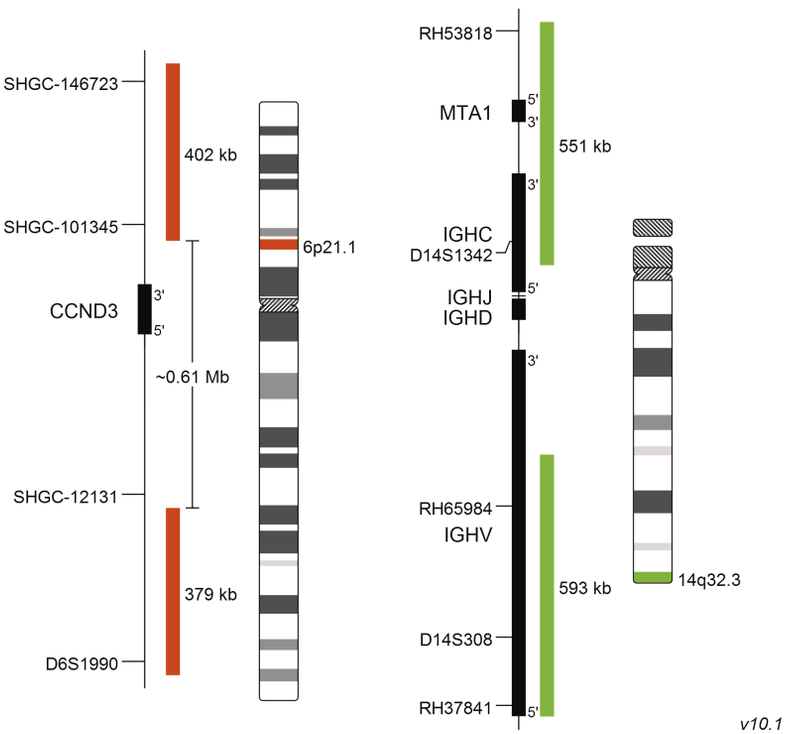
The most frequent primary abnormalities in multiple myeloma (MM) are trisomies of odd-numbered chromosomes or translocations involving the immunglobulin heavy chain (IGH) gene locus. The most common MM-associated IGH translocations are t(11;14), t(4;14), t(6;14), t(14;16) and t(14;20) in the order of their occurrence. The consequence of these rearrangements is the dysregulation of genes juxtaposed to transcriptional enhancers in the IGH gene locus. Prognosis and risk stratification strongly depend on the detection and interpretation of cytogenetic primary abnormalities. Translocations t(14;16) and t(14;20) are considered as high risk, t(4;14) as intermediate risk and t(6;14) and t(11;14) as standard risk cytogenetic aberrations in patients with MM based on FISH testing. Secondary aberrations are also influencing the outcome.

Cyclins of the D-family are essential for the transition from G1- to S-Phase during the cell cycle. t(6;14)(p21;q32) moves the cyclin D3 gene in proximity to 3´ IGH enhancer sequences and is associated with cyclin D3 overexpression. The chromosomal translocation has been reported as a rare and recurrent event not only in myeloma but also in other B-cell malignancies such as diffuse large B-cell lymphoma.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci.



Literature

- Shaughnessy et al (2001) Blood 98:217-223
- Sonoki et al (2001) Blood 98:2837-2844
- Rajan and Rajkumar (2015) Blood Cancer J 5:e365

Order No:
D-5147-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Translocation/Dual Fusion Probe

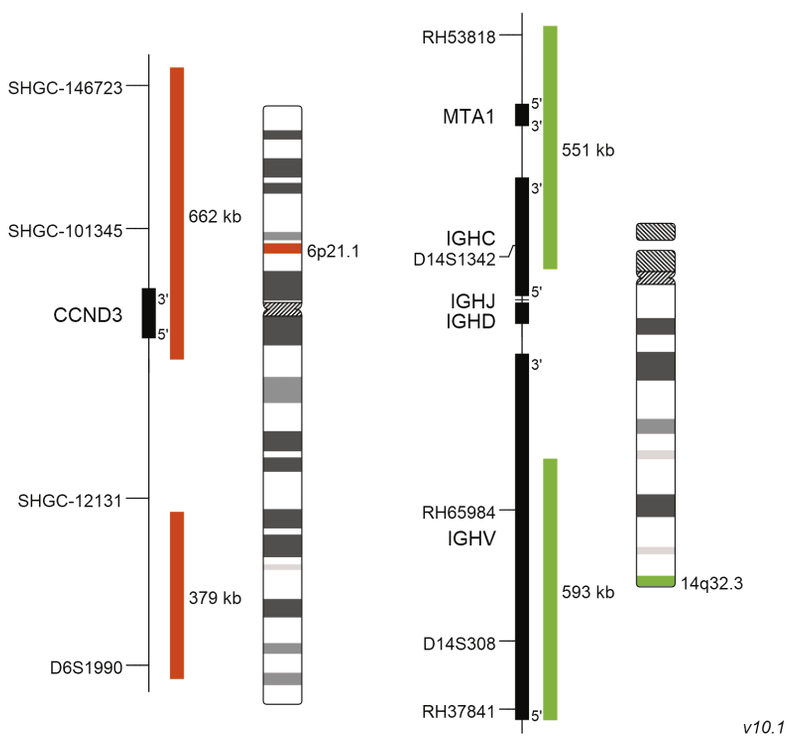
XL

IVD XL CCND3/IGH DF

XL CCND3/IGH DF consists of an orange-labeled probe hybridizing to the CCND3 gene and flanking regions at 6p21.1 and a green-labeled probe hybridizing to the IGH gene region at 14q32.3.

The most frequent primary abnormalities in multiple myeloma (MM) are trisomies of odd-numbered chromosomes or translocations involving the immunoglobulin heavy chain (IGH) gene locus. The most common MM-associated IGH translocations are t(11;14), t(4;14), t(6;14), t(14;16) and t(14;20) in the order of their occurrence. The consequence of these rearrangements is the dysregulation of genes juxtaposed to transcriptional enhancer elements in the IGH gene locus. Prognosis and risk stratification strongly depend on the detection and interpretation of cytogenetic primary abnormalities. Translocations t(14;16) and t(14;20) are considered as high risk, t(4;14) as intermediate risk and t(6;14) and t(11;14) as standard risk cytogenetic aberrations in patients with MM based on FISH testing. Secondary aberrations are also influencing the outcome.

Cyclins of the D-family are essential for the transition from G1 to S phase during the cell cycle progression. t(6;14)(p21;q32) moves the cyclin D3 (CCND3) gene in proximity to 3' IGH enhancer sequences and is associated with CCND3 overexpression. The chromosomal translocation has been reported as a rare but recurrent event not only in myeloma but also in other B-cell malignancies such as diffuse large B-cell lymphoma.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange fusion (2GO) (adjacent green and orange) signals.

Literature

- Shaughnessy et al (2001) Blood 98:217-223
- Sonoki et al (2001) Blood 98:2837-2844
- Rajan and Rajkumar (2015) Blood Cancer J 5:e365

Order No:
D-5043-100-TC

Size: **100 µl**

XL 7q22/7q36 IVD

XL 7q22/7q36 consists of an orange-labeled probe hybridizing to the KMT2E gene region at 7q22, a green-labeled probe hybridizing to the CUL1/EZH2 gene region at 7q36 and an aqua-labeled probe hybridizing to the centromere of chromosome 7.

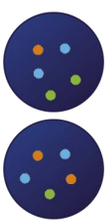
Myelodysplastic neoplasms (MDS) and myeloproliferative neoplasms (MPN) are associated with deregulated production of myeloid cells. According to WHO classification (2017), recurrent cytogenetic aberrations are observed in about 50% of MDS cases. The most common aberrations are 5q-, 7/7q-, trisomy 8, del(20q), and inv(3) or t(3;3).

Loss of chromosome 7 (-7) or deletion of the long arm (7q-) are recurrent chromosome abnormalities in myeloid leukemias such as MDS or acute myeloid leukemia (AML). The association of -7/7q with myeloid leukemia suggests that certain regions contain tumor suppressor gene(s), whose loss of function contribute to leukemic transformation or tumor progression. Multiple critical regions have been identified: one in band 7q22 (including the KMT2E gene) as well as the more telomeric region 7q31 and 7q35-q36 (including the EZH2 gene).

Expected Patterns

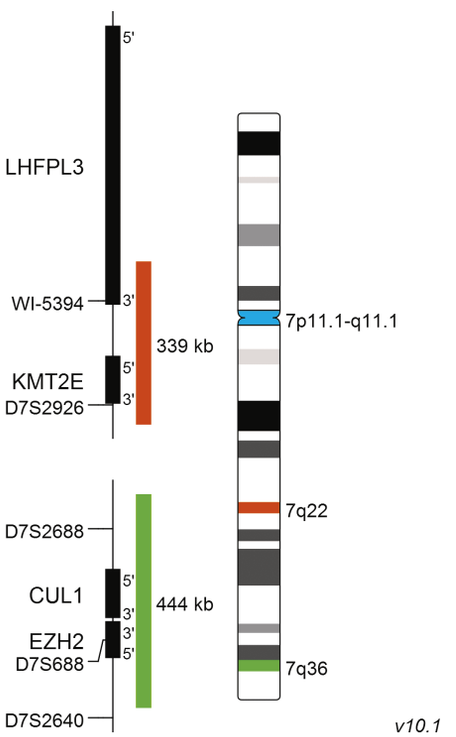
Normal Cell
Two green (2G), two orange (2O), and two blue (2B) signals.

Aberrant Cell (typical results)
Two green (2G), one orange (1O) and 2 blue (2B) indicating the deletion of a 7q22 locus or one green (1G), two orange (2O), and 2 blue (2B) signals, indicating the deletion of a 7q36 locus.



Aberrant Cell (typical results)
One green (1G), one orange (1O), and two blue (2B) signals indicating the deletion of a 7q22 locus and of a 7q36 locus.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and one blue (1B) signal indicating a monosomy 7.



Literature

- Le Beau et al (1996) Blood 88:1930-1935
- Emerling et al (2002) Oncogene 21:4849-4854
- De Weer et al (2010) PLoS One 13:e8676

Order No:
D-5068-100-TC

Size: **100 µl**

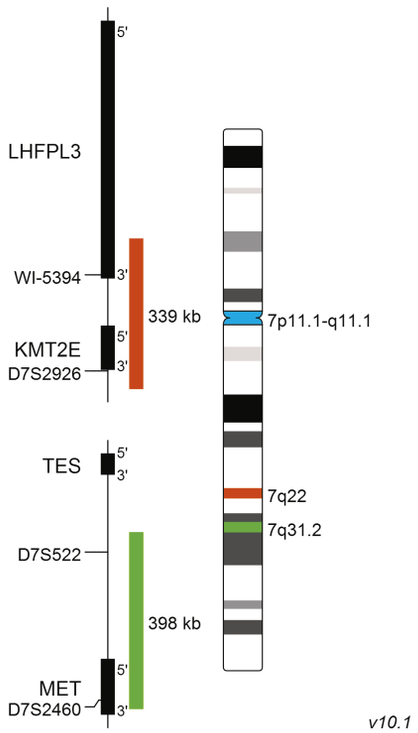
XCyting Locus-Specific Probes
Deletion Probe **XL**

IVD XL del(7)(q22q31)

XL del(7)(q22q31) consists of an orange-labeled probe hybridizing to the KMT2E gene region at 7q22, a green-labeled probe hybridizing to the MET gene region at 7q31.2 and an aqua-labeled probe hybridizing to the centromere of chromosome 7.

Myelodysplastic neoplasms (MDS) and myeloproliferative neoplasms (MPN) are associated with deregulated production of myeloid cells. According to WHO classification (2017), recurrent cytogenetic aberrations are observed in about 50% of MDS cases. The most common aberrations are 5q-, 7/7q-, trisomy 8, del(20q), and inv(3) or t(3;3).

Loss of chromosome 7 (-7) or deletion of the long arm (7q-) are recurrent chromosome abnormalities in myeloid leukemias such as MDS or acute myeloid leukemia (AML). The association of -7/7q with myeloid leukemia suggests that certain regions contain tumor suppressor gene(s), whose loss of function contribute to leukemic transformation or tumor progression. Multiple critical regions have been identified: one in band 7q22 (including the KMT2E gene) as well as the more telomeric region 7q31 and 7q35-q36 (including the EZH2 gene).



Expected Patterns

Normal Cell
Two green (2G), two orange (2O), and two blue (2B) signals.

Aberrant Cell (typical results)
Two green (2G), one orange (1O), and 2 blue (2B) signals indicating the deletion of a 7q22 locus or one green (1G), two orange (2O), and 2 blue (2B) signals, indicating the deletion of a 7q31 locus.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two blue (2B) signals indicating the deletion of a 7q22 locus and of a 7q31 locus.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and one blue (1B) signal indicating a monosomy 7.

Literature

- LeBeau et al (1996) Blood 88:1930-1935
- Emerling et al (2002) Oncogene 21:4849-4854
- De Weer et al (2010) PLoS One 13:e8676

Order No:
D-5144-100-TC

Size: **100 µl**

XL CUX1/EZH2/7cen IVD

XL CUX1/EZH2/7cen consists of an orange-labeled probe hybridizing to the CUX1 gene region at 7q22, a green-labeled probe hybridizing to the EZH2 gene region at 7q36 and an aqua-labeled probe hybridizing to the centromere of chromosome 7.

Partial deletions of the long arm of chromosome 7 [del(7q),7q-] or monosomy 7 (-7) are highly recurrent chromosomal aberrations frequently observed in myelodysplastic neoplasms (MDS) and acute myeloid leukemia (AML). In MDS and AML, del(7q) as sole cytogenetic aberration has a prevalence of less than 5%. However, many of the examined patients with del(7q) have additional cytogenetic aberrations. Furthermore, whole-exome sequencing studies analyzed the coincidence of mutated genes (e.g. CUX1, LUCL2, CUL1, and EZH2) and -7 or del(7q).

7q deletions are assigned to the intermediate genetic prognostic risk group (ELN risk stratification) or the high risk prognostic group (revised MRC classification), in AML. However, 7q- are classified by the revised IPSS (International prognostic scoring system) as 'intermediate cytogenetic prognostic risk' or 'poor risk' - if coincide with another abnormality, in MDS.

Several deleted regions have been identified along the long arm of chromosome 7, but two critical genomic regions are known to be commonly deleted regions (CDRs): 7q22 and 7q31-q36. Studies focusing on CDRs on 7q have highlighted the significance of the gene loci of EZH2, SAMD9L, CUX1, MLL3, and DOCK4, whose assumed roles as tumor suppressor genes could explain the criticality of their haploinsufficiency.

The CUX1 gene locus has been described as frequently deleted locus in case of 7q deletions, increasing the accuracy of the diagnosis of 7q22 deletions.

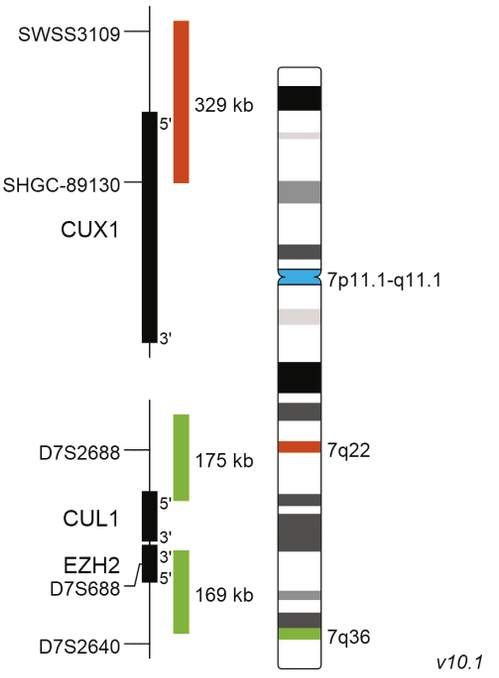
Expected Patterns

Normal Cell
Two Blue (2B), two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G), one orange (1O) and 2 blue (2B) signals resulting from loss of one orange signal or one green (1G), two orange (2O) and 2 blue (2B) signals resulting from loss of one green signal.

Aberrant Cell (typical results)
Two blue (2B), one green (1G) and one orange (1O) signal resulting from the loss of one green and one orange signal.

Aberrant Cell (typical results)
One blue (1B), one green (1G) and one orange (1O) signal resulting from the loss of one chromosome.



Literature

- Le Beau et al (1996) Blood 88:1930-1935
- Struski and Luquet (2019) Ann Biol Clin (Paris) 77:229-230
- Hartmann et al (2019) Genes Chromosomes Cancer 58:698-704

Order No:
D-6005-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Amplification Probe
XL

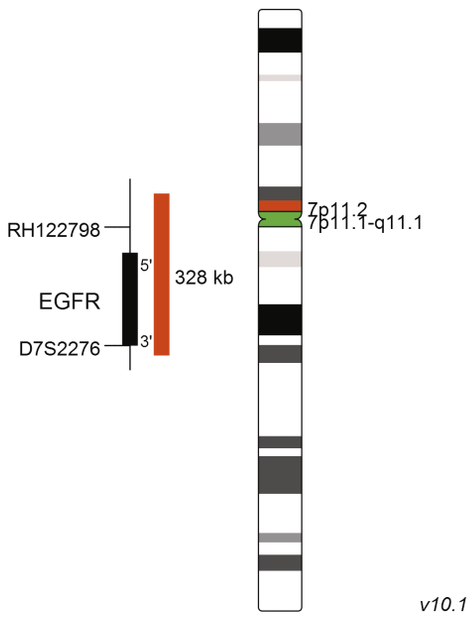
IVD XL EGFR amp

XL EGFR amp consists of an orange-labeled probe hybridizing to the EGFR gene region at 7p11.2 and a green-labeled probe hybridizing to the centromere of chromosome 7.

EGFR (epidermal growth factor receptor) gene amplification generally results in increased protein expression in breast carcinomas. About 6% of breast carcinomas show moderate to low-level EGFR amplification associated with genuine EGFR protein overexpression. Studies in non-small cell lung cancer (NSCLC) have shown that EGFR expression is associated with reduced survival, frequent lymph node metastasis, and poor chemosensitivity.

EGFR is a member of the ErbB family of receptors, a subfamily of four closely related receptor tyrosine kinases which all play an important role in controlling normal cell growth, apoptosis, and other cellular functions. Mutations of EGFRs can lead to NSCLC, pancreatic cancer, breast cancer, colon cancer, and some other cancers.

New drugs such as gefitinib and erlotinib directly target the EGFR. EGFR-positive patients have shown a 60% response rate, which exceeds the response rate for conventional chemotherapy.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one separate orange (1O) signal, and orange signal clusters indicating amplification of EGFR (homogeneously staining region = HSR).

Aberrant Cell (typical results)
Two green (2G) and multiple copies of orange signals indicating amplification of EGFR (double minute = dm).

Literature

- Okada et al (2003) Cancer Res 63:413-416
- Bhargava et al (2006) Mod Patho 18:1027-1033
- Sholl et al (2009) Cancer Res 69:8341-8348

Order No:
D-5101-100-OG

Size: **100 µl**

XL t(7;12) MNX1/ETV6 IVD

XL t(7;12) MNX1/ETV6 consists of an orange-labeled probe hybridizing to the MNX1 gene region at 7q36 and a green-labeled probe hybridizing to the ETV6 gene region at 12p13.2.

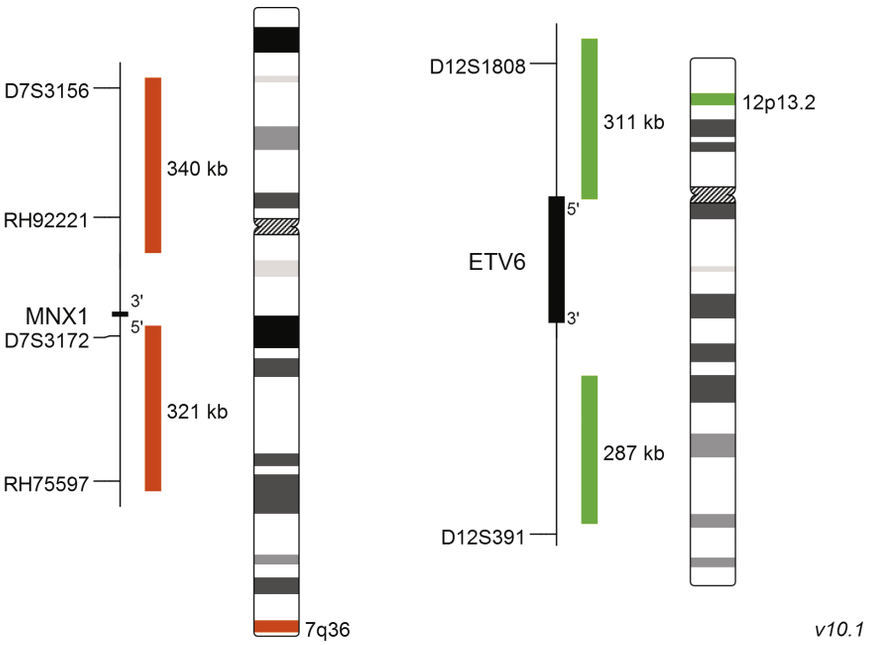
Several recurrent balanced translocations and inversions, and their variants, are recognized in the WHO category acute myeloid leukemia (AML) with recurrent genetic abnormalities. Furthermore, several cytogenetic abnormalities are considered sufficient to establish the WHO diagnosis of AML with myelodysplasia-related features if 20% or more blood or marrow blasts are present.

The t(7;12)(q36;p13) translocation is a recurrent chromosome abnormality which involves the ETV6 gene on chromosome 12 and has been identified in 20–30% of infant patients with AML. The detection of t(7;12) rearrangements relies on the use of fluorescence in situ hybridization (FISH) because this translocation is hardly visible by chromosome banding methods. The clinical outcome of t(7;12) patients is believed to be poor, therefore an early and accurate diagnosis is important in the clinical management and treatment.

Expected Patterns

Normal Cell
Two green (2G) and two orange signals (2O).

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange fusion (2GO) (adjacent green and orange) signals.



Literature

- Ballabio et al (2009) Leukemia 23:1179-1182
- Naiel et al (2013) Cancers 5:281-295
- Owokaet al (2015) Hematol Leuk 3:1-4

Order No:
D-5041-100-OG

Size: **100 µl**

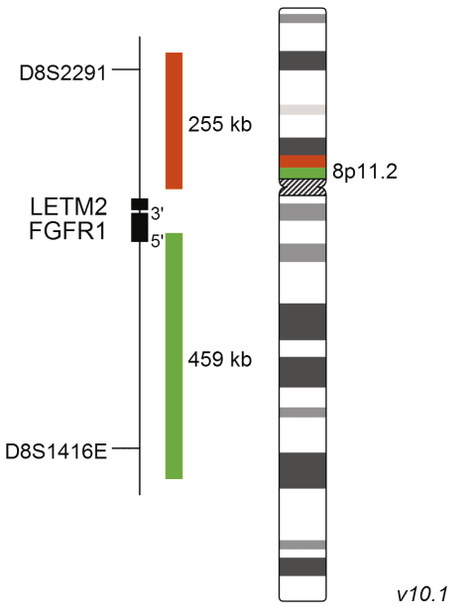
XCyting Locus-Specific Probes
Break Apart Probe XL

IVD XL FGFR1

XL FGFR1 consists of a green-labeled probe hybridizing proximal to the FGFR1 gene region at 8p11.2 and an orange-labeled probe hybridizing distal to the FGFR1 gene region at 8p11.2.

In 2008, the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues introduced a new category for myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1. Many of these cases present as a myeloproliferative neoplasm, usually with eosinophilia.

The 8p11 myeloproliferative syndrome (MPD) also known as stem cell leukemia-lymphoma syndrome (SCLL) is associated with translocations disrupting FGFR1. Imatinib, which induces durable responses in MPDs with PDGFRA and PDGFRB fusion genes, is inactive in patients with FGFR1 translocations.



Expected Patterns

Normal Cell
Two green-orange (2GO, may appear yellow 2Y) fusion signals.

Aberrant Cell (typical results)
One green-orange (1GO, may appear as yellow) fusion signal and one green (1G), one orange (1O) indicating a chromosome break in the FGFR1 locus.

Literature

- Cross et al (2002) Leukemia 16:1207-1212
- Walz et al (2005) Leukemia 19:1005-1009
- Chase et al (2007) Blood 110:3729-3734

Order No:
D-6008-100-OG

Size: **100 µl**

XL MYC amp IVD

XL MYC amp consists of an orange-labeled probe hybridizing to the MYC gene region at 8q24.21 and a green-labeled probe hybridizing to the centromere of chromosome 8.

Amplification of MYC has been described in many types of tumor, including breast, cervical and colon cancers, as well as in squamous cell carcinomas of the head and neck, myeloma, non-Hodgkin lymphoma, gastric adenocarcinomas and ovarian cancer. MYC is the most frequently amplified oncogene and the elevated expression of its gene product correlates with tumor aggression and poor clinical outcome.

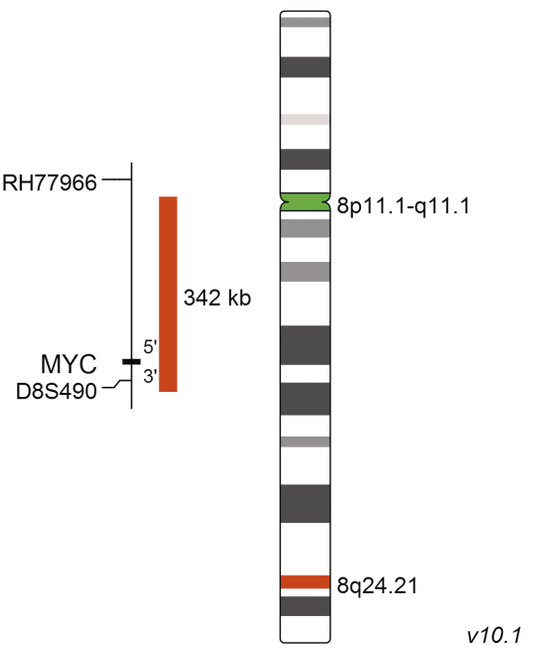
The proto-oncogene MYC, located at 8q24.1, encodes a nuclear phosphoprotein transcription factor which has an integral role in a variety of cellular processes, such as cell cycle progression, proliferation, metabolism, adhesion, differentiation, and apoptosis.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one separate orange (1O) signal, and orange signal clusters indicating amplification of MYC (homogeneously staining region = HSR).

Aberrant Cell (typical results)
Two green (2G) and multiple copies of orange signals indicating amplification of MYC (double minute = dm).



Literature

- Rummukainen et al (2001) Mod Pathol 14:1030-1035
- Blancato et al (2004) Br J Cancer 90:1612-1619
- Singhi et al (2012) Mod Pathol 25:378-387

Order No:
D-6023-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe XL

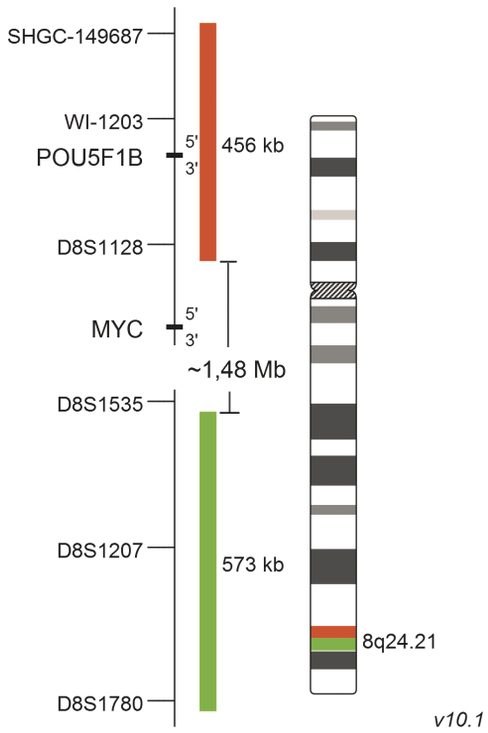
IVD

XL MYC BA

XL MYC BA consists of an orange-labeled probe hybridizing proximal to the MYC gene region at 8q24.21 and a green-labeled probe hybridizing distal to the MYC gene region at 8q24.21.

Translocations involving MYC are observed in diffuse large-B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, and other lymphomas. In Burkitt Lymphoma, the MYC gene, located at 8q24, is activated by a translocation next to an immunoglobulin constant gene. Most frequently, MYC is positioned near the immunoglobulin heavy-chain (IGH) constant region on chromosome 14q32. However, in some tumors MYC can also be positioned near the light-chain region on chromosome 2p11 (IGK) or 22q11 (IGL). In addtion, other translocation partners have been identified (e.g. BCL11A, PAX5, ZCCHC7).

The XL MYC BA probe is designed as a break apart probe with two probes juxtaposed and differentially labeled. The proximal and distal regions are sufficiently large to achieve intense signals also on paraffin-embedded tissue sections. The wide gap between the orange and green part of this probe allows for the detection of the t(2;8) translocation as well as t(8;14) and t(8;22).



Expected Patterns

Normal Cell
Two green-orange (2GO) fusion signals.

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.

Literature

- Hummel et al (2006) N Engl J Med 354:2419-2430
- Einerson et al (2006) Leukemia 20:1790-1799
- Bertrand et al (2007) Leukemia 21:515-523

Order No:
D-6030-100-TC

Size: **100 µl**

XL MYC BA triple-color IVD

XL MYC BA triple-color consists of an orange-labeled probe hybridizing proximal to the MYC gene region at 8q24.21, an aqua-labeled probe hybridizing to the MYC gene region at 8q24.21 and a green-labeled probe hybridizing distal to the MYC gene region at 8q24.21.

Translocations involving MYC are observed in diffuse large-B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, and other lymphomas. In Burkitt Lymphoma, the MYC gene, located at 8q24, is activated by a translocation next to an immunoglobulin constant gene. Most frequently, MYC is positioned near the immunoglobulin heavy-chain (IGH) constant region on chromosome 14q32. However, in some tumors MYC can also be positioned near the light-chain region on chromosome 2p11 (IGK) or 22q11 (IGL). In addtion, other translocation partners have been identified (e.g. BCL11A, PAX5, ZCCHC7).

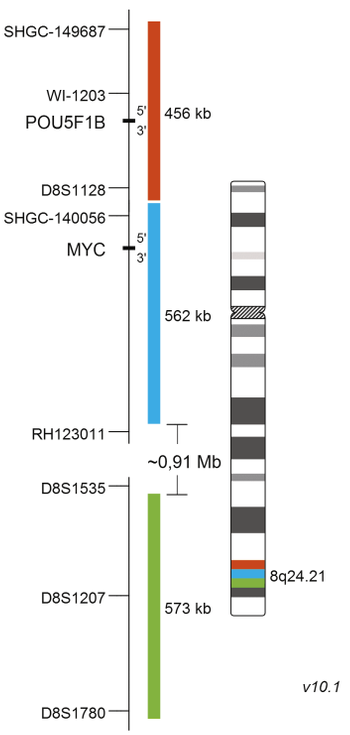
The XL MYC BA Triple-color probe is designed as a break apart probe with three probes juxtaposed and differentially labeled. In cases with 8q24 rearrangment, the co-localization patterns of orange-blue versus green-blue allows to distinguish different breakpoints in MYC translocations which can be an aid in diagnosis.

Expected Patterns

Normal Cell
Two green-orange-blue (2GOB) fusion signals.

Aberrant Cell (typical results)
One green-blue (1GB), one orange (1O), and one green-orange-blue (1GOB) fusion signal.

Aberrant Cell (typical results)
One orange-blue (1OB), one green (1G), and one green-orange-blue (1GOB) fusion signal.



Literature

- Hummel et al (2006) N Engl J Med 354:2419-2430
- Einerson et al (2006) Leukemia 20:1790-1799
- Bertrand et al (2007) Leukemia 21:515-523

Order No:
D-5120-100-OG

Size: **100 µl**

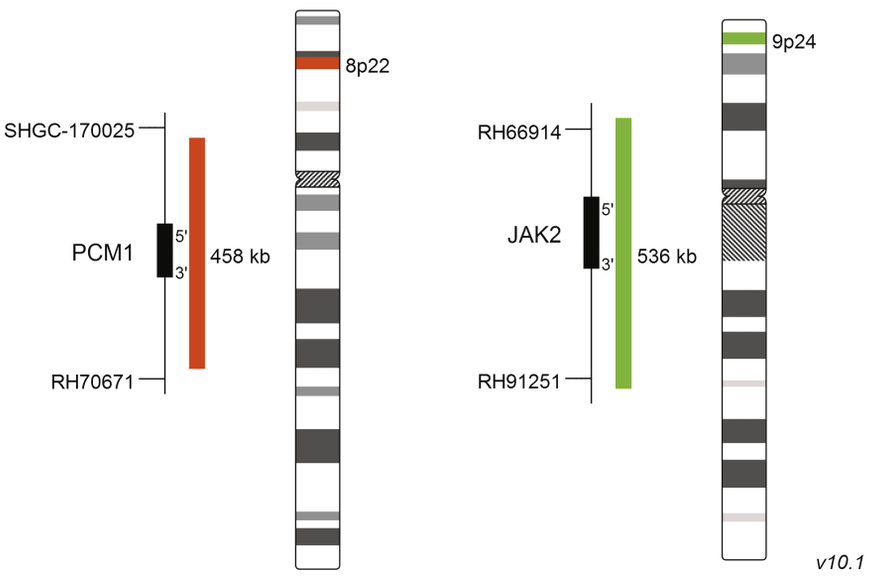
XCyting Locus-Specific Probes
Translocation/Dual Fusion Probe XL

IVD XL t(8;9) PCM1/JAK2 DF

XL t(8;9) PCM1/JAK2 DF consists of an orange-labeled probe hybridizing to the PCM1 gene region at 8p22 and a green-labeled probe hybridizing to the JAK2 gene region at 9p24.

Receptor tyrosine kinases as well as Janus kinases (JAKs) have multiple functions in the signal transmission of cytokines and growth factors. Furthermore, constitutively enhanced JAK phosphorylation levels play critical roles in chronic inflammatory processes and cancer development. Chromosomal rearrangements involving JAK2, leading to constitutive activation of the kinase, have been detected in several patients with myeloproliferative neoplasm (MPN) or myelodysplastic neoplasm (MDS). While ETV6-JAK2 and BCR-JAK2 fusion genes, resulting from translocations of the type t(9;12)(p24;p13) and t(9;22)(p24;q11), respectively, have been reported only in a small number of patients, pericentriolar material 1 (PCM1)-JAK2 represents the most frequent JAK2 fusion gene. The responsible translocation generating the described fusion is t(8;9)(p22;p24.1). Multiple breakpoints have been identified.

In 2017, the WHO updated the category 'myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement' by adding a provisional entity, PCM1-JAK2. All mentioned neoplasms described in this category are associated with rearrangements or (rarely) mutations of four tyrosine kinases: PDGFRA, PDGFRB, FGFR1 or JAK2, respectively. As PCM1-JAK2 fusions are associated with a poor prognosis, only allogeneic hematopoietic stem cell transplantation is considered to be rather successful, although first small studies using the JAK2 inhibitor ruxolitinib as treatment for patients with PCM1-JAK2 positive chronic eosinophilic leukemia, not otherwise specified, have shown promising short term remission.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci.

Literature

- Lierman et al (2012) Blood 120:1529-1531
- Rumi et al (2013) J Clin Oncol 31:e269-e271
- Reiter and Gotlib (2017) Blood 129:704-714

Order No:
D-5110-100-OG

Size: **100 µl**

XL t(8;14) MYC/IGH DF IVD

XL t(8;14) MYC/IGH DF consists of an orange-labeled probe hybridizing to the MYC gene region at 8q24.21 and a green-labeled probe hybridizing to the IGH gene region at 14q32.3.

Chromosomal translocations involving the IGH locus are recurrent in many types of lymphomas. Burkitt lymphoma (BL) is a rare, but fast growing type of non-Hodgkin lymphoma (NHL). The translocation between the MYC gene locus at 8q24 and the immunoglobulin genes (IG) for the kappa light chain at 2p12 (IGK), for the heavy chain at 14q32 (IGH) or for the lambda light chain at 22q11 (IGL), juxtapose the MYC gene to an IG enhancer, resulting in overexpression of MYC. About 80% of BL patients show the MYC rearrangement t(8;14)(q24;q32) while approximately 10% show a translocation between the MYC gene region and IGK or IGL. Additional breakpoints in BCL2, BCL6 and CCND1 are indicators for an aggressive course and short overall survival.

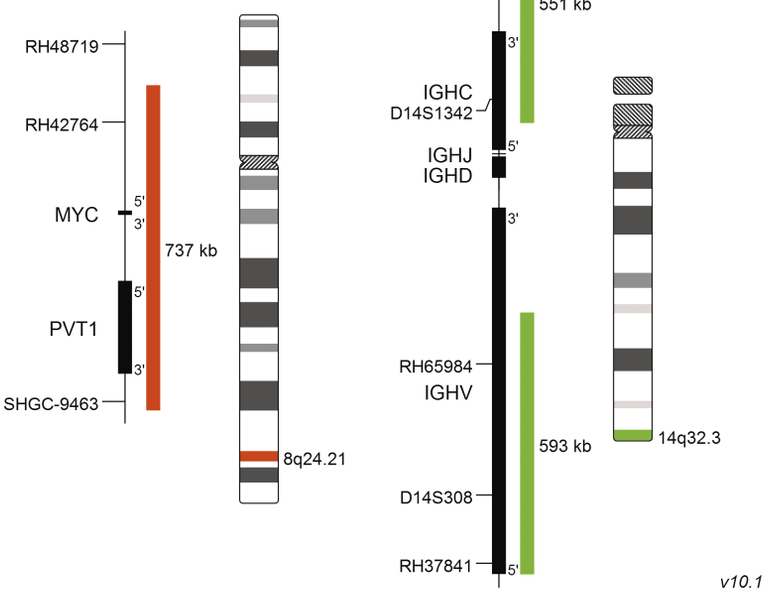
MYC translocations are also present in other types of lymphomas such as diffuse large B-cell lymphoma (DLBCL), which is difficult to distinguish from BL by morphology and immunophenotype alone. The use of different techniques including FISH, genomic and cytogenetic profiling can provide additional information.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci.

Aberrant Cell (typical results)
Two green (2G) and three orange (3O) signals resulting from a translocation between the orange labeled and an unknown chromosome.



Literature

- Siebert et al (1998) Blood 91:984-990
- Boerma et al (2009) Leukemia 23:225-234
- Nguyen et al (2017) Genes 8:1-23

Order No:
D-5125-100-TC

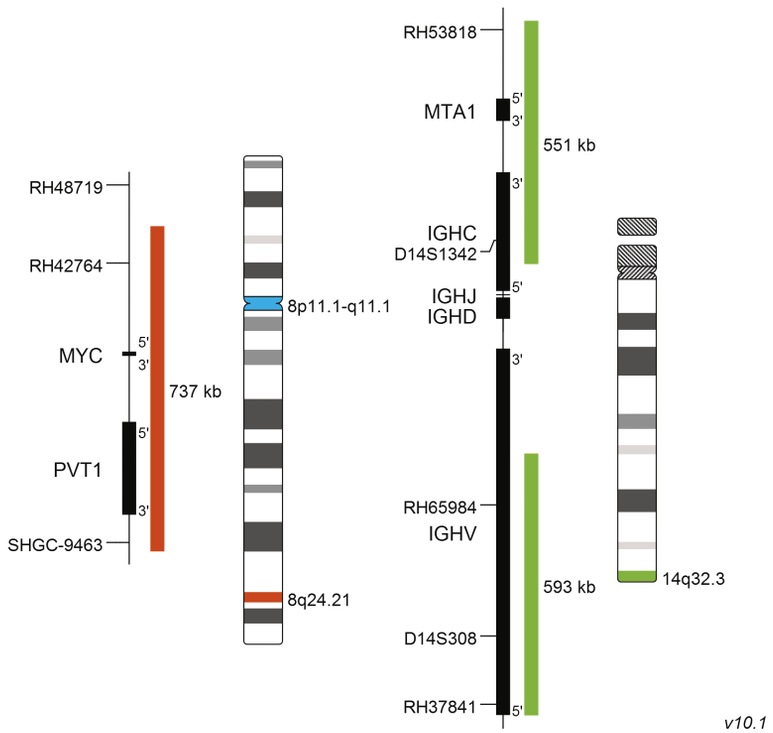
Size: **100 µl**

IVD XL t(8;14) MYC/IGH DF 8cen

XL t(8;14) MYC/IGH DF 8cen consists of an aqua-labeled probe hybridizing to the centromere of chromosome 8, an orange-labeled probe hybridizing to the MYC gene region at 8q24.21 and a green-labeled probe hybridizing to the IGH gene region at 14q32.3.

Chromosomal translocations involving the IGH locus are recurrent in many types of lymphomas. Burkitt lymphoma (BL) is a rare, but fast growing type of non-Hodgkin lymphoma (NHL). The translocation between the MYC gene locus at 8q24 and the immunoglobulin genes (IG) for the kappa light chain at 2p12 (IGK), for the heavy chain at 14q32 (IGH) or for the lambda light chain at 22q11 (IGL), juxtapose the MYC gene to an IG enhancer, resulting in overexpression of MYC. About 80% of BL patients show the MYC rearrangement t(8;14)(q24;q32) while approximately 10% show a translocation between the MYC gene region and IGK or IGL. Additional breakpoints in BCL2, BCL6 and CCND1 are indicators for an aggressive course and short overall survival.

MYC translocations are also present in other types of lymphomas such as diffuse large B-cell lymphoma (DLBCL), which is difficult to distinguish from BL by morphology and immunophenotype alone. The use of different techniques including FISH, genomic and cytogenetic profiling can provide additional information.



Expected Patterns

Normal Cell
Two blue (2B), two green (2G), and two orange (2O) signals.

Aberrant Cell (typical results)
Two blue (2B), one green (1G), one orange (1O), and two green-orange colocalization/ fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci.

Aberrant Cell (typical results)
Three blue (3B), two green (2G), and three orange (3O) signals resulting from a triso-my of the orange/blue labeled chromosome.

Aberrant Cell (typical results)
Two blue (2B), two green (2G), and three orange (3O) signals resulting from a reciprocal translocation between the or-ange labeled and an unknown chromosome.

Literature

- Siebert et al (1998) Blood 91:984-990
- Boerma et al (2009) Leukemia 23:225-234
- Nguyen et al (2017) Genes 8:1-23

Order No:
D-5114-100-OG

Size: **100 µl**

XL t(8;21) plus IVD

XL t(8;21) plus consists of a green-labeled probe hybridizing to the RUNX1T1 gene region at 8q21.3-22.1 and an orange-labeled probe hybridizing to the RUNX1 gene region at 21q22.1.

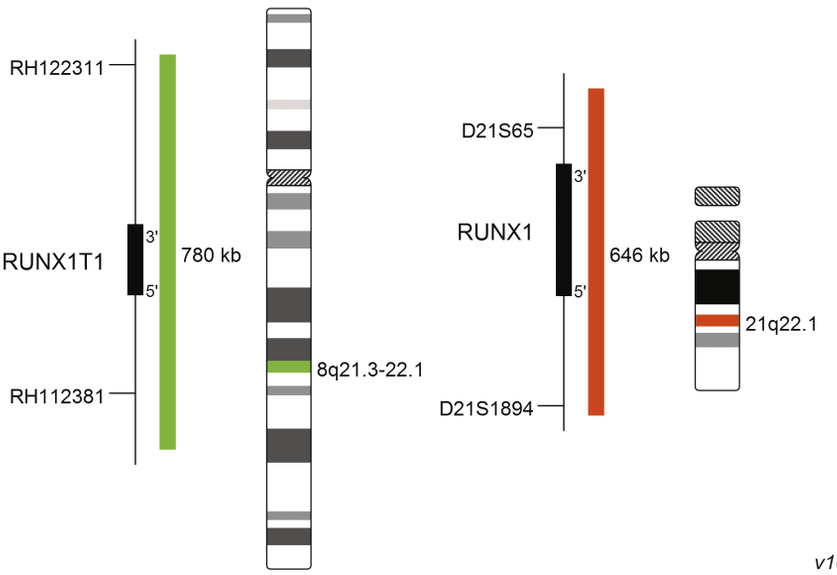
Several recurrent balanced translocations and inversions, and their variants, are recognized in the WHO category acute myeloid leukemia (AML) with recurrent genetic abnormalities. Furthermore, several cytogenetic abnormalities are considered sufficient to establish the WHO diagnosis of AML with myelodysplasia-related features if 20% or more blood or marrow blasts are present.

t(8;21)(q21;q22) is the most common translocation in de novo AML occurring in up to 20% of adult and 40% of pediatric cases. The translocation fuses RUNX1 with RUNX1T1 to produce a RUNX1/RUNX1T1 fusion gene located on the derivative chromosome 8. For these patients, the prognosis after intensive chemotherapy is better than for the majority of AML patients. Small hidden interstitial insertions resulting in a RUNX1/RUNX1T1 rearrangement have been found, necessitating the use of a breakpoint spanning rather than a breakpoint flanking FISH probe.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci.



v10.1

Literature

- Zhang et al (2002) PNAS 99:3070-3075
- Gamerdinger et al (2003) Gene Chromosome Canc 36:261-272
- Jang et al (2010) Ann Clin Lab Sci 40:80-84

Order No:
D-5148-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe XL

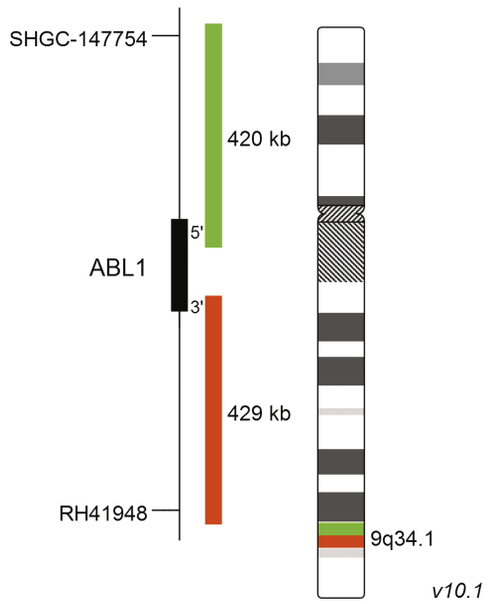
IVD XL ABL1 BA

XL ABL1 BA consists of a green-labeled probe hybridizing proximal to the ABL1 gene region at 9q34.1 and an orange-labeled probe hybridizing distal to the ABL1 gene region at 9q34.1.

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children with a prevalence of approximately 1:1500. Children with Down syndrome have a 10- to 20-fold increased risk of developing acute leukemia (B-cell precursor-ALL, acute myeloid leukemia, and particularly acute megakaryoblastic leukemia).

In 2017, the WHO recognized BCR-ABL1-like ALL, a subtype of B-lymphoblastic leukemia/lymphoma, as a new entity. BCR-ABL1-like ALL, also known as Philadelphia chromosome (Ph)-like ALL, is found in 10-20% of childhood and in 20-30% of all adult B-cell dependent ALL cases. BCR-ABL1-like ALL is characterized by a gene expression profile sharing significant overlap with that of Ph-positive (Ph+) ALL. In contrast to Ph+ ALL, defined by the presence of the BCR-ABL1 fusion resulting from t(9;22)(q34;q11), BCR-ABL1-like cases include a variety of genomic alterations enhancing kinase and cytokine receptor signaling.

Prominent genes involved in the pathogenesis of BCR-ABL1-like ALL are CRLF2, EPOR, JAK2, ABL1, ABL2, CSF1R and PDGFRB. The already known heterogenous 5' fusion partners of ABL1 are CENPC, ETV6, FOXP1, LSM14A, NUP153, NUP214, RANBP2, RCSD1, SFPQ, SNX1, SNX2, SPTAN1 and ZMIZ1. The kinase domain of ABL1 is present in all identified chimeric fusion proteins.



Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.

Literature

- Tasian et al (2017) Blood 130:2064-2072
- Conant and Czuchlewski (2019) Int J Lab Hematol 41 Suppl 1:126-130
- Jain and Abraham (2019) Arch Pathol Lab Med:doi:10.5858/arpa.2019-0194-RA

Order No:
D-5053-100-OG

Size: **100 µl**

XL CDKN2A IVD

XL CDKN2A consists of an orange-labeled probe hybridizing to the CDKN2A (p16)/CDKN2B (p15) gene region at 9p21 and a green-labeled probe hybridizing to the centromere of chromosome 9.

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer type. T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive and quickly progressing type of ALL affecting T-lymphocytes. Inactivation of the tumor suppressor genes CDKN2A/2B, located at chromosomal region 9p21, is a significant event in the development of T-ALL and other cancer types. Principally, loss of function might happen by deletion, methylation of promotor regions or mutations, whereas deletion of chromosomal region 9p21 seems to be the predominant mechanism.

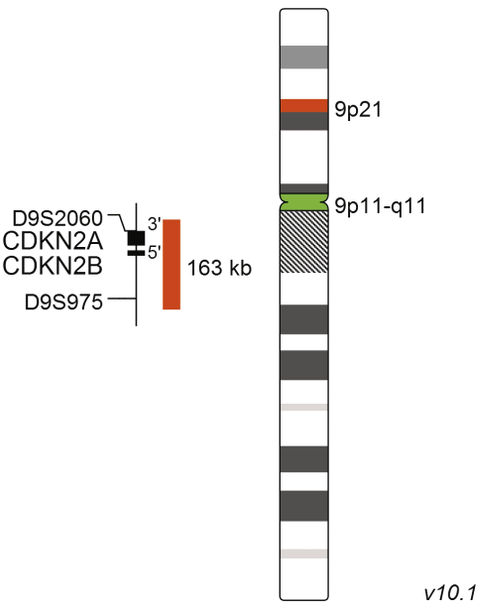
CDKN2A/2B deletions can be detected in about 60% of pediatric and about 50% of adult T-ALL cases. Most deletions are within the resolution of the FISH technique. Genetic alterations of the 9p21 locus result in loss of regulation of the cell cycle which is critical to cancer development.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal, indicating the deletion of the CDKN2A (P16) at 9p21.

Aberrant Cell (typical results)
Two green (2G) and no orange (no O) signal, indicating a homozygous deletion of the CDKN2A (P16) at 9p21.



Literature

- Novara et al (2009) Human Genet 126:511-520
- Sulong et al (2009) Blood 113:100-107
- Girardi et al (2017) Blood 129:1113-1123

Order No:
D-5118-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Deletion Probe
XL

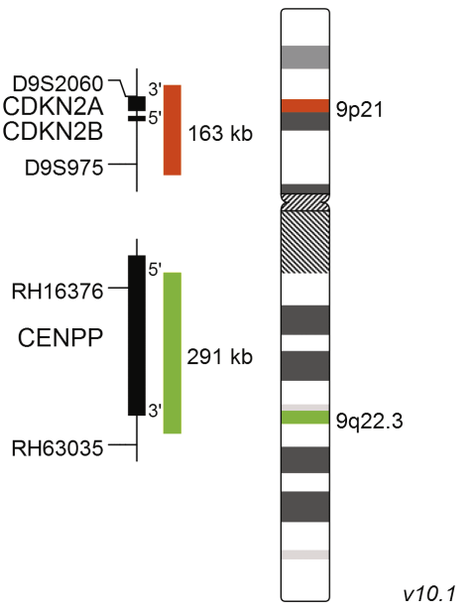
IVD

XL CDKN2A/9q22

XL CDKN2A/9q22 consists of an orange-labeled probe hybridizing to the CDKN2A(p16)/CDKN2B (p15) gene region at 9p21 and a green-labeled probe hybridizing to the CENPP gene region at 9q22.3.

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer type. T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive and quickly progressing type of ALL affecting T-lymphocytes. Inactivation of the tumor suppressor genes CDKN2A/2B, located at chromosomal region 9p21, is a significant event in the development of T-ALL and other cancer types. Principally, loss of function might happen by deletion, methylation of promotor regions or mutations, whereas deletion of chromosomal region 9p21 seems to be the predominant mechanism.

CDKN2A/2B deletions can be detected in about 60% of pediatric and about 50% of adult T-ALL cases. Most deletions are within the resolution of the FISH technique. Genetic alterations of the 9p21 locus result in loss of regulation of the cell cycle which is critical to cancer development.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal resulting from loss of one orange signal.

Aberrant Cell (typical results)
Two green (2G) and no orange (no O) signal resulting from homozygous deletion of the locus covered by the orange probe.

Literature

- Novara et al (2009) Human Genet 126:511-520
- Sulong et al (2009) Blood 113:100-107
- Girardi et al (2017) Blood 129:1113-1123

Clinical Applications
ALL

Chromosome **9** | Page **57**

Order No:
D-5098-100-OG

Size: **100 µl**

XL JAK2 BA IVD

XL JAK2 BA consists of an orange-labeled probe hybridizing proximal to the JAK2 gene region at 9p24 and a green-labeled probe hybridizing distal to the JAK2 gene region at 9p24.

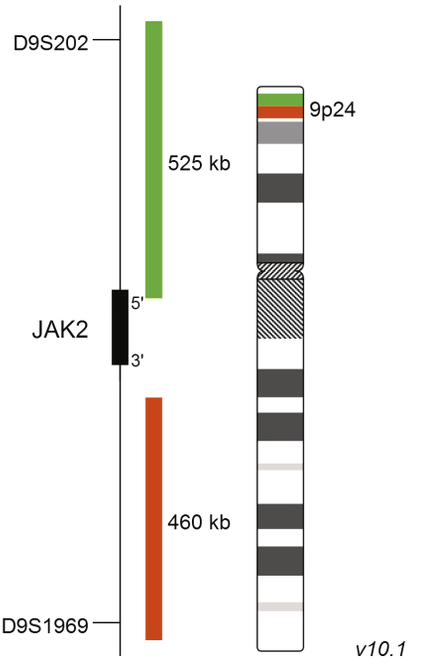
Patients with clinical characteristics of chronic myelogenous leukemia (CML) lacking a BCR/ABL fusion gene are usually referred to as having atypical CML. Most commonly, diverse tyrosine kinase genes such as the receptors FGFR1, PDGFRA, or PDGFRB are involved. In addition, the Janus (tyrosine) kinases (JAK) can be deregulated in leukemia/lymphoma by copy number alterations, mutations and chromosomal translocations.

Chromosomal translocations targeting JAK2 are rare but recurrent abnormalities in myeloproliferative neoplasms, acute myeloid leukemia, acute lymphoblastic leukemia and lymphoma. In cell line models and primary patient material, it could be shown that treatment with ruxolitinib has significant activity against JAK2 activated by gene rearrangement and presents evidence for potential activity against cells with JAK2 amplification.

Expected Patterns

Normal Cell
Two green-orange (2GO) fusion signals representing the two normal JAK2 loci.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and one green-orange (1GO) fusion signal, indicating a chromosome break in the JAK2 locus.



Literature

- Bousquet et al (2005) Oncogene 24:7248-7252
- Chase et al (2012) Haematologica 93:404-408
- Ehrentraut et al (2013) PLOSone 8:e53767

Order No:
D-5143-100-OG

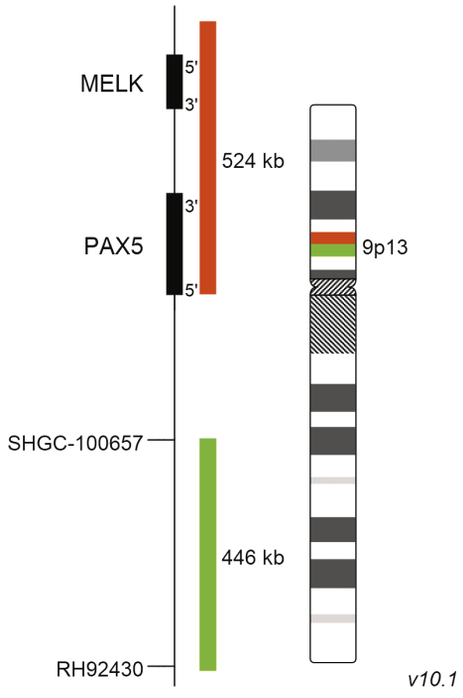
Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe
XL

IVD
XL PAX5 BA

XL PAX5 BA consists of an orange-labeled probe hybridizing to the PAX5 gene and distal gene regions at 9p13 and a green-labeled probe hybridizing proximal to the PAX5 gene region at 9p13.

PAX5 (paired box 5), also known as B-cell specific activator protein (BSAP), is located on 9p13 and is a member of the paired box (PAX) family of transcription factors. The central characteristic is a highly conserved DNA-binding motif (paired box). PAX5 is a master regulator of B cell identity and development. It is expressed from early pro-B stage until final plasmacytic differentiation playing a dual role by activating B-cell commitment genes while repressing non–B-lineage genes. PAX5 alterations in B-cell acute lymphoblastic leukemia (B-ALL) include deletions of the whole gene, focal deletions, sequence mutations, intragenic amplification, and rearrangements. PAX5 rearrangements occurred at an incidence of about 2.5% in childhood B-ALL (Nebral et al) and PAX5 internal rearrangements are observed in 21% of B-ALL patients harboring 9p abnormalities (Coyaud et al). Two B-ALL subtypes, PAX5P80R and PAX5-altered (PAX5alt) are defined by different gene expression profiles and differential PAX5 alterations and considered as potential novel entities in the 5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours (2022). PAX5alt is characterized by various PAX5 alterations including chromosomal rearrangements resulting in dysregulated expression of PAX5 and subsequent transcriptional targets. Until 2019, 24 fusion partner genes of PAX5 were found, the most frequent being ETV6, NOL4L, AUTS2, CBFA2T3. PAX5::ETV6 results from dic(9;12)(p13;p13) which is associated with early suppression of B-cell differentiation. In PAX5::IGH/ t(9;14)(p13;q32), identified in a subset of aggressive B-cell non-Hodgkin lymphoma, the intronic Eμ enhancer of the IGH locus is juxtaposed next to the upstream promoter of PAX5, resulting in increased PAX5 expression.



Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the respective locus.

Literature

- Cobaleda et al (2007) Nat Immunol 8:463-470
- Nebral et al (2009) Leukemia 23:134-143
- Coyaud et al (2010) Blood 115:3089–309
- Gu et al (2019) Nat Genet 51:296-307

Clinical Applications
ALL

Chromosome **9** | Page **59**

Order No:
D-5133-100-OG

Size: **100 µl**

XL t(9;11) MLLT3/KMT2A DF IVD

XL t(9;11) MLLT3/KMT2A DF consists of an orange-labeled probe hybridizing to the MLLT3 gene region at 9p21 and a green-labeled probe hybridizing to the KMT2A gene region at 11q23.3.

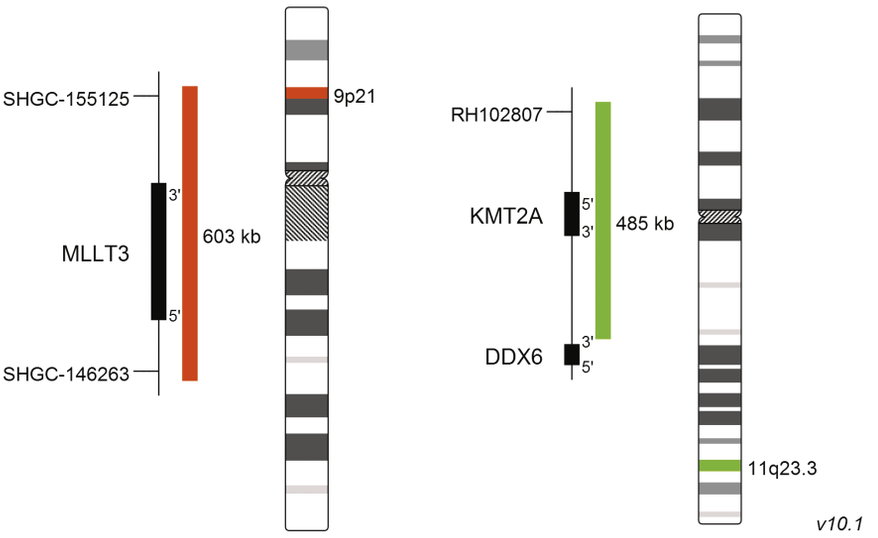
The KMT2A (formerly MLL) gene, located on chromosome 11q23, is rearranged in about 10% of all acute leukemia patients. Most of them suffer from acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML), only a minority shows mixed lineage leukemia which has given the gene its original name ´MLL´. In infants, the incidence of KMT2A rearrangements in leukemia is 70-80%. KMT2A encodes a nuclear protein with methyltransferase activity and is part of multiprotein complexes involved in the regulation of target genes essential during early development and hematopoiesis. Today, more than 80 translocation partners of KMT2A have been identified. Translocations are resulting in in-frame fusions between the KMT2A part N-terminal to the breakpoint cluster region and the respective fusion partners. The most common translocation partners in KMT2A associated leukemia are, in the order of their prevalence, AFF1, MLLT3, MLLT1, MLLT10, ELL and AFDN.

KMT2A is involved in about 3-5% of adult de novo AML cases and the most common aberration in this subgroup is t(9;11)(p22;q23) involving the MLLT3 gene. Pediatric patients carrying this aberration do have a favorable outcome which is comparable to AML patients without KMT2A involvement. FISH is described as a reliable method for the identification of t(9;11).

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O) and two green-orange fusion (2GO) (adjacent green and orange) signals.



Literature

- Cavazzini et al (2006) Haematologica 91:381-385
- Meyer et al (2013) Leukemia 27:2165-2176
- Winters and Bernt (2017) Front Pediatr 5:doi:10.3389/fped.2017.00004

Order No:
D-5052-100-OG

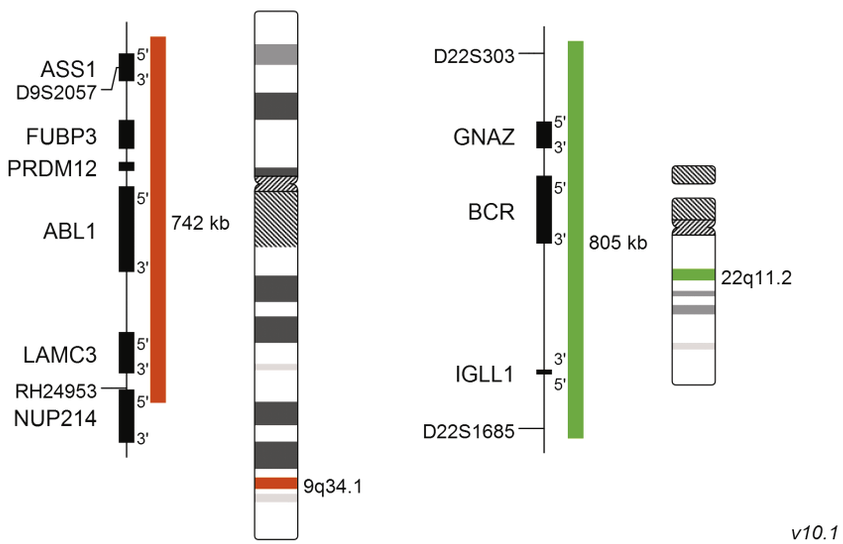
Size: **100 µl**

XCyting Locus-Specific Probes
Translocation/Dual Fusion Probe **XL**

IVD XL BCR/ABL1 plus

XL BCR/ABL1 plus consists of an orange-labeled probe hybridizing to the ABL1 gene region at 9q34.1 and a green-labeled probe hybridizing to the BCR gene region at 22q11.2.

Chronic myelogenous leukemia (CML) is genetically characterized by the presence of the reciprocal translocation t(9;22)(q34;q11), resulting in a BCR/ABL gene fusion on the derivative chromosome 22, called the Philadelphia (Ph) chromosome. The same translocation can also be found in acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) with some variation in the breakpoint region. Glivec® (imatinib mesylate) treatment targeting the BCR/ABL active tyrosine kinase has become a major drug in treating CML, gastrointestinal stromal tumors, and other cancers.



v10.1

Expected Patterns

Normal Cell
Two green (2G) and two orange signals (2O).

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange fusion (2GO) (adjacent green and orange) signals.

Literature

- Dewald et al (1998) Blood 91:3357-3365
- Huntly et al (2003) Blood 102:1160-1168
- Primo et al (2003) Leukemia 17:1124-1129

Order No:
D-5082-100-TC

Size: **100 µl**

XL BCR/ABL1/ASS IVD

XL BCR/ABL1/ASS consists of an aqua-labeled probe hybridizing to the ASS1 gene region at 9q34.1, an orange-labeled probe hybridizing to the ABL1 gene region at 9q34.1 and a green-labeled probe hybridizing to the BCR gene region at 22q11.2.

Chronic myelogenous leukemia (CML) is genetically characterized by the presence of the reciprocal translocation t(9;22)(q34;q11), resulting in a BCR/ABL1 gene fusion on the derivative chromosome 22, called the Philadelphia (Ph) chromosome. The same translocation can also be found in acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) with some variation in the breakpoint region. Glivec® (imatinib mesylate) treatment targeting the BCR/ABL1 active tyrosine kinase has become a major drug in treating CML, gastrointestinal stromal tumors, and other cancers.

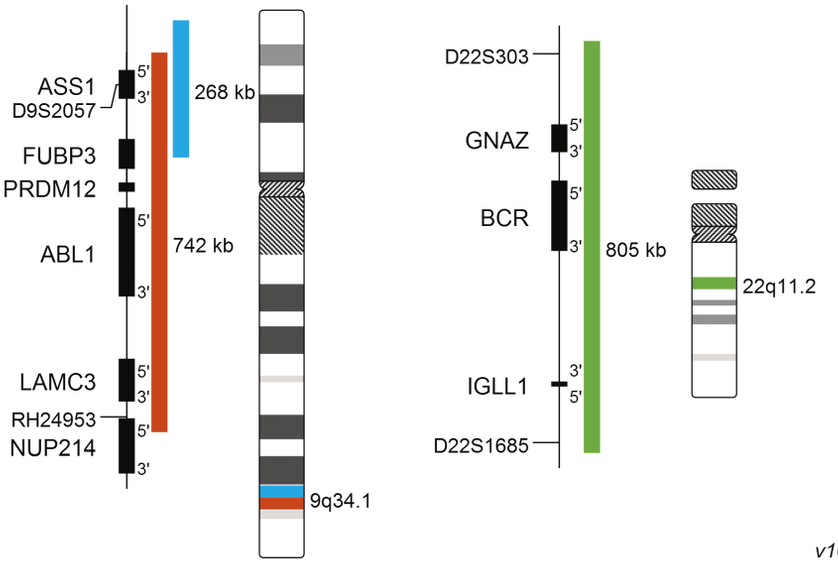
Deletions at the t(9;22) breakpoint regions, found in 5% of CML patients with a Ph translocation, have been associated with resistance to treatment in patients receiving tyrosine kinase inhibitors.

Expected Patterns

Normal Cell
Two blue-orange (2BO) fusion signals and two separate green signals (2G).

Aberrant Cell (typical results)
One blue-orange (1BO), one green (1G), one blue-green-orange (1BGO) and one green-orange (1GO) fusion signal.

Aberrant Cell (typical results)
One blue-orange (1BO), two green (2G), and one green-orange (1GO) fusion signal, indicating a deletion at 9q34 in addition to a t(9;22).



v10.1

Literature

- Dewald et al (1998) Blood 91:3357-3365
- DeMelo et al (2008) Canc Genet Cytogenet 182:111-115
- Luatti et al (2012) Blood 120:761-767

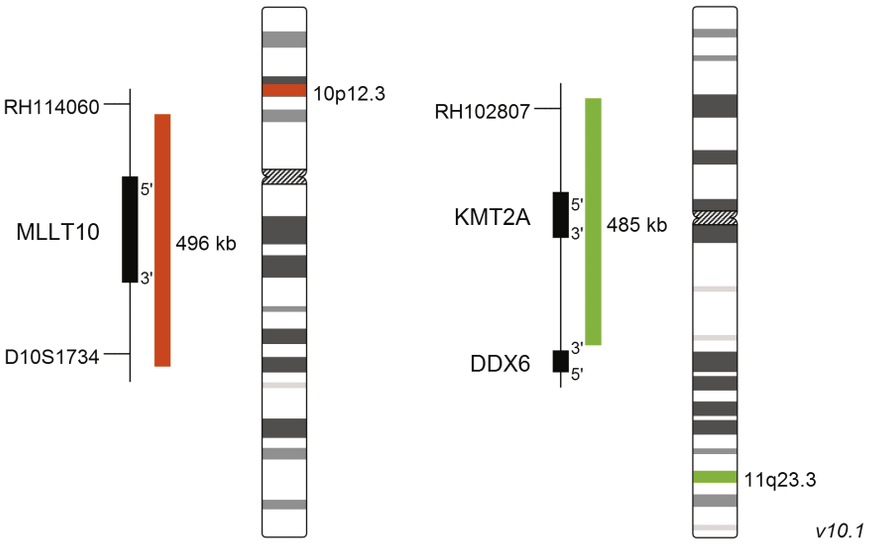
Order No:
D-5134-100-OG

Size: **100 µl**

IVD XL t(10;11) MLLT10/ KMT2A DF

XL t(10;11) MLLT10/KMT2A DF consists of an orange-labeled probe hybridizing to the MLLT10 gene region at 10p12.3 and a green-labeled probe hybridizing to the KMT2A gene region at 11q23.3.

Chromosomal rearrangements of the KMT2A (lysine methyltransferase 2A) gene, formerly MLL (mixed lineage leukemia) gene, are associated with various hematological disorders. Most patients suffer from acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), while only a minority develops mixed lineage leukemia (MLL). Several chromosomal aberrations involving the KMT2A gene have been identified. However, the majority of leukemias result from translocations leading to KMT2A fusions. More than 90 KMT2A translocation partner genes fused to the 5´- KMT2A portion have been identified. The most common translocation partners in KMT2A associated leukemia are AFF1, MLLT3, MLLT1, MLLT10, ELL and AFDN, described here in the order of their frequency. MLLT10 (MLLT10 Histone Lysine Methyltransferase DOT1L Cofactor), previously known as AF10, is one of the most frequent fusion partners of KMT2A across all acute leukemia cases. KMT2A-MLLT10 fusions result from multiple breakpoints in both gene loci. The subsequent chromosomal rearrangements include reciprocal translocations, insertions, inversions, deletions and duplications. MLLT10 is a cofactor of the histone H3K79 methyltransferase DOT1L and mediates the interaction of AFF1, MLLT1 and MLLT3 with DOT1L. The consequence of the presence of KMT2A-AFF1, AFF1-KMT2A, KMT2A-MLLT3, KMT2A-MLLT1, and KMT2A-MLLT10 fusions is an increased and extended H3K79 methylation signature that is a requirement for the maintenance of RNA transcription. DOT1L inhibitors are promising candidates for clinical treatment which are currently being evaluated.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G), one orange (1O), and one green-orange colocalization/fusion signal (1GO).

Aberrant Cell (typical results)
Two green (2G), two orange (2O), and one green-orange colocalization/fusion signal (1GO).

Literature

- De Braekeleer et al (2011) Mol Oncol 5:555-563
- Meyer et al (2013) Leukemia 27:2165- 2176
- Peterson et al (2019) Genes Chromosomes Cancer 58:567-577

Order No:
D-5102-100-OG

Size: **100 µl**

XL ATM/11cen IVD

XL ATM/11cen consists of an orange-labeled probe hybridizing to the ATM gene region at 11q22.3 and a green-labeled probe hybridizing to the centromere of chromosome 11.

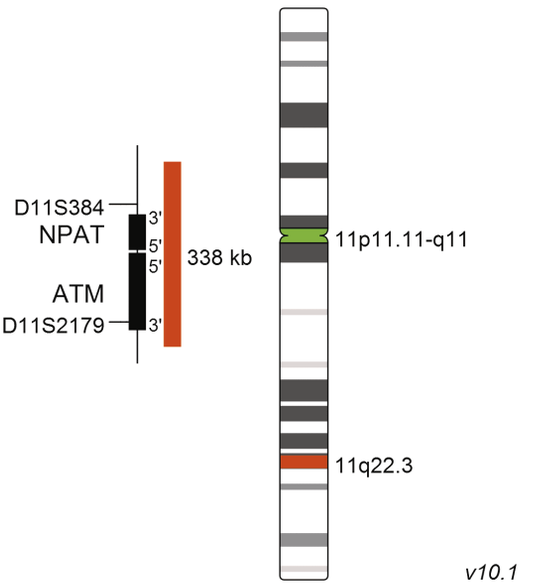
The prognosis and clinical course of chronic lymphocytic leukemia (CLL) are heterogeneous. Conventional banding techniques in CLL are hampered by the low mitotic index of the neoplastic cells. The introduction of interphase cytogenetics using fluorescent *in situ* hybridization (FISH) has greatly increased the sensitivity of cytogenetic analyses. With FISH, abnormalities can be detected in more than 80% of patients by using a 4-probe panel for the detection of trisomy 12q13-15 and deletions 13q14, 17p13, and 11q22-23. An additional 10% of patients can be shown to carry a 6q21 deletion, 14q32 translocation, and partial trisomy 3q or 8q.

Chromosome 11q22.3-23.1 deletions involving the ataxia-telangiectasia mutated (ATM) locus are detected at diagnosis in 15-20% of cases of B-cell CLL and are associated with a more aggressive disease.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal, indicating the deletion of an ATM locus.



Literature

- Doehner et al (1997) Blood 89:2516-2522
- Cuneo et al (2002) Haematologica 87:44-51
- Tsimberidou et al (2009) Cancer 115:373-380

Order No:
D-5071-100-OG

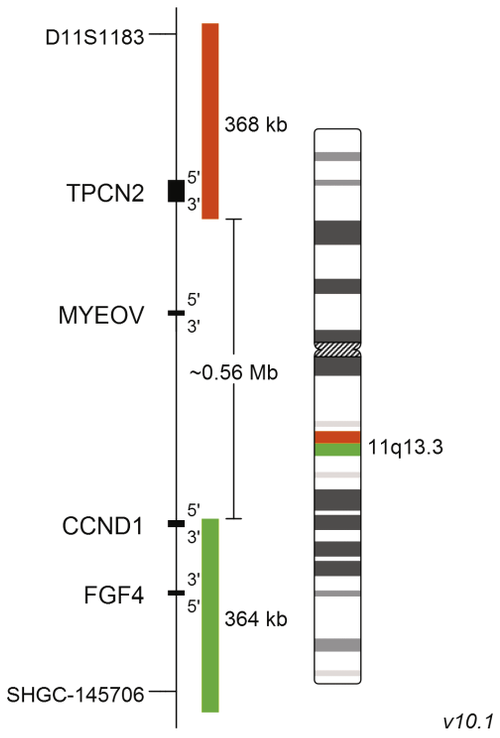
Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe XL

IVD XL CCND1

XL CCND1 consists of an orange-labeled probe hybridizing proximal to the MYEOV gene region at 11q13.3 and a green-labeled probe hybridizing to CCND1 and distal to the CCND1 gene region at 11q13.3.

The t(11;14)(q13;q32) chromosomal translocation is the hallmark of mantle cell lymphoma (MCL) and is found in approximately 30% of multiple myeloma (MM) tumors with a 14q32 translocation. Variant translocations can fuse CCND1 with other genes, such as IGK or IGL.



Expected Patterns

Normal Cell
Two green-orange (2GO) fusion signals representing the two normal CCND1 loci.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and one green-orange (1GO) fusion signal, indicating a chromosome break in the CCND1 locus.

Literature

- Vandraager et al (1997) Blood 89:349-350
- Fonseca et al (2002) Blood 99:3735-3741
- Wlodarska et al (2004) Leukemia 18:1705-1710

Order No:
D-5090-100-OG

Size: **100 µl**

XL KMT2A BA IVD

XL KMT2A BA consists of an orange-labeled probe hybridizing proximal to the KMT2A gene region at 11q23.3 extending into the gene up to intron 24 and a green-labeled probe hybridizing distal to the KMT2A gene region at 11q23.3 extending into the gene up to intron 20 and thus overlapping each other for 3.4kb (GRCh37/hg19).

The KMT2A (fomerly MLL) gene, located on chromosome 11q23, is rearranged in about 10% of all acute leukemia patients. Most of them suffer from acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). Only a minority shows mixed lineage leukemia which has given the gene its original name ´MLL´. In infants, the incidence of KMT2A rearrangements in leukemia is 70-80%. KMT2A encodes a nuclear protein with methyltransferase activity and is part of multiprotein complexes involved in the regulation of target genes essential during early development and hematopoiesis. Today, more than 80 translocation partners of KMT2A have been identified. Translocations are resulting in in-frame fusions between the KMT2A part N-terminal to the break point cluster region and the respective fusion partners. The most common translocation partners in KMT2A associated leukemia are, in the order of their prevalence, AFF1, MLLT3, MLLT1, MLLT10, ELL and AFDN. Fusion genes may also be the result of an insertion of genetic material including portions of KMT2A into other chromosomal locations. Some examples of fusion genes reported as a result of this mechanism are KMT2A-AFF1, KMT2A-MLLT3 and KMT2A-MLLT10.

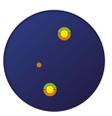
The proven MetaSystems XL MLL plus D-5060-100-OG is designed to detect breaks in the KMT2A gene region. Featuring a new gene covering design, XL KMT2A BA D-5090-100-OG allows the detection of cryptic insertion of portions of KMT2A into other chromosomes as an added benefit, provided that the inserted DNA fragment is in the size range detectable by fluorescence microscopy.

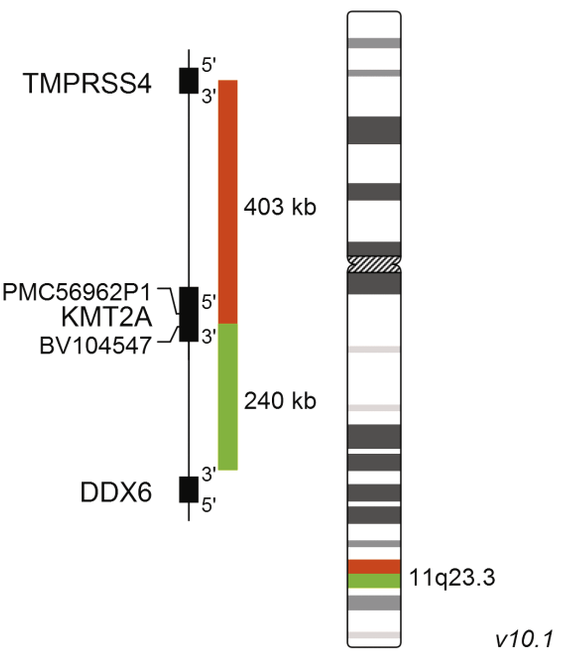
Expected Patterns

Normal Cell
Two green-orange (2GO) colocalization/fusion signals.

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the respective locus. Translocations with breakpoints within the KMT2A breakpoint cluster region result in a small orange split signal remaining with the separated green signal. The residual orange signal is significantly smaller than the separated orange signal and might even be invisible.

Aberrant Cell (typical results)
Two green-orange colocalization/fusion signals (2GO) and one separate usually small orange (1O) signal indicating an insertion of the respective genomic region to an unknown chromosome.





Literature

- Soler et al (2008) Cancer Genet Cytogenet 183:53-59
- Meyer et al (2013) Leukemia 27:2165-2176
- Winters and Bernt (2017) Front Pediatr 5:4.doi:10.3389/fped.2017.00004

Order No:
D-5060-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe XL

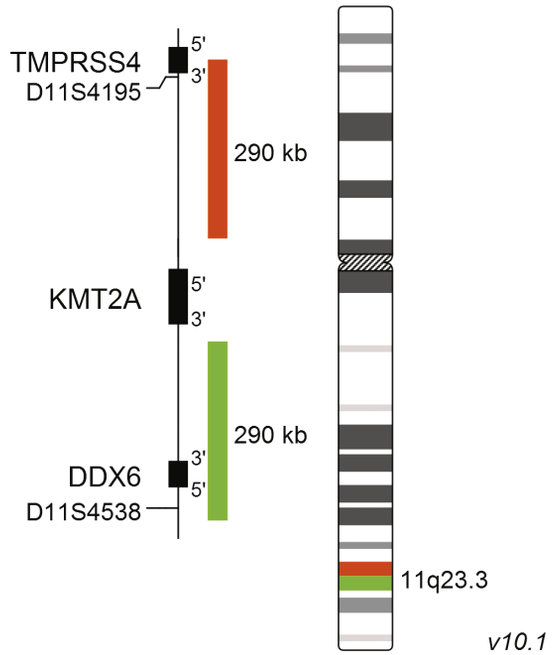
IVD

XL MLL plus

XL MLL plus consists of an orange-labeled probe hybridizing proximal to the KMT2A gene region at 11q23.3 and a green-labeled probe hybridizing distal to the KMT2A gene region at 11q23.3.

A number of recurrent chromosomal abnormalities have been shown to have prognostic significance in acute lymphoblastic leukemia (ALL), especially in B-precursor ALL. Some chromosomal abnormalities, such as high hyperdiploidy and the TEL-AML1 fusion, are associated with more favorable outcomes, while others, including the t(9;22), rearrangements of the KMT2A gene (chromosome 11q23), and intrachromosomal amplification of the AML1 gene (iAMP21), are associated with a poorer prognosis.

Chromosomal rearrangements involving the human KMT2A gene are recurrently associated with the disease phenotype of acute leukemias. The identification of KMT2A gene rearrangements is necessary for rapid clinical decisions resulting in specific therapy regimens. Amplification of KMT2A in myelodysplastic syndrome and acute myeloid leukemia has also been observed, and transcriptional similarities between KMT2A amplified and KMT2A rearranged leukemias were identified.



Expected Patterns

Normal Cell
Two green-orange (2GO) fusion signals representing the two normal KMT2A loci.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and one green-orange (1GO) fusion signal, indicating a chromosome break in the KMT2A locus.

Literature

- Poppe et al (2004) Blood 103:229-235
- Meyer et al (2006) Leukemia 20:777-784
- Cavazzini et al (2006) Haematologica 91:381-385

Order No:
D-5077-100-OG

Size: **100 µl**

XL NUP98 IVD

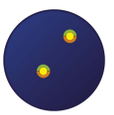
XL NUP98 consists of an orange-labeled probe hybridizing proximal to the NUP98 gene region at 11p15.4 and a green-labeled probe hybridizing distal to the NUP98 gene region at 11p15.4.

Several recurrent balanced translocations and inversions, and their variants, are recognized in the WHO category acute myelogenous leukemia (AML) with recurrent genetic abnormalities. Furthermore, several cytogenetic abnormalities are considered sufficient to establish the WHO diagnosis of AML with myelodysplasia-related features if 20% or more blood or marrow blasts are present.

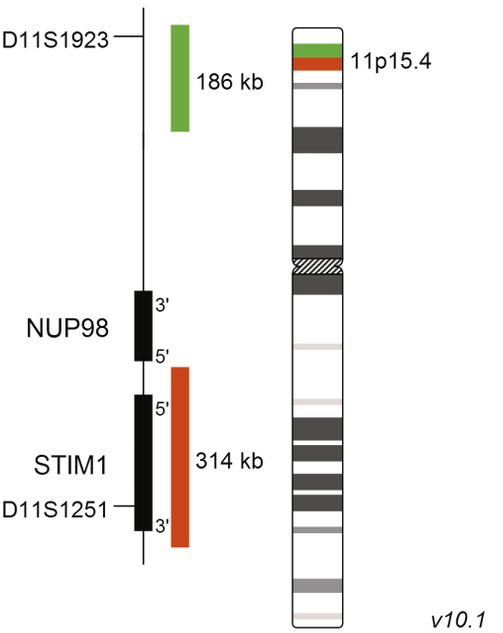
Translocations involving nucleoporin 98kD (NUP98) on chromosome 11p15 occur at relatively low frequency in AML, but can be missed with routine karyotyping. NUP98 is known to be fused to at least 28 different partner genes in patients with hematopoietic malignancies, including acute myeloid leukemia, chronic myeloid leukemia in blast crisis, myelodysplastic syndrome, acute lymphoblastic leukemia, and bilineage/biphenotypic leukemia.

Expected Patterns

Normal Cell
Two green-orange (2GO) fusion signals representing the two normal NUP98 loci.



Aberrant Cell (typical results)
One green (1G), one orange (1O), and one green-orange (1GO) fusion signal, indicating a chromosome break in the NUP98 locus.



Literature

- Nebral et al (2005) Haematologica 90:746-752
- Romana et al (2006) Leukemia 20:696-706
- Gough et al (2011) Blood 118:6247-6257

Order No:
D-5145-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe XL

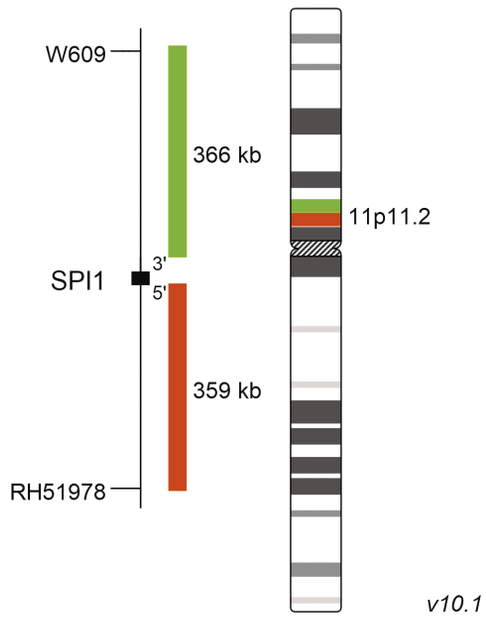
IVD

XL SPI1 BA

XL SPI1 BA is designed as a break apart probe. The orange labeled probe hybridizes proximal to the breakpoint in the SPI1 gene region at 11p11.2, the green labeled probe hybridizes distal to the breakpoint.

The SPI1 (SFFV provirus integration site-1) gene encodes the ETS-family transcription factor PU.1, which mediates gene expression during normal development of hematopoietic stem cells. SPI1 gene fusions were detected in 7 of 181 (3.9%) pediatric T-cell acute lymphoblastic leukemia (T-ALL) cases, analyzed and described by Seki et al. Genetic consequences of chromosomal rearrangements involving SPI1 are gene fusions containing 3' exons of SPI1 and 5' portions of TCF7, STMN1 and BCL11B. The C-terminal DNA binding domain (ETS domain) of the PU.1 protein is present in all known fusions, irrespective of the fusion partner. Fusion-positive samples show strongly increased SPI1 expression levels, as the rearranged portion of SPI1 is placed under the control of heterologous promoters of the above-mentioned genes. As SPI1 is normally expressed as an early phase gene in T-cell development, expression of wildtype SPI1 or SPI1 fusion genes at later stages results in higher cell proliferation and differentiation/ maturation blockade during T-cell development. Fusion-positive cases show significantly shorter overall survival and are incurable when treated with standard chemotherapy.

SPI1 has recently been found to interact with the PML-RARα complex. Additionally, SPI1 itself is transcriptionally regulated by the PML-RARα fusion protein.



Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.

Literature

- Martens and Stunnenberg (2010) FEBS Letters 584:2662-2669
- Seki et al (2017) Nat Genetics 49:1274- 1281
- Takei and Kobayashi (2019) Int J Hematol 109:28–34

Clinical Applications
ALL

Chromosome **11** | Page **69**

Order No:
D-5140-100-OG

Size: **100 µl**

XL t(11;14) CCND1/IGH DF IVD

XL t(11;14) CCND1/IGH DF is designed as a dual fusion probe. The orange labeled probe hybridizes to region 11q13 including CCND1, the green labeled probe flanks the IGH breakpoint region at 14q32.

Mantle cell lymphoma (MCL) is a rare subtype of B-cell non-Hodgkin lymphoma (NHL) with an aggressive clinical course. MCLs represent 6-8% of all NHLs. However, 95% of all MCLs are positive for the translocation t(11;14)(q13;q32). By lower frequency, t(11;14) is also detectable in B-cell prolymphocytic leukemia (B-PLL), mutiple myelomas (MM) and chronic lymphocytic leukemia (CLL). The breakpoints within the IGH locus are different in MM and MCL genomes containing translocation t(11;14). The translocation results in juxtaposition of the immunoglobulin heavy-chain (IgH) locus with the cyclin D1 (CCND1) gene locus, which is not transcribed in normal B-cells. As a result, cis IgH enhancer elements take over the transcriptional control of CCND1 leading to deregulated CCND1 expression (e.g. overexpression in MCL). CCND1 coordinates growth signals with cell cycle progression playing a key role in the regulation of the G1 to S phase transition. Additionally, it was shown that some oncogenic effects of t(11;14)(q13;q32) are not directly attributable to the deregulated CCND1 expression, but rather to epigenetic downstream mechanisms such as CCND1 locus methylation and histone acetylation.

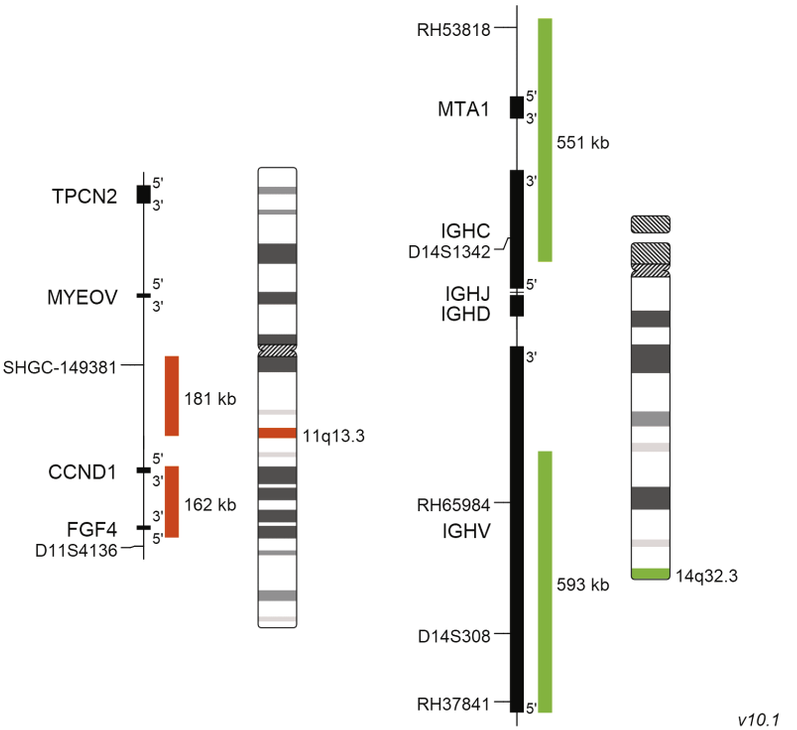
Since MCL is an aggressive B-cell neoplasm with a median survival of 3–5 years and has a poor response to traditional chemotherapeutic approaches, distinction of MCL from other lymphoproliferative disorders by differential diagnosis is of great importance.

In multiple myeloma (MM), t(11;14) is the most common translocation, detectable by FISH in about 15-20% of all MM patients. Conventional cytogenetics has a much lower sensitivity, detecting t(11;14) in about 5% of MM patients.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange fusion (2GO) (adjacent green and orange) signals.



Literature

- Fonesca et al (2002) Blood 99:3735-3741
- Bentz et al (2004) Canc Cytopath 102:124-131
- Hasanali et al (2012) Best Pract Res Clin Haematol 25:143-52

Order No:
D-5111-100-OG

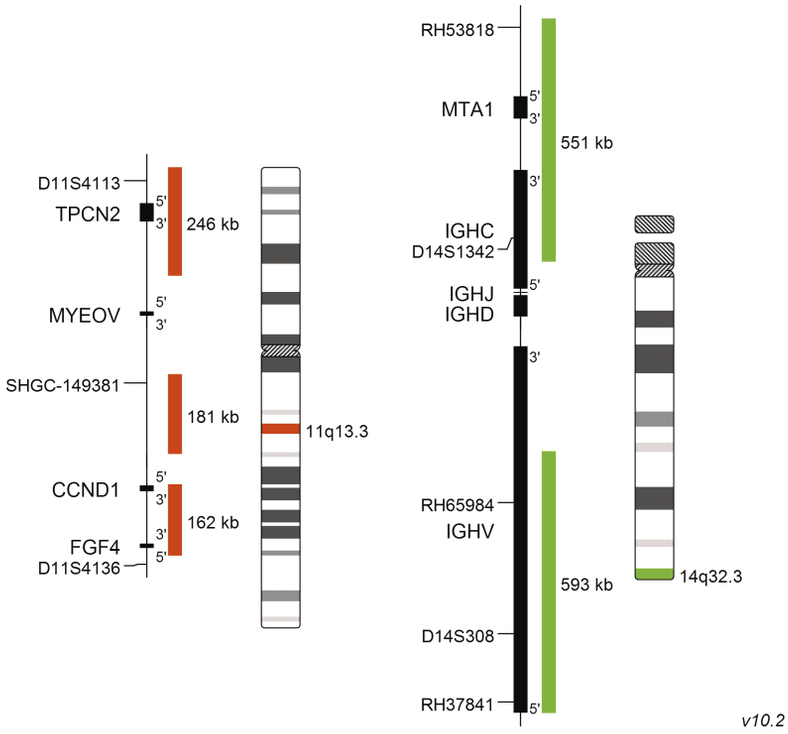
Size: **100 µl**

IVD XL t(11;14) MYEOV/IGH DF

XL t(11;14) MYEOV/IGH DF consists of an orange-labeled probe hybridizing to the MYEOV/CCND1 gene region at 11q13.3 and a green-labeled probe hybridizing to the IGH gene region at 14q32.3.

Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin lymphoma (NHL) with an aggressive clinical course. It is genetically characterized by t(11;14)(q13;q32) which is present in about 95% of MCL patients. By lower frequency, t(11;14) is also detectable in B-cell prolymphocytic leukemia, myelomas and chronic lymphocytic leukemia. The translocation induces overexpression of CCND1 which is normally not detected in B lymphocytes. CCND1 is a major player in cell cycle regulation and involved in the G1/S-phase transition. The oncogenic potential of CCND1 overexpression is related to its role in the cell cycle but also to other, non-cell cycle-related mechanisms such as increased genomic instability and cell survival. t(11;14) is considered as a primary event, often followed by secondary chromosome alterations.

In multiple myeloma (MM), t(11;14) is the most common translocation, detectable by FISH in about 15-20% of all MM patients. Conventional cytogenetics has a much lower sensitivity, detecting t(11;14) in about 5% of MM patients. MM t(11;14) patients do have a relatively favorable outcome compared to other recurrent IGH translocations.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci.

Literature

- Fonesca et al (2002) Blood 99:3735-3741
- Bentz et al (2004) Canc Cytopath 102:124-131
- Jares et al (2012) J Clin Invest 122:3416-3423

Order No:
D-5046-100-OG

Size: **100 µl**

XL ATM/TP53 IVD

XL ATM/TP53 consists of a green-labeled probe hybridizing to the ATM gene region at 11q22.3 and an orange-labeled probe hybridizing to the TP53 gene region at 17p13.

The prognosis and clinical course of chronic lymphocytic leukemia (CLL) are heterogeneous. Conventional banding techniques in CLL are hampered by the low mitotic index of the neoplastic cells. The introduction of interphase cytogenetics using fluorescent *in situ* hybridization (FISH) has greatly increased the sensitivity of cytogenetic analyses. With FISH, abnormalities can be detected in more than 80% of patients by using a 4-probe panel for the detection of trisomy 12q13-15 and deletions 13q14, 17p13, and 11q22-23. An additional 10% of patients can be shown to carry a 6q21 deletion, 14q32 translocation, and partial trisomy 3q or 8q.

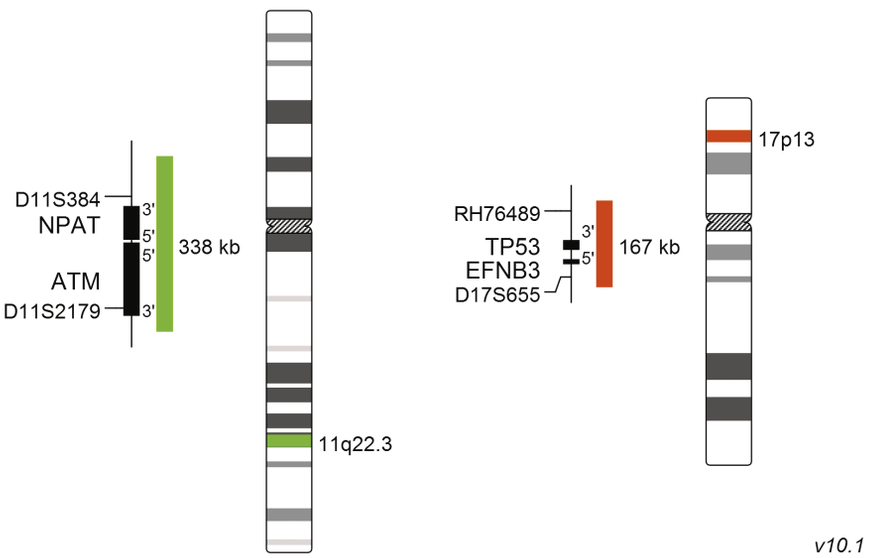
TP53 is a tumor suppressor gene which stops cell division when DNA damage is present. Loss of TP53 at 17p13 is a powerful predictor of resistance to therapy with purine analogues and alkylating agents, and of poor prognosis in CLL. Chromosome 11q22.3-23.1 deletions involving the ataxia telangiectasia mutated (ATM) locus are detected at diagnosis in 15 - 20% of cases of B-cell CLL and are associated with a more aggressive disease.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G) and two orange (2O) signals indicating a deletion of a ATM locus.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal indicating a deletion of a TP53 locus.



v10.1

Literature

- Doehner et al (2000) N Engl J Med 343:1910-1916
- Stilgenbauer et al (2002) Leukemia 16:993-1007
- Gunn at al (2008) J Mol Diagn 10:442-451

Order No:
D-5135-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Translocation/Dual Fusion Probe

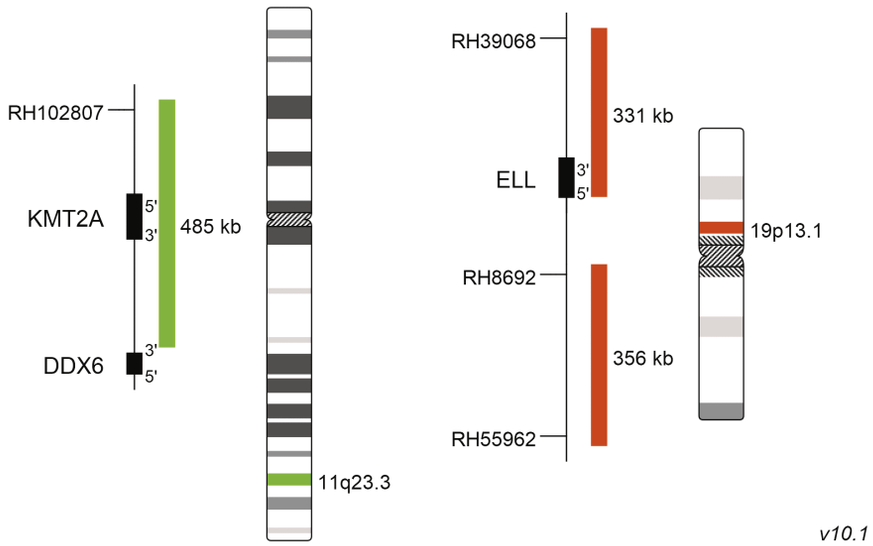
XL

IVD XL t(11;19) KMT2A/ELL DF

XL t(11;19) KMT2A/ELL DF consists of a green-labeled probe hybridizing to the KMT2A gene region at 11q23.3 and an orange-labeled probe hybridizing to the ELL gene region at 19p13.1.

Chromosomal rearrangements of the KMT2A (lysine methyltransferase 2A) gene, formerly MLL (mixed lineage leukemia) gene, are associated with various hematological disorders. Most patients suffer from acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), while only a minority develops mixed lineage leukemia (MLL). Several chromosomal aberrations involving the KMT2A gene have been identified. However, the majority of leukemias result from translocations leading to KMT2A fusions. More than 90 KMT2A translocation partner genes fused to the 5´- KMT2A portion have been identified. The most common translocation partners in KMT2A associated leukemia are AFF1, MLLT3, MLLT1, MLLT10, ELL and AFDN, described here in the order of their frequency.

Fusions between KMT2A and ELL (elongation factor for RNA polymerase II), caused by translocations of the type t(11;19)(q23;p13.1), belong to the most common KMT2A fusion genes in AML. Approximately 11% of AML patients carrying KMT2A rearrangements are characterized by the KMT2A-ELL fusion gene. The breakpoints within the KMT2A gene resulting in KMT2A-ELL fusions are found in intron 9 in the case of patients younger than one year and in intron 11 in the case of patients older than one year. This breakpoint distribution is unique among all KMT2A fusions. The outcome of patients with breakpoints in KMT2A intron 11 is worse compared to patients with upstream breakpoints. ELL is a component of the super elongation complex (SEC). Chimeric KMT2A-ELL fusion proteins have the ability to recruit SEC resulting in aberrant gene expression.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical result)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the respective loci.

Literature

- De Braekeleer et al (2011) Mol Oncol 5:555-563
- Meyer et al (2017) Leukemia 32:273–284
- Chan and Chen (2019) Front Cell Dev:doi:10.3389/fcell.2019.00081

Order No:
D-5136-100-OG

Size: **100 µl**

XL t(11;19) KMT2A/MLLT1 DF IVD

XL t(11;19) KMT2A/MLLT1 DF consists of a green-labeled probe hybridizing to the KMT2A gene region at 11q23.3 and an orange-labeled probe hybridizing to the MLLT1 gene region at 19p13.3.

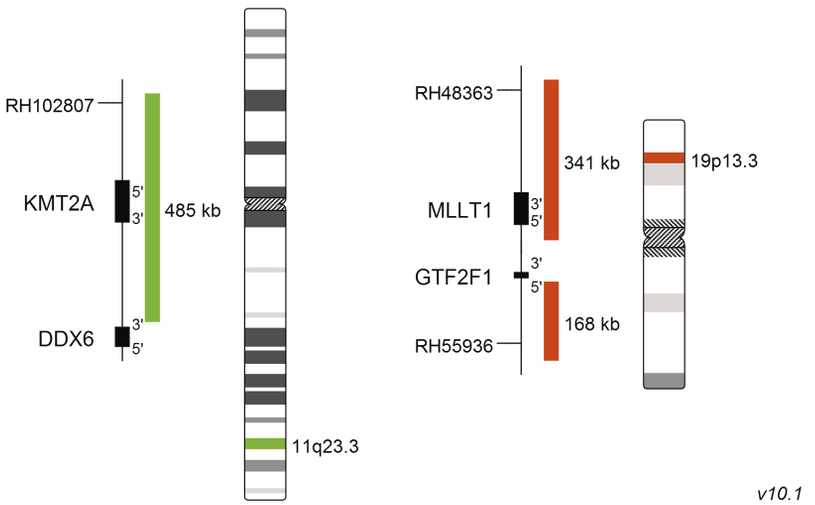
Chromosomal rearrangements of the KMT2A (lysine methyltransferase 2A) gene, formerly MLL (mixed lineage leukemia) gene, are associated with various hematological disorders. Most patients suffer from acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), while only a minority develops mixed lineage leukemia (MLL). Several chromosomal aberrations involving the KMT2A gene have been identified. However, the majority of leukemias result from translocations leading to KMT2A fusions. More than 90 KMT2A translocation partner genes fused to the 5´- KMT2A portion have been identified. The most common translocation partners in KMT2A associated leukemia are AFF1, MLLT3, MLLT1, MLLT10, ELL and AFDN, described here in the order of their frequency.

MLLT1 (MLLT1 super elongation complex subunit), originally designated as ENL, is one of the most common KMT2A fusion partners. KMT2A-MLLT1 fusions result from translocations of the type t(11;19)(q23;p13.3). Most patients carrying a KMT2A-MLLT1 fusion have breakpoints in intron 11 of the KMT2A gene. KMT2A-MLLT1 fusions are prevalent in both AML and ALL. Multiple KMT2A translocation partner genes, including MLLT1, are organized within the DOT1L transcriptional complex. AFF1 serves as DOT1L complex docking platform for MLLT1 and MLLT3, while MLLT10 directly mediates this interaction. More precisely, the MLLT1 protein has been shown to interact with AFF1 via its C-terminus. Due to the close interaction of these KMT2A fusion partners with DOT1L, DOT1L inhibitors are considered as promising candidates for treatment of such leukemia cases.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical result)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the respective loci.



v10.1

Literature

- Meyer et al (2005) Proc Natl Acad Sci USA 102:449-454
- De Braekeleer et al (2011) Mol Oncol 5:555-563
- Winters and Bernt (2017) Front Pediatr 5 (4):doi:10.3389/fped.2017.00004

Order No:
D-5044-100-TC

Size: **2x 100 µl**

IVD XL CLL Probe Kit (XL DLEU/ LAMP/12cen + XL ATM/TP53)

XL CLL contains different probe mixes provided in separate test vials.

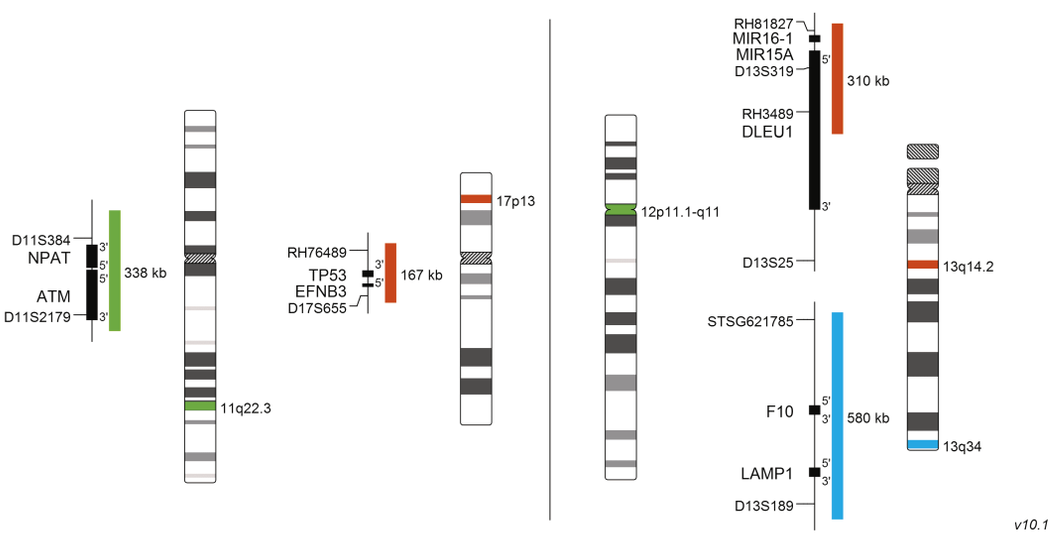
XL DLEU/LAMP/12cen consists of a green-labeled probe hybridizing to the centromere of chromosome 12, an orange-labeled probe hybridizing to the DLEU1/MIR15A/MIR16-1 gene region at 13q14.2 including D13S319 and an aqua-labeled probe hybridizing to the LAMP1 gene region at 13q34.

XL ATM/TP53 consists of a green-labeled probe hybridizing to the ATM gene region at 11q22.3 and an orange-labeled probe hybridizing to the TP53 gene region at 17p13.

The XL CLL Probe Kit is a combination of probes covering the most frequent chromosomal aberrations in chronic lymphocytic leukemia (CLL). For a more detailed description, please refer to product XL DLEU/LAMP/12cen (D-5055-100-TC) and XL ATM/TP53 (D-5046-100-OG).

Expected Patterns

Please refer to XL DLEU/ LAMP/12cen (D-5055-100-TC) and XL ATM/TP53 (D-5046-100-OG) for signal patterns.



Literature

- Doehner et al (2000) N Engl J Med 343:1910-1916
- DeWald et al (2003) Brit J Haem 121:287-295
- Nelson et al (2007) Am J Clin Pathol 128:323-332

Order No:
D-6032-100-OG

Size: **100 µl**

XL DDIT3 BA IVD

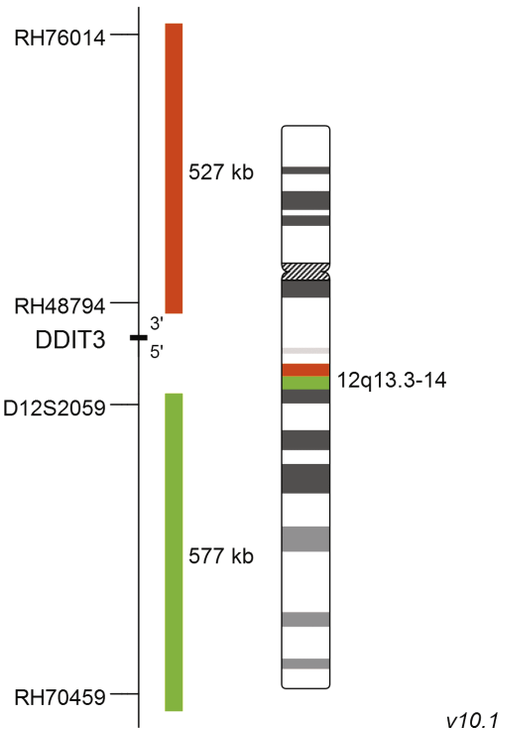
XL DDIT3 BA consists of an orange-labeled probe hybridizing proximal to the DDIT3 gene region at 12q13.3 and a green-labeled probe hybridizing distal to the DDIT3 gene region at 12q13.3-14.

Histological similarities and a subset of common immunohistochemical features make the diagnosis of soft tissue neoplasms challenging. Several entities characterizing reciprocal translocations have been identified and FISH based assays specific for the detection of these aberrations have become a valuable tool in diagnostics today. Myxoid/round cell liposarcoma (MRCLS) is the most common liposarcoma with an increased incidence in the extremities. Compared to other liposarcomas, MRCLS has a greater tendency for metastasis. It is characterized by the reciprocal translocation t(12;16)(q13;p11) which is present in up to 95% of cases. The resulting FUS-DDIT3 fusion protein has oncogenic potential and interferes with adipogenic differentiation. A paralog of FUS with high sequence homology is the EWS RNA Binding Protein 1 (EWSR1). EWSR1 is an alternative translocation partner of DDIT3 and the resulting fusion protein EWSR1-DDIT3, originating from t(12;22)(q13;q12), accounts for <5% of MRCLS cases. DDIT3 rearrangements are highly specific for MRCLS due to the presence of FUS-DDIT3 or EWSR1-DDIT3 fusion genes.

Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.



Literature

- Cristina et al (2000) JMD 2:132-138
- Downs-Kelly et al (2008) Am J Surg Pathol 32:8-13
- Tanas et al (2009) Adv Anat Pathol 16:383-391

Order No:
D-5073-100-OG

Size: **100 µl**

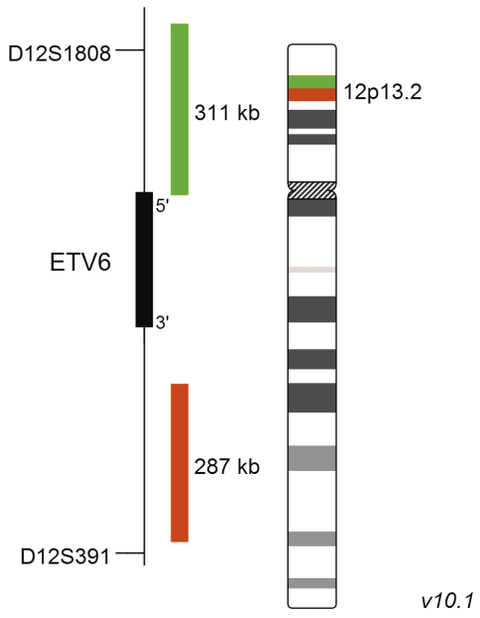
XCyting Locus-Specific Probes
Break Apart Probe XL

IVD **XL ETV6**

XL ETV6 consists of an orange-labeled probe hybridizing proximal to the ETV6 gene region at 12p13.2 and a green-labeled probe hybridizing distal to the ETV6 gene region at 12p13.2.

The ETV6 gene, located on 12p13.2, is involved in numerous translocations found in myeloid and lymphoid malignancies. Two mechanisms are common: fusion to a tyrosine kinase resulting in a constitutively active tyrosine kinase and fusions to transcription factors driving aberrant expression of target genes. The frequent translocation t(12;21)(p13;q22) results in the formation of the chimeric transcription factor ETV6-RUNX1 which can be identified in about 25% of childhood B-cell acute lymphoblastic leukemia (B-ALL) cases. ETV6-RUNX1 causes expansion of B-cell precursors with impaired ability of differentiation to mature B-cells. Another important aberration is t(5;12)(q33;p13), found in chronic myelomonocytic leukemia (CML) and myeloproliferative diseases, resulting in the fusion of ETV6 with the receptor tyrosine kinase PDGFRB. The resulting oncogene is sensitive to the kinase inhibitor imatinib. t(7;12)(q36;p13) can be identified in pediatric acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) and is resulting in the fusion gene MNX1-ETV6.

Besides hematological malignancies, ETV6 is also involved in the development of the pediatric congenital mesoblastic nephroma and fibrosarcoma. t(12;15)(p13;q25) fuses ETV6 to the tyrosin receptor kinase NTRK3 resulting in the ETV6-NTRK3 fusion gene, a constitutively active tyrosine kinase.



Expected Patterns

Normal Cell
Two green-orange (2GO) fusion signals representing the two normal ETV6 loci.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and one green-orange (1GO) fusion signal, indicating a chromosome break in the ETV6 locus.

Literature

- Lierman and Cools (2007) Haematologica 92:145-147
- Adem et al (2001) Mod Pathol 14:1246-1251
- Naiel et al (2013) Cancers 5:281-295

Clinical Applications
ALL | AML | CML/MPN

Chromosome **12** | Page **77**

Order No:
D-5139-100-OG

Size: **100 µl**

XL ETV6 BA IVD

XL ETV6 BA consists of an orange-labeled probe hybridizing proximal to the ETV6 gene region at 12p13.2 and a green-labeled probe hybridizing distal to the ETV6 gene region at 12p13.2 extending into the 5´gene region.

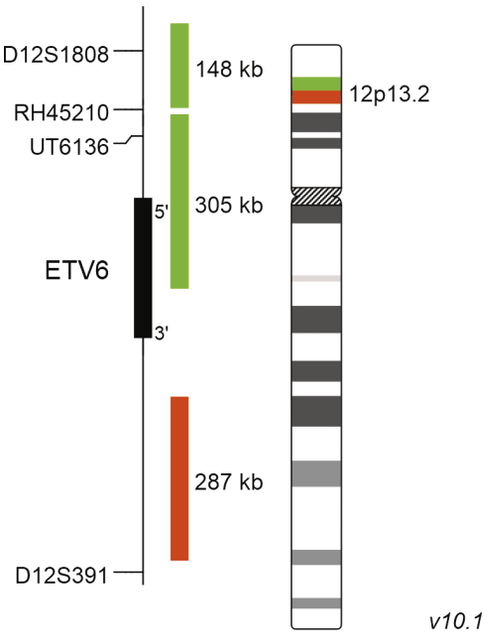
The ETV6 gene (ETS variant gene 6) located on 12p13.2 codes for a transcription factor which is involved in a variety of rearrangements. Several potential mechanisms of ETV6-mediated leukemogenesis are discussed including deletions and translocations. Numerous translocations and partner genes have been identified so far. The mechanisms well described are fusion to a tyrosine kinase resulting in a constitutively active tyrosine kinase and fusions to transcription factors driving aberrant expression of target genes. The frequent translocation t(12;21)(p13;q22) results in the formation of the chimeric transcription factor ETV6::RUNX1 which can be identified in about 25% of childhood B-cell acute lymphoblastic leukemia (B-ALL) cases. The t(5;12)(q33;p13) translocation fuses ETV6 to the receptor tyrosine kinase PDGFRB (ETV6::PDGFRB). The t(9;12)(q34;p13) ETV6::ABL1 has been included in the 5th edition of the WHO Classification of Haematolymphoid Tumours in the disease type myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK). The study by Haferlach et al confirms the variety of ETV6 rearrangements in acute myeloid leukemia (AML), myelodysplastic neoplasms (MDS), and MPNs, which have been shown to be associated with other genetic events. The recurrent translocation t(7;12)(q36;p13) can be identified in pediatric acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) and is resulting in the fusion gene MNX1::ETV6.

XL ETV6 BA is a further developed version of XL ETV6 (D-5073-100-OG), featuring a new, partially ETV6 gene covering design, extending into the 5´-region of the ETV6 gene.

Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.



Literature

- Haferlach et al (2012) Genes Chromosomes Cancer 51(4):328-337
- De Braekeleer et al (2012) Leukemia Research 36:945-961
- Naiel et al (2013) Cancers 5:281-295
- Khoury et al (2022) Leukemia 36:1703–1719

Order No:
D-5047-100-OG

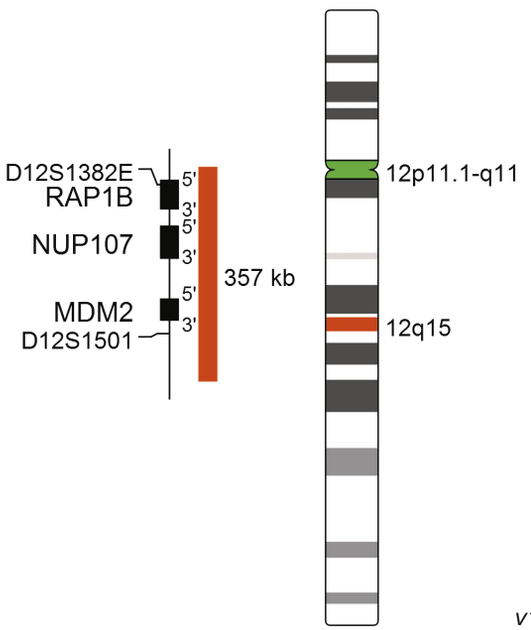
Size: **100 µl**

XCyting Locus-Specific Probes
Amplification Probe
XL

IVD **XL MDM2**

XL MDM2 consists of an orange-labeled probe hybridizing to the MDM2 gene region at 12q15 and a green-labeled probe hybridizing to the centromere of chromosome 12.

The tumor suppressor gene TP53 is a key regulator in the cell cycle and is involved in apoptosis, genomic stability and angiogenesis. Inactivation of TP53 function prevents the antiproliferative effect and contributes to the development of many types of cancer. Several mechanisms of TP53 loss of function are known such as gene mutations, interaction of p53 with viral proteins and association of p53 with the MDM2 oncoprotein. MDM2 is an ubiquitin ligase negatively regulating p53. MDM2 is amplified in about 7% of all human cancers with the highest frequency of about 20% in soft tissue tumors. MDM2 might also have p53-independent transforming capabilities. Well-differentiated liposarcomas/atypical lipomatous tumors (WDL-ALT) and dedifferentiated liposarcomas are among the most common soft tissue tumors in adults. Both entities share the same genetic aberration, an amplification of the chromosomal region including MDM2. WDL-ALT and benign lipomatous tumors can be morphologically similar and a clear assignment based on histological features might be difficult. The analysis of the MDM2 amplification status by FISH is considered as a useful technique for the differential diagnosis of WDL-ALT and benign lipomatous tumors since benign lesions do not harbor MDM2 amplifications. Furthermore, MDM2 overexpression has been reported to be a potential cause of p53 dysfunction in chronic lymphoblastic leukemia.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and three orange (3O) signals, indicating a duplication of the MDM2 locus.

Literature

- Haidar et al (1997) Am J Hematol 54:189-195
- Momand et al (1998) Nucleic Acids Res 26:3453-3459
- Weaver et al (2008) Mod Pathol 21:943-949

Order No:
D-5115-100-OG

Size: **100 µl**

XL t(12;21) ETV6/RUNX1 DF IVD

XL t(12;21) ETV6/RUNX1 DF consists of a green-labeled probe hybridizing to the ETV6 gene region at 12p13.2 and an orange-labeled probe hybridizing to the RUNX1 gene region at 21q22.1.

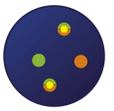
Acute lymphoblastic leukemia (ALL) is a rapidly progressing cancer type characterized by the malignant transformation of lymphoid progenitor cells. It is the most common childhood cancer type and the second most common leukemia in adults. Treatment of children usually results in good prognosis whereas the outcome for adults is less optimistic. Most patients show a transformation of precursors of the B-cell type, but also the T-cell phenotype is frequently observed. The most common aberration in pediatric B-cell ALL is t(12;21)(p13;q22) with an incidence of about 25%, compared to <5% in adults. The result of this reciprocal translocation is an ETV6/RUNX1 fusion gene. Scientific data suggest that ETV6/RUNX1 is already established prenatally, but additional chromosomal aberrations are necessary for the development of ALL postnatally. The ETV6/RUNX1 fusion gene is transcriptionally active and is dysregulating a cascade of downstream genes. One study has shown, that all positive t(12;21) cases harbored the ETV6/RUNX1 fusion gene but not the reciprocal gene. This suggests, that ETV6/RUNX1 is involved in the manifestation of ALL, but not RUNX1/ETV6.

Since t(12;21) is not detectable by conventional cytogenetic methods, FISH is one of the methods of choice.

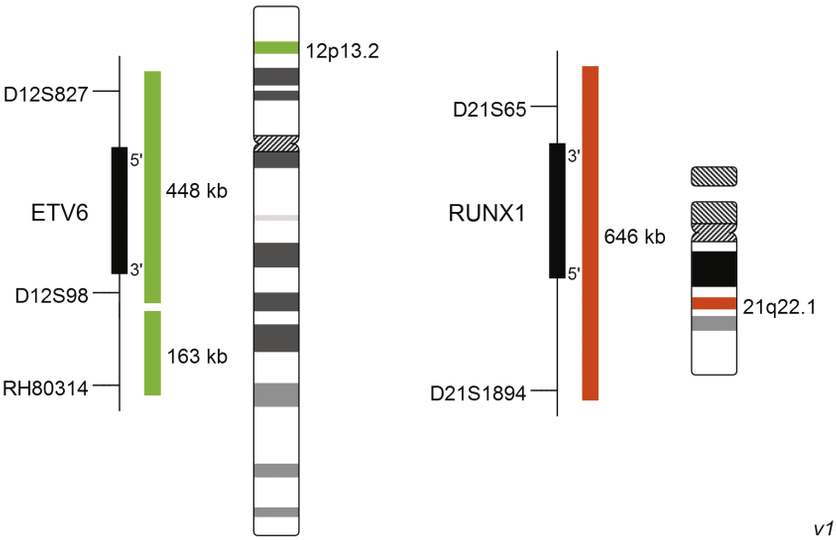
Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci.



Aberrant Cell (typical results)
No green (no G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci and a deletion of the locus covered by the green probe.



v10.1

Literature

- Romana et al (1995) Blood 85:3662-3670
- Al-Obaidi et al (2002) Leukemia 16:669-674
- Sun et al (2017) Oncotarget 8:35445-35459

Order No:
D-6034-100-OG

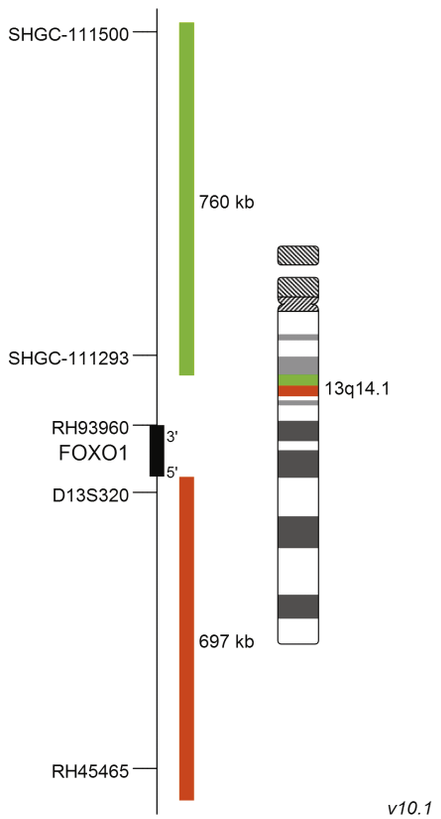
Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe XL

IVD XL FOXO1 BA

XL FOXO1 BA consists of a green-labeled probe hybridizing proximal to the FOXO1 gene region at 13q14.1 and an orange-labeled probe hybridizing distal to the FOXO1 gene region at 13q14.1.

Rhabdomyosarcoma (RMS) is a relatively rare cancer type but it is the most common soft tissue sarcoma in children and adolescents. The histopathological classification includes several subtypes: embryonal rhabdomyosarcoma (ERMS) and alveolar rhabdomyosarcoma (ARMS) are the most common variants, in the order of their occurrence. ARMS is associated with a worse outcome and is characterized by the two reciprocal translocations t(2;13)(q35;q14) and t(1;13) (p36;q14), affecting the FOXO1 gene region and PAX3 or PAX7 respectively, in about 80% of cases. The result is an in-frame fusion of the PAX DNA binding domain with the transcriptional active domain of FOXO1 generating a highly potent chimeric activator for PAX target genes. Patients harboring FOXO1-PAX3/7 fusions have an inferior event-free survival compared to patients without translocation, suggesting that the molecular status in RMS provides valuable prognostic information.



Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.

Literature

- McManus et al (1996) J Pathol 178:410–414
- Barr (2001) Oncogene 20:5736-5746
- Skapek et al (2013) Pediatr Blood Cancer 60:1411-1417

Order No:
D-5054-100-OG

Size: **100 µl**

XL DLEU/LAMP IVD

XL DLEU/LAMP consists of an orange-labeled probe hybridizing to the DLEU1/MIR15A/MIR16-1 gene region at 13q14.2 including D13S319 and a green-labeled probe hybridizing to the LAMP1 gene region at 13q34.

The prognosis and clinical course of chronic lymphocytic leukemia (CLL) are heterogeneous. Conventional banding techniques in CLL are hampered by the low mitotic index of the neoplastic cells. The introduction of interphase cytogenetics using fluorescent *in situ* hybridization (FISH) has greatly increased the sensitivity of cytogenetic analyses. With FISH, abnormalities can be detected in more than 80% of patients by using a 4-probe panel for the detection of trisomy 12q13-15 and deletions 13q14, 17p13 and 11q22-23. An additional 10% of patients can be shown to carry a 6q21 deletion, 14q32 translocation, and partial trisomy 3q or 8q.

The most frequently deleted region in B-CLL is located in 13q14.3 distal to RB1. The minimal deleted region (MDR) is 350kb in size and includes the gene loci for the mi-RNAs 15 and 16. CLL with 13q deletion as the sole cytogenetic abnormality usually have a good prognosis.

Deletions of chromosomal region 13q14 have also been reported in a variety of human tumors, including other types of lymphoid tumors and myeloid leukemias, as well as prostate, head and neck, and non-small-cell lung cancers.

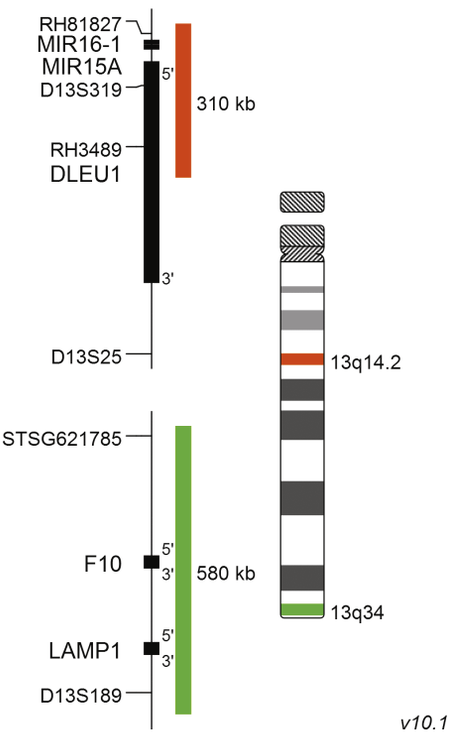
Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal, indicating the deletion of a 13q14.3 locus.

Aberrant Cell (typical results)
One green (1G) and two orange (2O) signals, indicating a deletion of the terminal region of the long arm of chromosome 13.

Aberrant Cell (typical results)
One green (1G) and one orange (1O) signal, indicating deletions of both loci in 13q14 and 13qter.



Literature

- Doehner et al (2000) N Engl J Med 343:1910-1916
- Calin et al (2002) Proc Natl Acad Sci USA 99:15524-15529
- Gunn at al (2008) J Mol Diagn 10:442-451

Order No:
D-5070-100-TC

Size: **100 µl**

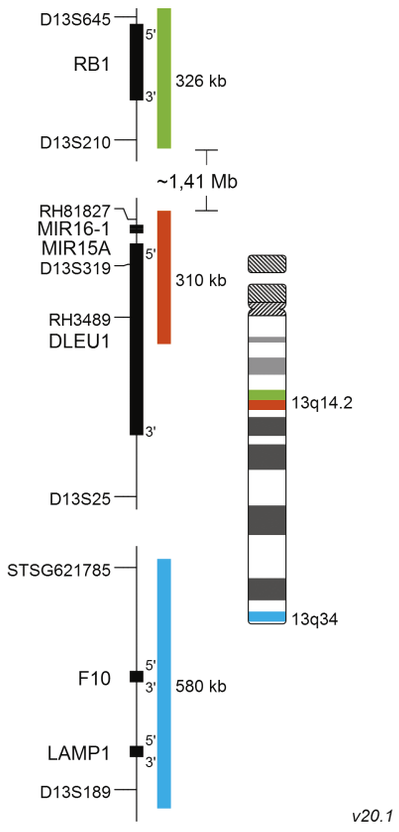
XCyting Locus-Specific Probes
Deletion Probe **XL**

IVD XL RB1/DLEU/LAMP

XL RB1/DLEU/LAMP consists of a green-labeled probe hybridizing to the RB1 gene region at 13q14.2, an orange-labeled probe hybridizing to the DLEU1/MIR15A/MIR16-1 gene region at 13q14.2 including D13S319 and an aqua-labeled probe hybridizing to the LAMP1 gene region at 13q34.

In chronic lymphocytic leukemia (CLL), deletion at 13q14 with at least one allele occurs in more than 50% of cases. A minimal deleted region (MDR) of 350kb in size has been identified and is usually seen as an indicator for good prognosis. However, recent studies using high resolution arrays have shown, that the 13q14 deletion can vary in size and, if it is including the RB1 gene, may lead to a change in the prognosis of CLL patients. RB1 is a critical regulator of cell cycle progression and genomic stability and its loss could explain this change of interpretation in CLL.

Deletions of chromosomal region 13q14 have been reported in a variety of human tumors, including other types of lymphoid tumors and myeloid leukemias, as well as prostate, head and neck, and non-small-cell lung cancers.



Expected Patterns

Normal Cell
Two green (2G), two orange (2O), and two blue (2B) signals.

Aberrant Cell
Two green (2G), one orange (1O), and two blue (2B) signals.

Aberrant Cell
One green (1G), one orange (1O), and two blue (2B) signals.

Aberrant Cell
One green (1G), one orange (1O), and one blue (1B) signal.

Literature

- Doehner et al (2000) N Engl J Med 34:1910-1916
- Ouillette et al (2008) Cancer Res 68:1012-1021
- Dal Bo et al (2011) Genes Chromosomes Cancer 50:633-643

Order No:
D-5055-100-TC

Size: **100 µl**

XL DLEU/LAMP/12cen IVD

XL DLEU/LAMP/12cen consists of a green-labeled probe hybridizing to the centromere of chromosome 12, an orange-labeled probe hybridizing to the DLEU1/MIR15A/MIR16-1 gene region at 13q14.2 including D13S319 and an aqua-labeled probe hybridizing to the LAMP1 gene region at 13q34.

The prognosis and clinical course of chronic lymphocytic leukemia (CLL) are heterogeneous. Conventional banding techniques in CLL are hampered by the low mitotic index of the neoplastic cells. The introduction of interphase cytogenetics using fluorescent *in situ* hybridization (FISH) has greatly increased the sensitivity of cytogenetic analyses. With FISH, abnormalities can be detected in more than 80% of patients by using a 4-probe panel for the detection of trisomy 12q13-15, and deletions 13q14, 17p13, and 11q22-23. An additional 10% of patients can be shown to carry a 6q21 deletion, 14q32 translocation, and partial trisomy 3q or 8q.

The most frequently deleted region in B-CLL is located in 13q14.3 distal to RB1. The minimal deleted region (MDR) is 350 kb in size and includes the gene loci for the mi-RNAs 15 and 16. CLL with 13q deletion as the sole cytogenetic abnormality usually have a good prognosis.

Deletions of chromosomal region 13q14 have also been reported in a variety of human tumors, including other types of lymphoid tumors and myeloid leukemias, as well as prostate, head and neck, and non-small-cell lung cancers.

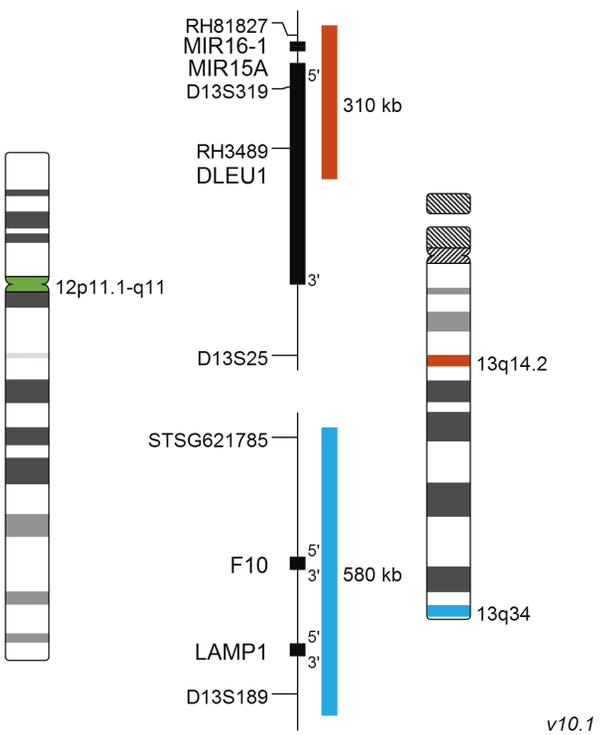
Expected Patterns

Normal Cell
Two green (2G), two orange (2O), and two blue (2B) signals.

Aberrant Cell
Three green (3G), two orange (2O), and two blue (2B) signals.

Aberrant Cell
Two green (2G), one orange (1O), and two blue (2B) signals.

Aberrant Cell
Two green (2G), one orange (1O), and one blue (1B) signal.



Literature

- Doehner et al (2000) N Engl J Med 34:1910-1916
- DeWald et al (2003) Brit J Haem 121:287-295
- Nelson at al (2007) Am J Clin Pathol 128:323-332

Order No:
D-5067-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Deletion Probe XL

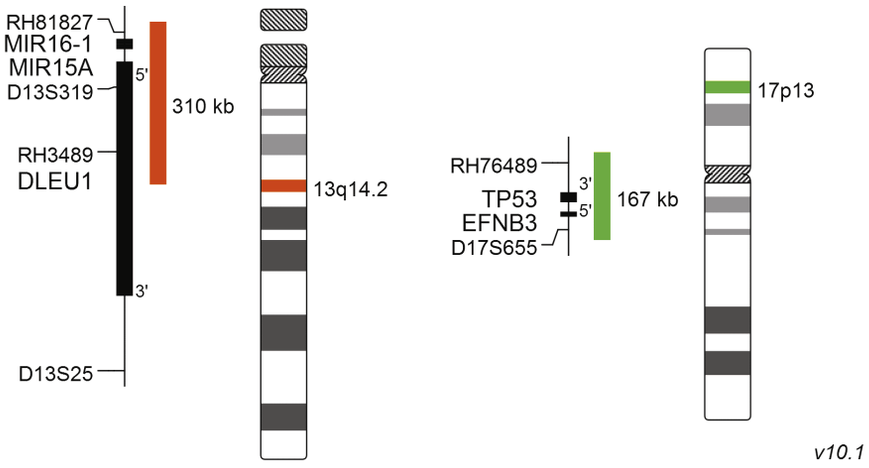
IVD

XL DLEU/TP53

XL DLEU/TP53 consists of an orange-labeled probe hybridizing to the DLEU1/MIR15A/MIR16-1 gene region at 13q14.2 including D13S319 and a green-labeled probe hybridizing to the TP53 gene region at 17p13.

The prognosis and clinical course of chronic lymphocytic leukemia (CLL) are heterogeneous. Conventional banding techniques in CLL are hampered by the low mitotic index of the neoplastic cells. The introduction of interphase cytogenetics using fluorescent *in situ* hybridization (FISH) has greatly increased the sensitivity of cytogenetic analyses. With FISH, abnormalities can be detected in more than 80% of patients by using a 4-probe panel for the detection of trisomy 12q13-15 and deletions 13q14, 17p13, and 11q22-23. An additional 10% of patients can be shown to carry a 6q21 deletion, 14q32 translocation, and partial trisomy 3q or 8q.

TP53 is a tumor suppressor gene which stops cell division when DNA damage is present. Loss of TP53 at 17p13 is a powerful predictor of resistance to therapy with purine analogues and alkylating agents and poor prognosis in CLL. The most frequently deleted region in B-CLL is located in 13q14.3 distal to RB1. The minimal deleted region (MDR) is 350kb in size and includes the gene loci for the mi-RNAs 15 and 16. CLL with 13q deletion as the sole cytogenetic abnormality (del13q-only) usually have a good prognosis.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal, indicating a deletion in 13q14.

Aberrant Cell (typical results)
One green (1G) and two orange (2O) signals, indicating a deletion in 17p13.

Literature

- Doehner et al (2000) N Engl J Med 343:1910-1916
- Stilgenbauer et al (2002) Leukemia 16:993-1007
- Gunn et al (2008) J Mol Diagn 10:442-451

Order No:
D-5142-100-OG

Size: **100 µl**

XL TCL1 BA IVD

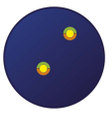
XL TCL1 BA is designed as a break apart probe. The orange labeled probe hybridizes proximal to the TCL1A/TCL1B gene region at 14q32.1, the green labeled probe hybridizes distal to TCL1A/TCL1B.

The gene TCL1A (TCL1 family AKT coactivator A, previously known as T-cell leukaemia/lymphoma 1A), has been described first in the early 1990s. It belongs to the TCL1 gene family including TCL1A (14q32.13), TCL1B (14q32.13) and MTCP1 (Xq28). Physiologically, the TCL1-encoded protein is expressed in fetal tissues and during early developmental stages of lymphocytes. It regulates many proteins responsible for cellular proliferation, survival and epigenetic modifications through multiple signalling pathways.

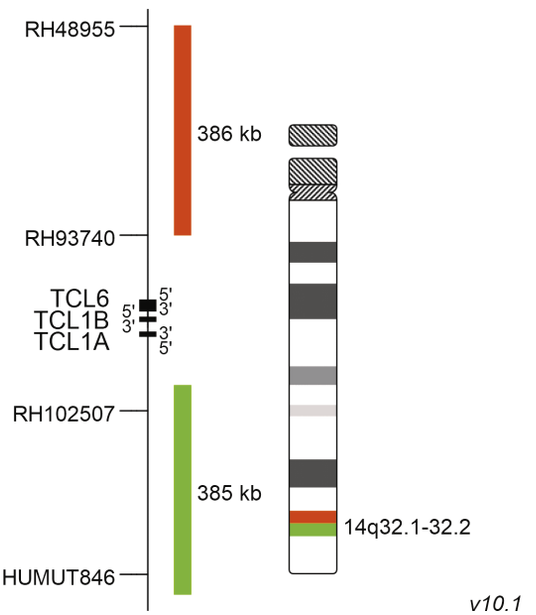
Dysregulated TCL1 expression levels have been detected in chronic lymphocytic leukaemia (CLL), various lymphomas and in T-cell prolymphocytic leukaemia (T-PLL). In T-cells, TCL1 dysregulation is caused by chromosomal rearrangement events bringing TCL1 under the control of T-cell receptor (TCR) enhancer elements. Two distinct breakpoint clusters have been described, which are located on both sides of a 160kb region flanking the TCL1A/TCL1B/TCL6 gene cluster. The rearrangements leading to TCL1A translocations with TCRα/TCRδ and TCRβ gene loci have been characterized precisely. The underlying chromosomal rearrangements are inv(14)(q11q32), being the most common aberration, t(14;14)(q11;q32.1) and t(7;14)(q35;q32.1). Phage display technology- and structure-based drug design approaches are used to target TCL1, due to its major role in the activation of different survival and proliferation maintaining pathways.

Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).



Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the respective locus.



Literature

- Virgilio et al (1994) PNAS 91: 12530- 12534
- Saitou et al (2000) Oncogene 19: 2796- 2802
- Paduano et al (2018) Front Oncol doi:10.3389/fonc.2018.00317

Order No:
D-5106-100-OG

Size: **100 µl**

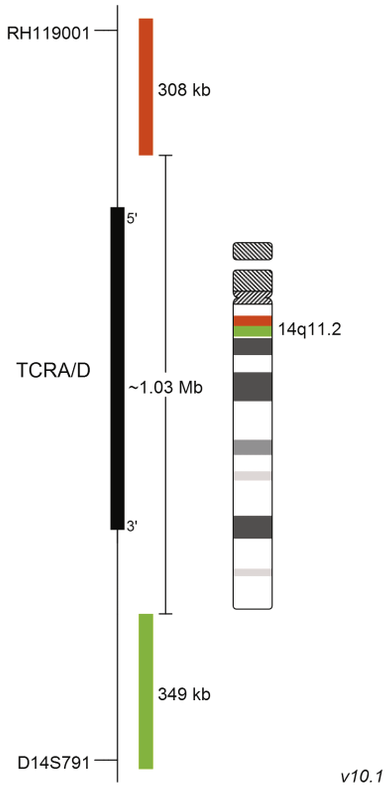
XCyting Locus-Specific Probes
Break Apart Probe XL

IVD XL TCRA/D

XL TCRA/D consists of an orange-labeled probe hybridizing proximal to the TCRA/D gene region at 14q11.2 and a green-labeled probe hybridizing distal to TCRA/D gene region at 14q11.2.

Chromosomal aberrations with breakpoints in T-cell receptor (TCR) gene loci are recurrent in several T-cell malignancies. The chromosomal alterations juxtapose oncogenes next to TCR regulatory sequences leading to deregulated expression of those oncogenes.

T-cell prolymphocytic leukemia (T-PLL) harbors frequent alterations of the TCRA/D locus, usually caused by an inv(14)(q11q32). By molecular cytogenetic studies, the incidence of TCRA/D rearrangements is about 24% of all T-cell acute lymphoblastic leukemia (T-ALL) cases.



Expected Patterns

Normal Cell
Two green-orange (2GO) fusion signals representing the two normal TCRA/D loci.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and one green-orange (1GO) fusion signal, indicating a chromosome break in the TCRA/D locus.

Literature

- Gesk et al (2003) Leukemia 17:738-745
- Leich et al (2007) J Pathol 213:99-105
- Feldman et al (2009) Am J Clin Pathol 130:178-185

Clinical Applications
ALL | NHL

Chromosome **14** | Page **87**

Order No:
D-5107-100-OG

Size: **100 µl**

XL IGH BA IVD

XL IGH BA consists of an orange-labeled probe partly covering the constant region of the IGH locus at 14q32.3 and a green-labeled probe hybridizing to the variable distal region of the IGH locus at 14q32.3.

Chromosomal translocations affecting the immunglobulin heavy chain (IGH) locus at 14q32.3 are recurrent in many types of lymphomas and plasma cell neoplasms. The consequence of these rearrangements is the dysregulation of genes juxtaposed to transcriptional enhancers in the IGH locus.

Burkitt lymphoma (BL) is a rare but fast growing type of non-Hodgkin lymphoma (NHL). The translocation between the MYC gene locus at 8q24 and the immunoglobulin genes (IG) for the kappa light chain at 2p12 (IGK), for the heavy chain at 14q32 (IGH) or for the lambda light chain at 22q11 (IGL) juxtapose the MYC gene to an IG enhancer. About 80% of BL patients have the MYC rearrangement t(8;14) while approximately 10% show a translocation between the MYC gene region and IGK or IGL.

Follicular lymphoma (FL) is the most common indolent form of the NHL. The reciprocal translocation t(14;18) is observed in about 85% of patients with FL and results in overexpression of the BCL-2 protein which is involved in the regulation of apoptosis.

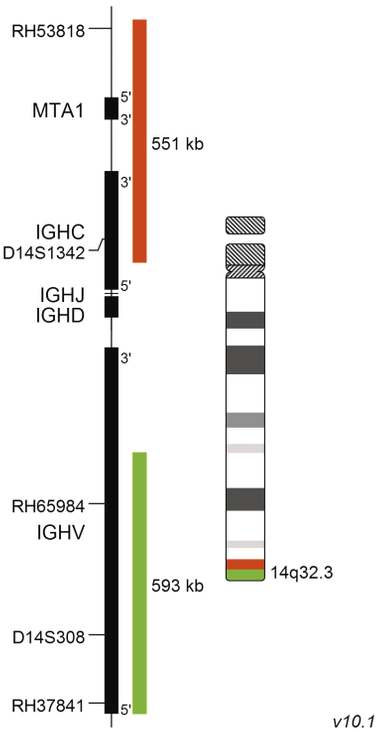
About 1% of all cancers and 10% of hematologic malignancies are caused by multiple myelomas (MM). Translocations affecting the IGH locus are observed in about 40% of MM cases.

Due to the telomeric position of the IGH locus, 14q32.3 translocations may be easily missed by conventional cytogenetics. FISH is therefore a valuable tool in the diagnostic of translocations affecting the IGH locus.

Expected Patterns

Normal Cell
Two green-orange (2GO) fusion signals.

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.



Literature

- Freedman (2014) Am J Hematol 89:429-436
- Rajan and Rajkumar (2015) Blood Canc J 5:1-7
- Nguyen et al (2017) Genes 8:1-23

Order No:
D-5112-100-OG

Size: **100 µl**

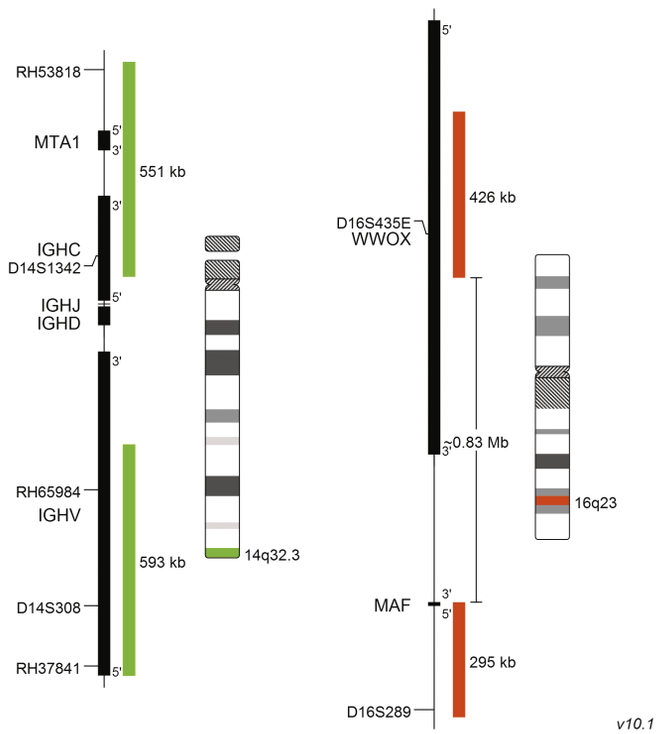
XCyting Locus-Specific Probes
Translocation/Dual Fusion Probe **XL**

IVD XL t(14;16) IGH/MAF DF

XL t(14;16) IGH/MAF DF consists of a green-labeled probe hybridizing to the IGH gene region at 14q32.3 and an orange-labeled probe hybridizing to the WWOX/MAF gene region at 16q23.

The most frequent primary abnormalities in multiple myeloma (MM) are trisomies of odd-numbered chromosomes or translocations involving the immunglobulin heavy chain (IGH) gene locus. The most common MM-associated IGH translocations are t(11;14), t(4;14), t(6;14), t(14;16) and t(14;20) in the order of their occurrence. The consequence of these rearrangements is the dysregulation of genes juxtaposed to transcriptional enhancers in the IGH locus. Prognosis and risk stratification strongly depend on the detection and interpretation of cytogenetic primary abnormalities. t(14;16) and t(14;20) are considered as high risk, t(4;14) as intermediate risk and t(6;14) and t(11;14) as standard risk cytogenetic aberrations in patients with MM based on FISH testing. Secondary aberrations are also influencing the outcome.

MAF overexpression caused by t(14;16)(q32;q23) increases gene expression levels of the downstream target genes cyclin D2 and integrin beta 7 and contributes to the pathogenesis of MM by at least two mechanisms. Cyclin D2 is a major player in cell cycle regulation and Cyclin D2 dysregulation promotes tumor development. Furthermore, overexpression of integrin beta 7 affects the interaction between myeloma cells and bone marrow stroma and thus promotes transformation of malignant plasma cells.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci.

Literature

- Chesi et al (1998) Blood 91:4457-4463
- Hurt et al (2004) Cancer Cell 5:191-199
- Rajan and Rajkumar (2015) Blood Cancer J 5:e365

Order No:
D-5113-100-OG

Size: **100 µl**

XL t(14;18) IGH/BCL2 DF IVD

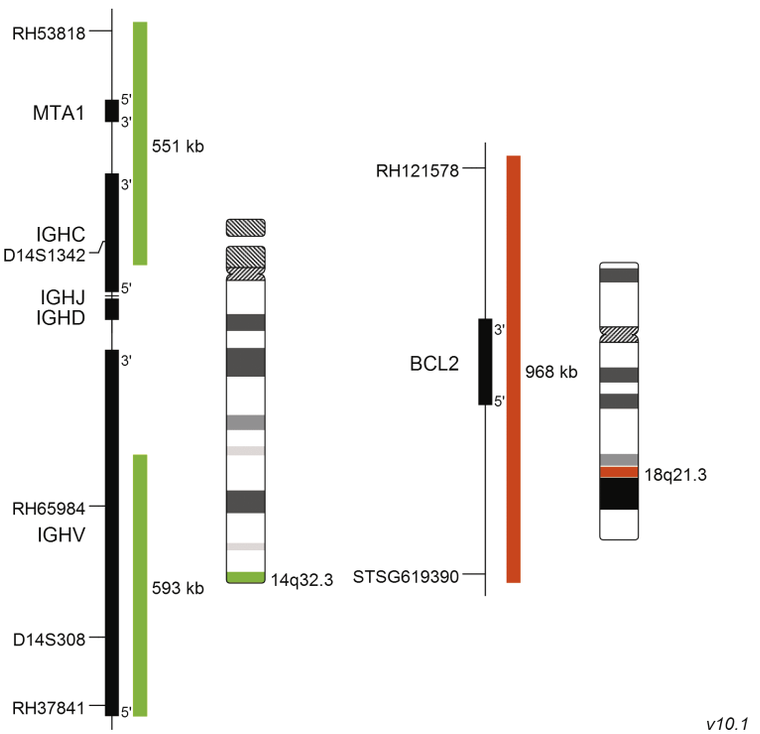
XL t(14;18) IGH/BCL2 DF consists of a green-labeled probe hybridizing to the IGH gene region at 14q32.3 and an orange-labeled probe hybridizing to the BCL2 gene region at 18q21.3.

Rearrangements of the immunoglobulin heavy chain (IGH) gene locus are present in about 50% of all non-Hodgkin lymphomas (NHL) including follicular lymphomas (FL) and diffuse large B-cell lymphomas (DLBCL). FL is the most common indolent form of NHL and accounts for about 20-30% of all lymphoid tumors. The reciprocal translocation t(14;18)(q32;q21) can be detected in about 85% of FL patients and in up to 35% of patients with DLBCL. t(14;18) juxtaposes BCL2 to transcriptional enhancers in the IGH locus and results in overexpression of the BCL-2 protein in neoplastic follicles. BCL2 is involved in the regulation of programmed cell death and shows anti-apoptotic characteristics. Overexpression of BCL2 leads to a high number of B-cells having a prolonged lifespan in germinal centers. This increases the chance to acquire additional chromosomal alterations required for the neoplastic transformation of B-cells.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci.



Literature

- Bernicot et al (2005) Anticancer Res 25:3179-3182
- Ott and Rosenwald (2008) Haemotologica 93:1773-1776
- Freedman (2014) Am J Hematol 89:429-436

Order No:
D-6020-100-OG

Size: **100 µl**

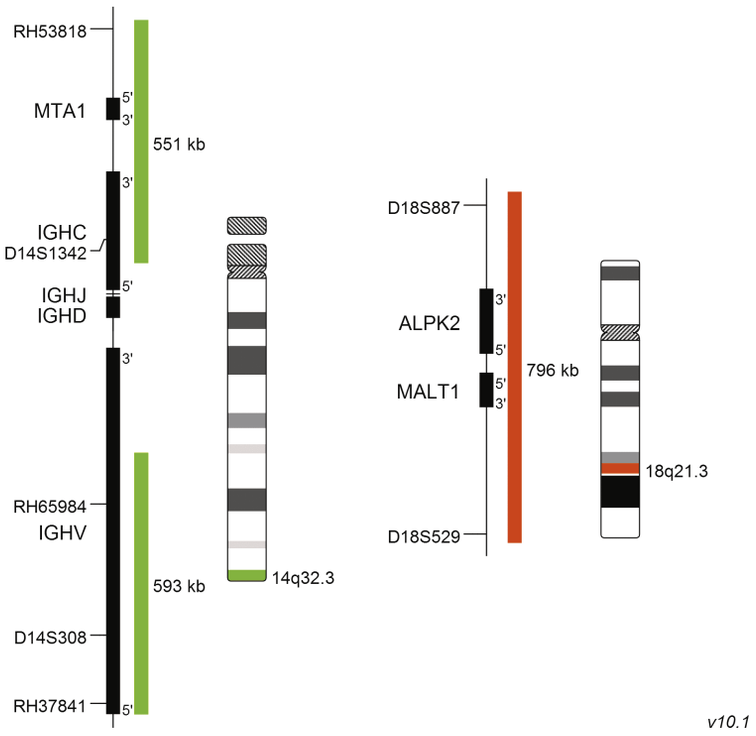
XCyting Locus-Specific Probes
Translocation/Dual Fusion Probe **XL**

IVD XL t(14;18) IGH/MALT1 DF

XL t(14;18) IGH/MALT1 DF consists of a green-labeled probe hybridizing to the IGH gene region at 14q32.3 and an orange-labeled probe hybridizing to the MALT1 gene region at 18q21.3.

MALT (mucosa-associated lymphoid tissue) lymphomas occur at diverse anatomic sites and are closely linked to several distinct chronic inflammatory disorders. Up to 50% of the MALT lymphoma cases analyzed demonstrate MALT1 rearrangements. The MALT1 gene was originally identified by its involvement in the MALT lymphoma associated translocation t(11;18)(q21;q21). This rearrangement is detected in 30% of all cases of MALT lymphoma and leads to BIRC3-MALT1 fusions. It is restricted to MALT lymphomas and has not been detected in nodal or splenic marginal zone lymphomas, diffuse large B-cell lymphomas, or other non-Hodgkin lymphomas.

Approximately 20% of MALT lymphoma cases analyzed are characterized by t(14;18)(q32;q21) leading to a IGH-MALT1 fusion. This reciprocal translocation juxtaposes MALT1 to transcriptional enhancers in the IGH locus and results in overexpression of the MALT1 gene. The distinct breakpoints on both chromosomes are precisely defined. The oncogenic potential of MALT1 is linked to its participation in the activation of nuclear factor-kappa B (NF-κB). This important transcription factor mediates the expression of anti-apoptotic, cell survival- and proliferation-promoting genes. Furthermore, there is emerging evidence indicating an oncogenic cross-link between the above-mentioned genetic rearrangements and immunological stimulation occurring during the pathogenesis of MALT lymphoma.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci.

Literature

- Streubel et al (2003) Blood 101:2335-2339
- Bacon et al (2007) J Clin Pathol 60:361-372
- Du (2017) Best Pract Res Clin Haematol 30:13-23

Order No:
D-5146-100-OG

Size: **100 µl**

XL IGH/MAFB DF IVD

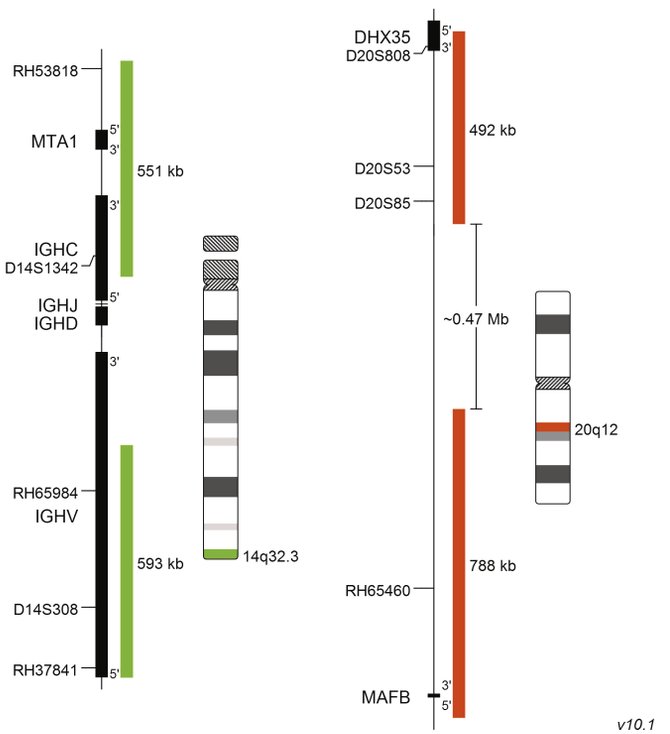
XL t(14;20) IGH/MAFB DF consists of a green-labeled probe hybridizing to the IGH gene region at 14q32.3 and an orange-labeled probe hybridizing to the the MAFB gene and flanking regions at 20q12.

The most frequent primary abnormalities in multiple myeloma (MM) are trisomies of odd-numbered chromosomes or translocations involving the immunoglobulin heavy chain (IGH) gene locus. The most common MM-associated IGH translocations are t(11;14), t(4;14), t(6;14), t(14;16) and t(14;20) in the order of their occurrence. As a consequence, translocation partner genes of IGH are dysregulated, as they are juxtaposed to transcriptional enhancers in the IGH locus. Prognosis and risk classification are strongly associated with the detection and interpretation of cytogenetic primary abnormalities. According to the International Myeloma Working Group (IMWG), risk classification of MM by FISH based analysis of IgH locus involving translocations represents one column of the entire diagnostics. Secondary effects are also influencing the outcome. Even if associated with poor prognosis in MM, MGUS/SMM cases characterized by the presence of t(14;20) can be stable for years before progression occurs, whereas MGUS/SMM cases with t(4;14) and t(14;16) show a significantly faster progression rate. The recurrent translocation t(14;20) (q32;q12) results in ectopic expression of the basic leucine zipper transcription factor MAFB (Vmaf musculoaponeurotic fibrosarcoma oncogene homolog B) which plays an important role in lineage-specific hematopoiesis. Furthermore, t(14;20) is associated with poor prognosis by promoting high cyclin D2 activity, thereby dysregulating normally balanced cell cycle.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci.



Literature

- Boersma-Vreugdenhil et al (2004) Brit J Haem 126:355-363
- Ross et al (2010) Haematologica 95:1221-1225
- Rajan and Rajkumar (2015) Blood Cancer J 5:e365

Order No:
D-5105-100-OG

Size: **100 µl**

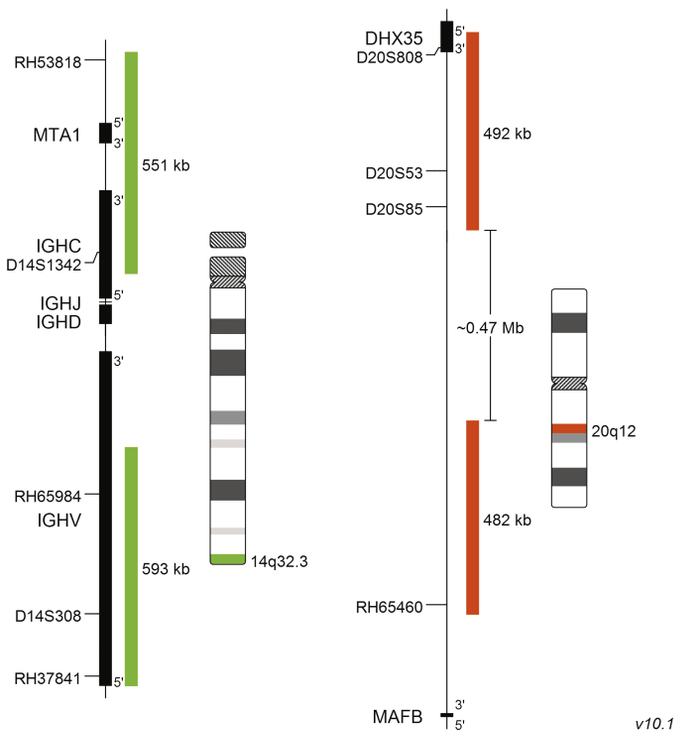
XCyting Locus-Specific Probes
Translocation/Dual Fusion Probe
XL

IVD XL t(14;20) IGH/MAFB DF

XL t(14;20) IGH/MAFB DF consists of a green-labeled probe hybridizing to the IGH gene region at 14q32.3 and an orange-labeled probe hybridizing proximal to the MAFB gene region 20q12.

The most frequent primary abnormalities in multiple myeloma (MM) are trisomies of odd-numbered chromosomes or translocations involving the immunglobulin heavy chain (IGH) gene locus. The most common MM-associated IGH translocations are t(11;14), t(4;14), t(6;14), t(14;16) and t(14;20) in the order of their occurrence. The consequence of these rearrangements is the dysregulation of genes juxtaposed to transcriptional enhancers in the IGH locus. Prognosis and risk stratification strongly depends on the detection and interpretation of cytogenetic primary abnormalities. t(14;16) and t(14;20) are considered as high risk, t(4;14) as intermediate risk, and t(6;14) and t(11;14) as standard risk cytogenetic aberrations in patients with MM based on FISH testing. Secondary aberrations are also influencing the outcome.

Even if associated with poor prognosis in MM, monoclonal gammopathy of undetermined significance/smoldering multiple myeloma (MGUS/SMM) cases characterized by t(14;20) can be stable for years before progression occurs, whereas MGUS/SMM cases with t(4;14) and t(14;16) are showing a higher progression rate. The recurrent t(14;20) results in ectopic expression of the basic leucine zipper transcription factor MAFB which has an important role in lineage-specific hematopoiesis.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the relevant loci.

Literature

- Boersma-Vreugdenhil et al (2004) Brit J Haem 126:355-363
- Ross et al (2010) Haematologica 95:1221-1225
- Rajan and Rajkumar (2015) Blood Cancer J 5:e365

Order No:
D-5086-100-OG

Size: **100 µl**

XL t(15;17) DF IVD

XL t(15;17) DF consists of an orange-labeled probe hybridizing to the PML gene region at 15q24 and a green-labeled probe hybridizing to the RARA gene region at 17q21.1-21.2.

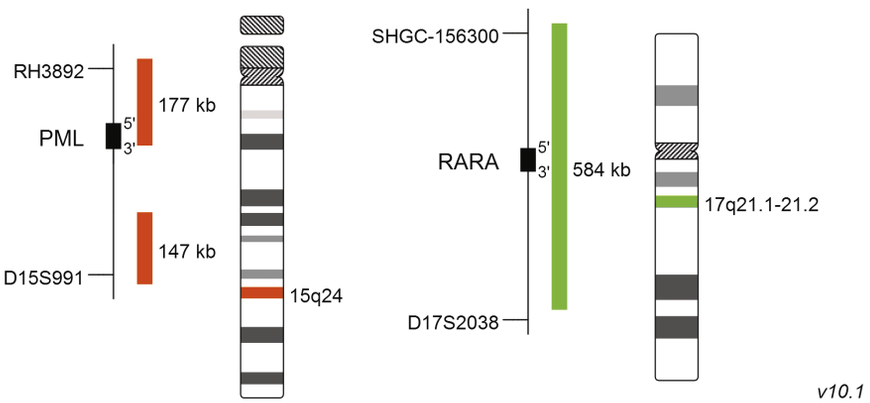
Several recurrent balanced translocations and inversions, and their variants, are recognized in the WHO category acute myeloid leukemia (AML) with recurrent genetic abnormalities. Furthermore, several cytogenetic abnormalities are considered sufficient to establish the WHO diagnosis of AML with myelodysplasia-related features if 20% or more blood or marrow blasts are present.

AML M3 and AML M3v are characterized by a reciprocal translocation between the long arm of chromosome 15 and the long arm of chromosome 17. This translocation leads to a rearrangement of the PML gene situated on chromosomal band 15q24 and the RARA gene situated on band 17q21. The PML-RARA rearrangement has gained major clinical importance because, in combination with all-trans retinoic acid (ATRA) and conventional anthracycline and cytarabine based chemotherapy, it leads to an improved prognosis in this subgroup of AML.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the respective loci.



v10.1

Literature

- Grimwade et al (2000) Blood 96:1297-1308
- Schoch et al (2002) Hematol J 3:259-263
- Campbell et al (2013) BioMed Res Int: Article ID 164501

Order No:
D-5092-100-OG

Size: **100 µl**

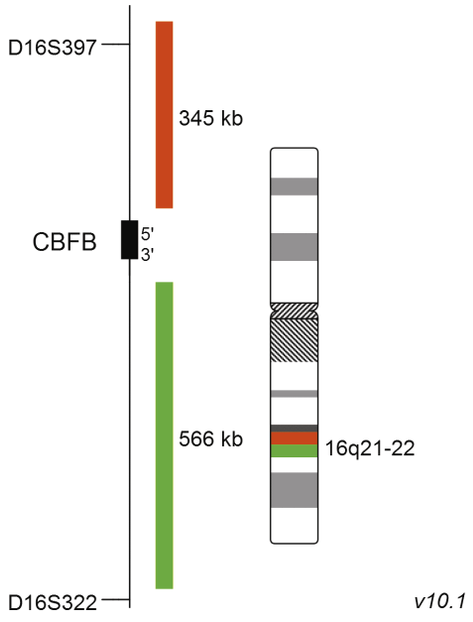
XCyting Locus-Specific Probes
Break Apart Probe
XL

IVD **XL CBFB**

XL CBFB consists of an orange-labeled probe hybridizing proximal to the CBFB gene region at 16q21-22 and a green-labeled probe hybridizing distal to the CBFB gene region at 16q22.

Several recurrent balanced translocations and inversions, and their variants, are recognized in the WHO category acute myelogenous leukemia (AML) with recurrent genetic abnormalities. Furthermore, several cytogenetic abnormalities are considered sufficient to establish the WHO diagnosis of AML with myelodysplasia-related features if 20% or more blood or marrow blasts are present.

The inv(16) and related t(16;16) are found in 10% of all cases of de novo AML. In these rearrangements, the core binding factor b (CBFB) gene on 16q22 is fused to the smooth muscle myosin heavy chain gene (MYH11) on 16p13. This cytogenetic group is usually associated with high complete remission rates and a relatively favorable outcome, especially when treated with repetitive cycles of high-dose cytarabine as consolidation therapy.



Expected Patterns

Normal Cell
Two green-orange (2GO) fusion signals representing the two normal CBFB loci.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and one green-orange (1GO) fusion signal, indicating a chromosome break in the CBFB locus.

Literature

- Doehner et al (2010) Blood 115:453-474
- Froehling et al (2002) J Clin Oncol 20:2480-2485
- Arber et al (2016) Blood 127:2391-2405

Clinical Applications
AML

Chromosome **16** | Page **95**

Order No:
D-5126-100-OG

Size: **100 µl**

XL CBFB/MYH11 plus IVD

XL CBFB/MYH11 plus consists of a green-labeled probe hybridizing to the MYH11 gene region at 16p13.1 and an orange-labeled probe hybridizing to the CBFB gene region at 16q22.

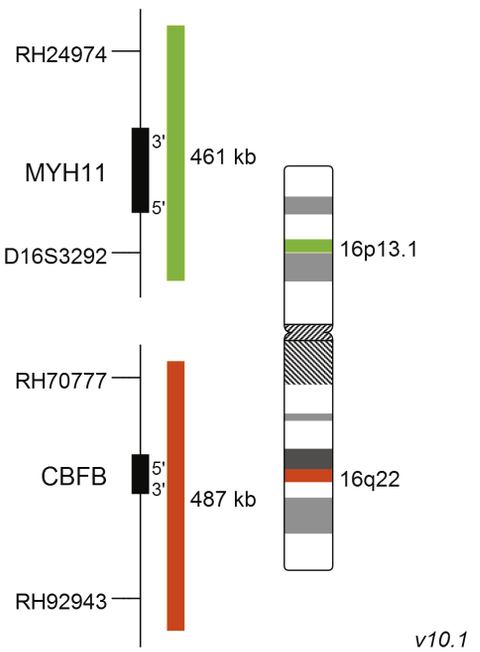
Acute myeloid leukemia (AML) with inv(16)(p13.1;q22) and t(16;16)(p13.1;q22) is listed in the World Health Organization (WHO) classification of tumors of the haematopoietic and lymphoid tissues. These recurrent rearrangements are present in about 10% of young AML patients. In cases with inv(16)/t(16;16), the core binding factor b (CBFB) gene on 16q22 is fused with the smooth muscle myosin heavy chain gene (MYH11) on 16p13.1. Patients carrying inv(16)/t(16;16) usually have a good prognosis. Cryptic insertions with no indication in cytogenetic analyses have been published. In these cases, a partial insertion of MYH11 into CBFB or a partial insertion of CBFB into the MYH11 gene was observed.

FISH probes with a break apart design might overlook this cryptic rearrangement because no separation of flanking regions of CBFB occurs, whereas translocation/dual fusion FISH probes are indicating this kind of cryptic rearrangement. FISH is a complementary method for the detection of inv(16)/t(16;16) increasing the sensitivity in combination with conventional cytogenetics. Furthermore, FISH is a valuable tool for cases without assessable metaphases.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and two green-orange colocalization/fusion signals (2GO) resulting from a reciprocal translocation between the respective loci.



Literature

- Fröhling et al (2005) Heamatologica 90:194-199
- Van Obbergh et al (2014) Cancer Genetics 207:231-232
- Zhang et al (2017) Adv in Mod Onc Res 3:12-14

Order No:
D-6035-100-OG

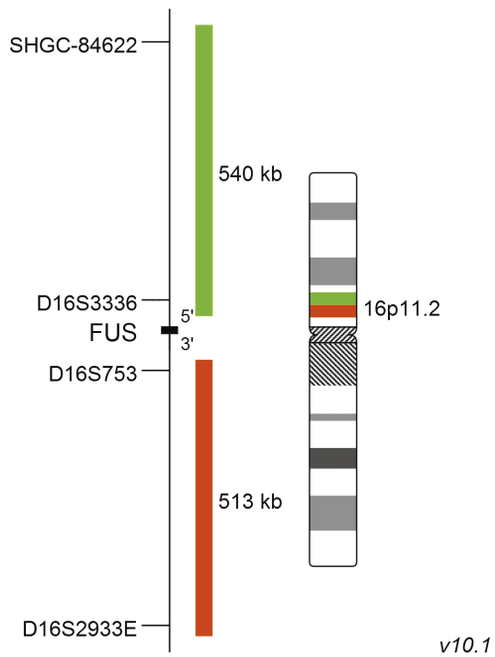
Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe
XL

IVD
XL FUS BA

XL FUS BA consists of an orange-labeled probe hybridizing proximal to the FUS gene region at 16p11.2 and a green-labeled probe hybridizing distal to the FUS gene region at 16p11.2.

Myxoid liposarcomas (MLS) are accounting for about 30% of liposarcomas and represent approximately 10% of adult soft tissue sarcomas. Patients with MLS showing progression to round-cell morphology have an inferior outcome. The most common aberration in MLS is the translocation t(12;16)(q13;p11) with a frequency of about 95% and to a much lesser extend t(12;22)(q13;q12), in which FUS is not involved. These reciprocal translocations are resulting in the generation of FUS-DDIT3 and EWSR1-DDIT3 fusion genes, respectively. As FUS is also involved in the development of low-grade fibromyxoid sarcoma with the rearrangement t(7;16)(q33;p11), FUS rearrangements are not highly specific for the detection of MLS. Human models of sarcomagenesis suggest that the FUS-DDIT3 fusion gene impedes with adipogenic differentiation of mesenchymal stem cells and thereby contributes to the development of liposarcoma.



Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.

Literature

- Knight et al (1995) Cancer Res 55:24-27
- Tanas et al (2009) Adv Anat Pathol 16:383-391
- Rodriguez et al (2013) Stem Cells 31:2061-2072

Order No:
D-6010-100-OG

Size: **100 µl**

XL ERBB2 (HER2/NEU) amp IVD

XL ERBB2 (HER2/NEU) amp consists of an orange-labeled probe hybridizing to the ERBB2 (HER2/NEU) gene region at 17q12 and a green-labeled probe hybridizing to the centromere of chromosome 17.

Amplification or over-expression of the ERBB2 (HER2/NEU) gene occurs in approximately 15-30% of breast cancers. It is strongly associated with increased disease recurrence and a poor prognosis. Over-expression is also known to occur in ovarian, stomach, and aggressive forms of uterine cancer, such as uterine serous endometrial carcinoma.

ERBB2, located on the long arm of human chromosome 17 (17q12), is a member of the epidermal growth factor receptor (EGFR/ErbB) family which is composed of four plasma membrane-bound receptor tyrosine kinases. Signaling through the ErbB family of receptors promotes cell proliferation and opposes apoptosis.

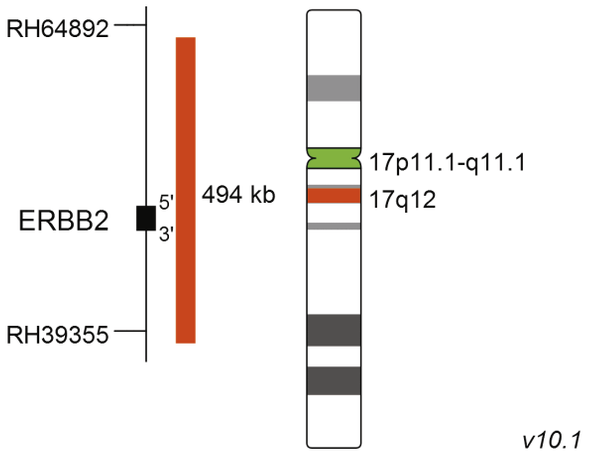
ERBB2 is the target of the monoclonal antibody trastuzumab (marketed as Herceptin®).

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one separate orange (1O) signal, and orange signal clusters indicating amplification of ERBB2 (HER2/NEU) (homogeneously staining region = HSR).

Aberrant Cell (typical results)
Two green (2G) and multiple copies of orange signals indicating amplification of ERBB2 (HER2/NEU) (double minute = dm).



Literature

- Isola et al (1999) Clin Cancer Res 5:4140-4145
- Blancato et al (2004) Br J Cancer 90:1612-1619
- Singhi et al (2012) Mod Pathol 25:378-387

Order No:
D-5087-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe XL

IVD

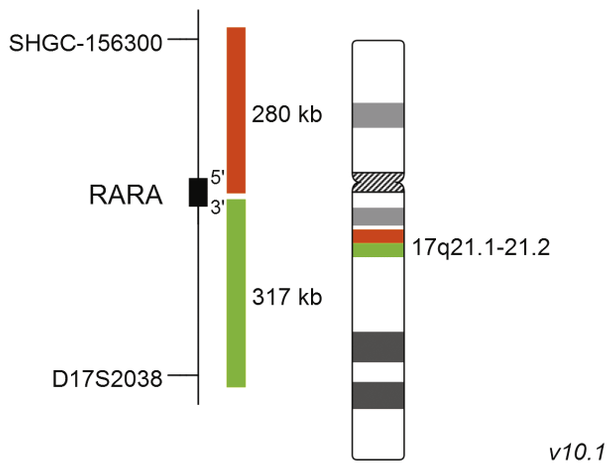
XL RARA BA

XL RARA BA consists of an orange-labeled probe hybridizing proximal to the RARA gene region at 17q21.1-21.2 and a green-labeled probe hybridizing distal to the RARA gene region at 17q21.1-21.2.

Acute promyelocytic leukemia (APL) is considered as a subtype of acute myeloid leukemia (AML) and accounts for about 5-8% of all AML cases. The most frequent aberration in APL is t(15;17) which results in the formation of the promyelocytic leukemia (PML) - retinoic acid receptor alpha (RARA) fusion gene (PML-RARA). Around 98% of all APL cases are characterized by PML-RARA, whereas translocations affecting RARA and other genes have been identified in only 1-2% of APL cases. Known fusion genes are ZBTB16-RARA, NPM1-RARA, NUMA1-RARA, STAT5B-RARA, PRKAR1A-RARA, BCOR-RARA and FIP1L1-RARA. ZBTB16-RARA comprises about 0.8% of all APL cases, the other rare fusions occur with lower frequency. Cryptic rearrangements resulting in the PML-RARA fusion gene are observed regularly, but also insertions of RARA into other locations have been found in a minority of APL cases.

RARA is a nuclear hormone receptor which forms heterodimers with the retinoid X receptor alpha and is involved in the regulation of promyelocyte differentiation. RARA fusion genes interfere with myeloid differentiation and contribute to the development of APL. The majority of APL patients are responsive to therapeutic doses of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) associated with chemotherapeutic drug regimen. Patients with ZBTB16-RARA or STAT5B-RARA fusions are resistant to ATRA and ATO.

The FISH break apart assay is a valuable tool for the detection of RARA rearrangements independent of the translocation partner.



Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.

Literature

- Grimwade et al (2000) Blood 15:1297-1308
- Schoch et al (2002) Hematol J 3:259-263
- Adams and Nassiri (2015) Arch Pathol Lab Med 139:1308-1313

Order No:
D-5048-100-OG

Size: **100 µl**

XL Iso(17q) IVD

XL Iso(17q) consists of a green-labeled probe hybridizing to the TP53 gene region at 17p13 and an orange-labeled probe hybridizing to the MPO gene region at 17q22.

An isochromosome of the long arm of chromosome 17, i(17q), is the most frequent genetic abnormality observed during the disease progression of Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML). The breakpoints are located in the short arm of chromosome 17 within the Smith-Magenis critical region at 17p11. In neuroblastoma and other hematologic malignancies, amplification of 17q is a significant predictive factor for adverse outcome.

Isochromosome 17q, or i(17q), is ocurring in primitive neuroectodermal tumor/medulloblastoma (50%), chronic myeloid leukemia (CML), acute myeloid leukemia (AML), and myelodysplastic neoplasms (MDS).

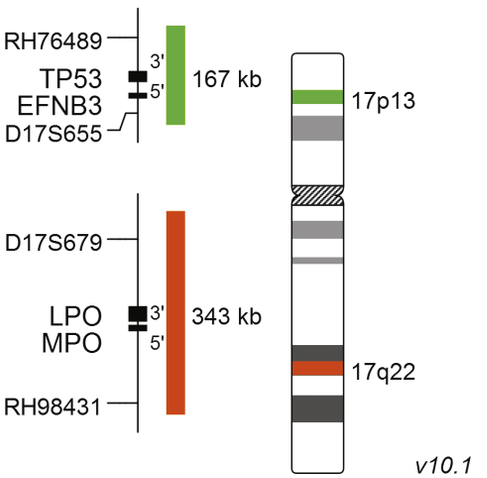
Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical result)
One green (1G), three orange (3O) signals, indicating the presence of i(17q).

Aberrant Cell (typical results)
Two green (2G), three orange (3O) signals, indicating a gain of 17q.

Aberrant Cells (typical results)
One green (1G) and two orange (2O) signals, indicating a deletion of the TP53 locus.



Literature

- Fioretos et al (1999) Blood 94:225-232
- Barbouti et al (2004) Am J Hum Genet 74:1-10
- Carvalho et al (2008) Genome Res 18:1724-1732

Order No:
D-5103-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Deletion Probe
XL

IVD

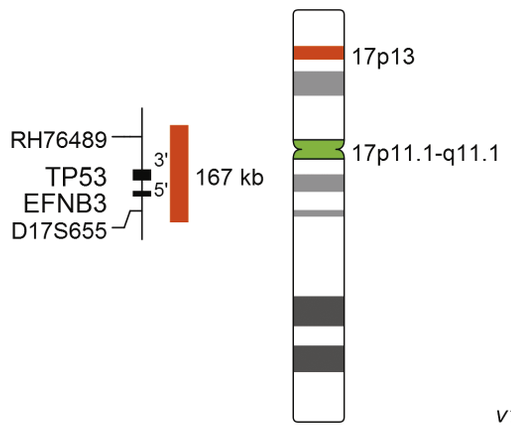
XL TP53/17cen

XL TP53/17cen consists of an orange-labeled probe hybridizing to the TP53 gene region at 17p13 and a green-labeled probe hybridizing to the centromere of chromosome 17.

TP53 is a central tumor suppressor gene involved in DNA repair, differentiation, cell cycle arrest and apoptosis. It is regarded as the "guardian of the genome" because of its role in conserving genome stability. TP53 alteration due to mutation or deletion plays a crucial role in tumorigenesis and is generally associated with advanced stages of disease, insufficient response to therapy and poor prognosis.

TP53 is also the most frequently mutated gene in human cancer with a mutation frequency of up to 90% in solid tumors and an average of 10% alterations in hematologic malignancies. TP53 deletions are often associated with mutations of the second allele, supporting the "two-hit" hypothesis of cancer development. If both mutation and deletion of TP53 are present, there is a significant negative impact on overall survival in hematological malignancies. In multiple myeloma, 33.8% of newly diagnosed patients carry a TP53 deletion, with even higher frequencies at relapse (54.5%). In acute myeloid leukemia (AML), 13% of patients show TP53 alterations, including 5% with mutations and deletions and 1% with deletion only. Patients with myelodysplastic neoplasms (MDS) show TP53 alterations in 7% of the cases, including 1% with mutations and deletions and 1% with deletion only. In AML and MDS, TP53 alterations and 17p deletion are associated with a complex karyotype, poor response to therapy, and reduced survival. In MDS, even TP53 deletion without mutation of the second allele has a significant negative impact on overall survival.

Deletions in TP53 frequently result from larger deletions of the short arm of chromosome 17. Interphase FISH for TP53 at 17p13 can be used to determine deletions of TP53 even in cells with a low proliferative capacity.



Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal resulting from loss of one orange signal.

Literature

- Drach et al (1998) Blood 92:802-809
- Soenen et al (1998) Blood 91:1008-1015
- Stengel et al (2017) Leukemia 31:705–711

Clinical Applications
AML | CLL | CML | MDS | MM

Chromosome **17**

Order No:
D-5089-100-OG

Size: **100 µl**

XL TP53/NF1 IVD

XL TP53/NF1 consists of an orange-labeled probe hybridizing to the TP53 gene region at 17p13 and a green-labeled probe hybridizing to the NF1 gene region at 17q11.2.

TP53 is a tumor suppressor gene often described as the guardian of the genome. Deletions and/or mutations can be detected in a wide range of hematological neoplasms and are the most common genetic aberrations in human cancer. The neurofibromin 1 gene (NF1), located at 17q11.2, is a tumor suppressor gene negatively regulating the RAS signal transduction pathway. Germline-loss of function can cause neurofibromatosis type I, a congenital genetic disorder of the nervous system which usually appears during childhood. Somatic deletions of NF1 are detected in about 3.5-7% of de novo acute myeloid leukemia (AML) cases and are often associated with a complex aberrant karyotype. Mutations in the remaining NF1 allele are reported with varying frequency. NF1 deleted cells have a decreased sensitivity to Ara-C in cell culture studies.

FISH is a valuable tool for the detection of NF1 deletions which might be easily overlooked by conventional cytogenetics due to the small size of the aberration.

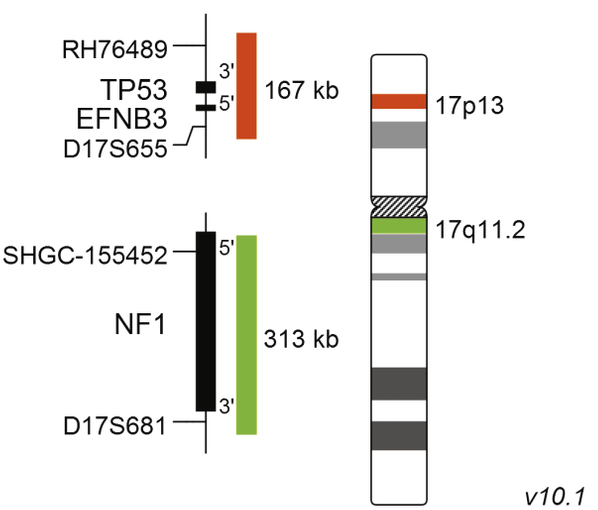
Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
One orange (1O), two green (2G) signals, indicating a deletion of TP53.

Aberrant Cell (typical results)
One green (1G) and one orange (1O) signal indicating the deletion of the TP53 and NF1 locus.

Aberrant Cell (typical results)
One orange (1O) and three green (3G) signals, indicating the presence of an isochromosome (17).



Literature

- Haferlach et al (2012) Leukemia 26:834-839
- Boudry-Labis et al (2013) Am J Hematol 88:306-311
- Tessoulin et al (2017) Blood Rev:doi:org/10.1016/j.blre.2017.03.001

Order No:
D-6018-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe XL

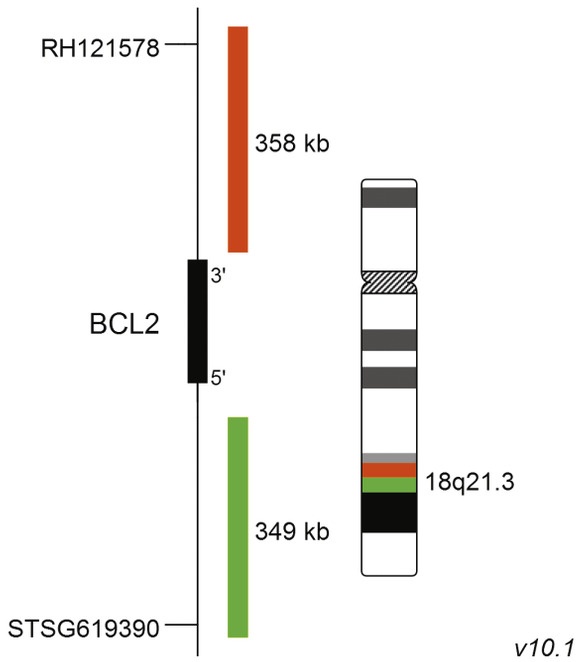
IVD XL BCL2 BA

XL BCL2 BA consists of an orange-labeled probe hybridizing proximal to the BCL2 gene region at 18q21.3 and a green-labeled probe hybridizing distal to the BCL2 gene region at 18q21.3.

The BCL2 gene rearrangement can be found in 50% of follicular lymphoma, 23.3% of B-cell lymphoma, and about 15% of diffuse large B-cell lymphoma. A consequence of this translocation is an overexpression of anti-apoptotic protein BCL2, which most likely represents the initial step of malignant transformation.

The majority of rearrangements in BCL2 occur at two distinct chromosomal regions, the major breakpoint cluster region (MBR) in 70% and the minor cluster region in 10% of patient's tumors.

FISH has been shown to be of higher sensitivity and of equivalent specificity when compared to PCR on paraffin-embedded tissue sections.



Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.

Literature

- Vaandrager et al (2000) Blood 96:1947-1952
- Godon et al (2003) Leukemia 17:255-259
- Weinberg et al (2007) J Mol Diagn 9:530-537

Order No:
D-6015-100-OG

Size: **100 µl**

XL MALT1 BA IVD

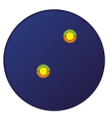
XL MALT1 BA consists of an orange-labeled probe hybridizing proximal to the MALT1 gene region at 18q21.3 and a green-labeled probe hybridizing distal to the MALT1 gene region at 18q21.3.

The MALT1 gene was identified through its involvement in t(11;18)(q21;q21), seen in 30% of cases of mucosa-associated lymphoid tissue (MALT) lymphoma. The t(11;18)(q21;q21) is restricted to MALT lymphomas and has not been detected in nodal or splenic marginal zone lymphomas, diffuse large B-cell lymphomas, or other non-Hodgkin lymphomas. The second most frequent translocation identified in MALT lymphoma is the t(14;18)(q32;q21) IGH/MALT1. The t(14;18)(q32;q21) IGH/MALT1 is found most often in MALT lymphomas arising at non-gastric sites and is identified in 5-25% of cases arising in the ocular adnexa, lung, salivary gland and skin.

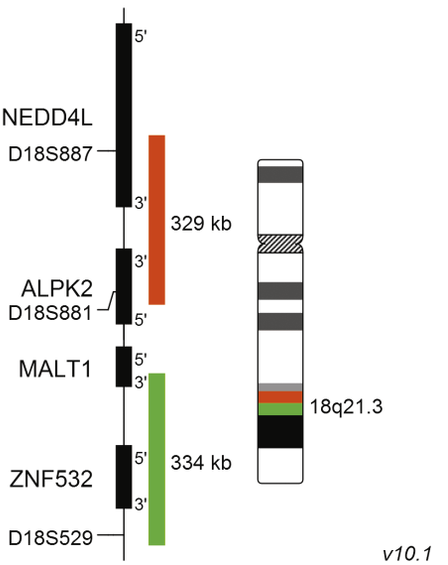
The oncogenic activity of MALT1 is linked to its involvement of the CARMA1-BCL10-MALT1 (CBM) complex in antigen receptor-mediated activation of the transcription factor NF-kB, which controls the expression of numerous anti-apoptotic and proliferation-promoting genes.

Expected Patterns

Normal Cell
Two green-orange (2GO) fusion signals representing the two normal MALT loci.



Aberrant Cell (typical results)
One green (1G), one orange (1O), and one green-orange (1GO) fusion signal, indicating a chromosome break in the MALT locus.



Literature

- Streubel et al (2003) Blood 101:2335-2339
- Murga Penas et al (2003) Leukemia 17:2225-2229
- Bacon et al (2007) J Clin Pathol 60:361-372

Order No:
D-6033-100-OG

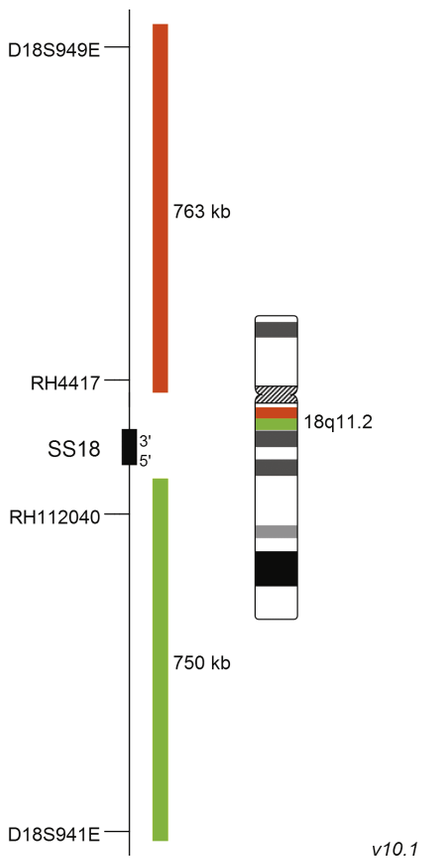
Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe
XL

IVD **XL SS18 BA**

XL SS18 BA consists of an orange-labeled probe hybridizing proximal to the SS18 gene region at 18q11.2 and a green-labeled probe hybridizing distal to the SS18 gene region at 18q11.2.

Synovial sarcoma is a highly aggressive and relatively rare soft tissue sarcoma. It often develops in the limbs of adolescents and young adults and comprises about 10-20% of soft tissue sarcomas in this population. The disease is characterized by the balanced translocation t(X;18) resulting in an in-frame fusion of ´synovial sarcoma translocation, chromosome 18´ (SS18) with members of the ´synovial sarcoma, X breakpoint´ family (SSX), located on the X chromosome. The chimeric fusion protein consists of almost the complete SS18 protein, only eight amino acids are missing, with the carboxy terminus of SSX1 or SSX2 and in rare cases SSX4. Several studies have shown that the SS18-SSX chimeric protein is interacting with the ATP-dependent chromatin remodeling complex SWI/SNF, interfering with its proper function. The absence of the der(18) in some cases suggests that it is not mandatory for the maintenance of the tumor. Generally, synovial sarcoma shows a low genetic complexity, about 50% of the cases harbor t(X;18) as a sole aberration. Since cytogenetic analysis of solid tumors is challenging, FISH provides an alternative method for the characterization of the status of SS18-SSX rearrangements.



Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.

Literature

- Shipley et al (1996) Am J Pathol 148:559-567
- Surace et al (2004) Lab Invest 84:1185-1192
- Nielsen et al (2015) Cancer Discov 5:124-134

Order No:
D-6019-100-OG

Size: **100 µl**

XL 19p/19q del IVD

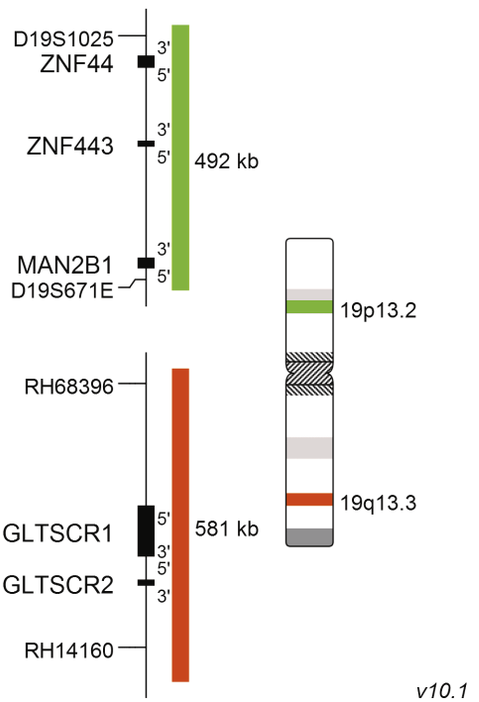
XL 19p/19q del consists of a green-labeled probe hybridizing to the ZNF443 gene region at 19p13.2 and an orange-labeled probe hybridizing to the GLTSCR1/ GLTSCR2 gene region at 19q13.3.

The 2016 ´World Health Organization Classification of Tumors of the Central Nervous System´(WHO 2016) combines, for the first time, histological features and molecular signatures for the definition of many tumor entities. Gliomas are a category of tumors of the brain and spinal cord originating in glia cells. Oligodendrogliomas are a subtype of gliomas accounting for up to 18% of all cases. According to the WHO 2016, the classification of an oligodendroglioma requires information about the isocitrate dehydrogenase mutation status and 1p/19q loss of heterozygosity (LOH). LOH of 19q can be detected in about 80% of oligodendroglial tumors and to a lower extend in mixed gliomas. Co-deletion of 1p/19q is a well-accepted prognostic biomarker in neuro-oncology. Patients suffering from anaplastic oligodendroglioma harboring 1p/19q deletion generally have a good prognosis. Co-deletion of 1p/19q also has a predictive character, the molecular status of 1p/19q is relevant for therapy decisions.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal resulting from loss of one orange signal.



Literature

- Reifenberger et al (1994) Am J Pathol 145:1175-1190
- Louis et al (2016) Acta Neuropathol 131:803-820
- Staedtke et al (2016) Trends Cancer 2:338-349

Order No:
D-5128-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe XL

IVD

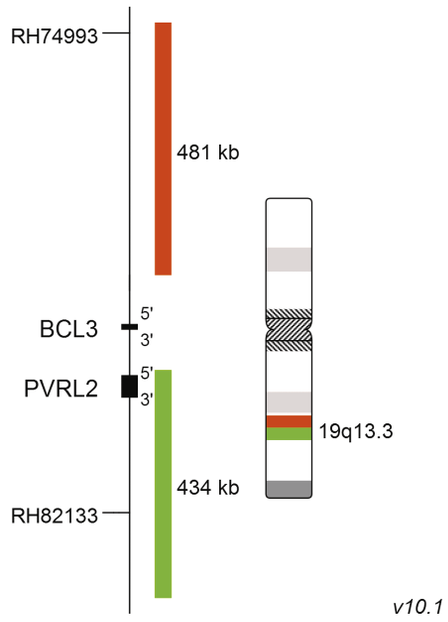
XL BCL3 BA

XL BCL3 BA consists of an orange-labeled probe hybridizing proximal to the BCL3 gene region at 19q13.3 and a green-labeled probe hybridizing distal to the BCL3 gene region at 19q13.3.

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults. The clinical course is heterogeneous and ranges from good outcome to very aggressive and fast progressing disease. CLL is not characterized by a well-defined chromosomal translocation as many other lymphoid neoplasms. The most frequent aberrations are deletions on 6q21 (3-6%), 11q22-23 (5-20%), 13q14.3 (>50%) or 17p13.1 (3-8%) and trisomy 12 (10-20%).

The recurrent t(14;19)(q32.3;q13.3) is a rare event with an incidence of <0.1% in B-cell neoplasms and is often associated with trisomy 12 or a complex karyotype. It is also considered as a poor prognostic marker in CLL with inferior outcome. The translocation juxtaposes BCL3 with the immunoglobulin heavy chain gene region on chromosome 14, resulting in overexpression of BCL3. BCL3 is an oncogene involved in the regulation of NF-kappa-B target genes.

Since it is difficult to obtain metaphases from CLL patients, interphase FISH offers great advantage over conventional cytogenetics.



Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.

Literature

- Michaux et al (1996) Genes Chrom Can 15:38-47
- Huh et al (2011) Am J Clin Pathol 135:686-696
- Puiggros et al (2014) Biomed Res Int 2014:Article ID 435983

Clinical Applications
CLL

Chromosome **19** | Page **107**

Order No:
D-5121-100-OG

Size: **100 µl**

XL 20q12/20qter plus IVD

XL 20q12/20qter plus consists of an orange-labeled probe hybridizing to the PTPRT gene region at 20q12 and a green-labeled probe hybridizing to a region at 20q13.3.

Myelodysplastic neoplasms (MDS) are a group of hematopoietic stem cell disorders associated with ineffective hematopoiesis and peripheral blood cytopenias. Approximately 40% of MDS cases are progressing to acute myeloid leukemia. In about 50% of de novo MDS, cytogenetic aberrations are observed; deletions are predominant, translocations are rare. Recurrent abnormalities are del(5q), monsomy 7, del(7q), del(20q), del(17p) and del(11q).

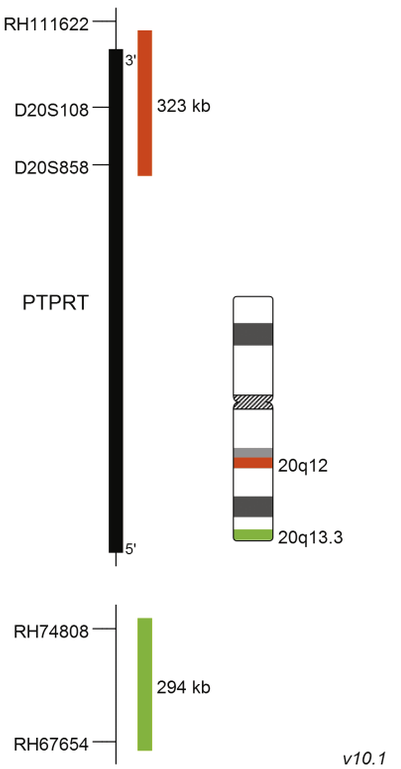
A chromosome 20q deletion is seen in about 2% of MDS cases. Patients with a sole del(20q) have a favourable outcome compared to patients with additional abnormalities such as del(5q), del(7q), monosomy 7 and trisomy 8. The majority of patients with del(20q) have an interstitial deletion between 20q11.2 and 20q13.3. In rare cases, the 20q deletion can occur as an isoderivative chromosome ider(20q) with loss of the p-arm of chromosome 20 and partial trisomy of the remaining regions on the q-arm.

Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal resulting from loss of one orange signal.

Aberrant Cell (typical results)
Three green (3G) and one orange (1O) signal resulting from the presence of ider(20q).



Literature

- Kurtin et al (1996) Am J Clin Pathol 106:680-688
- Douet-Gilbert et al (2008) Br J Haematol 143:716-720
- Bacher et al (2014) Br J Haematol 164:822-833

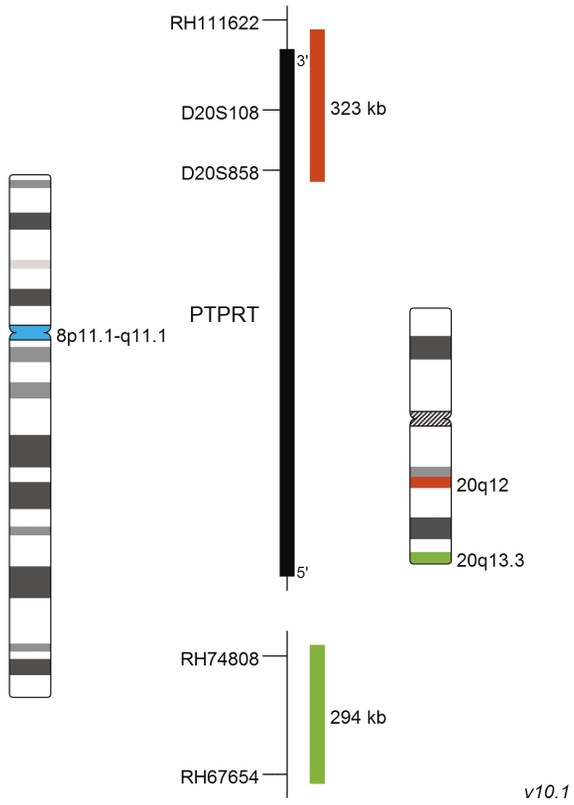
Order No:
D-5122-100-TC

Size: **100 µl**

IVD XL 20q12/20qter/8cen plus

XL 20q12/20qter/8cen plus consists of an aqua-labeled probe hybridizing to the centromere of chromosome 8, an orange-labeled probe hybridizing to the PTPRT gene region at 20q12 and a green-labeled probe hybridizing to a region at 20q13.3.

Myelodysplastic neoplasms (MDS) are a group of hematopoietic stem cell disorders associated with ineffective hematopoiesis and peripheral blood cytopenia. MDS patients have a high risk of progressing to acute leukemia. In about 50% of de novo MDS, cytogenetic aberrations are observed. A chromosome 20q deletion is seen in about 2% of MDS cases. Patients with a sole del(20q) have a favorable outcome. About 30% of all del(20q) patients are carrying additional recurrent chromosomal abnormalities such as del(5q), monosomy 7, del(7q) and trisomy 8. The presence of three or more additional aberrations is associated with an inferior outcome. In rare cases, the 20q deletion can occur as an isoderivative chromosome ider(20q) with loss of the p-arm of chromosome 20 and partial trisomy of the remaining regions on the q-arm. The knowledge of the cytogenetic status in MDS patients is of prognostic significance.



Expected Patterns

Normal Cell
Two blue (2B), two green (2G), and two orange (2O) signals.

Aberrant Cell (typical results)
Two blue (2B), two green (2G), and one orange (1O) signal resulting from the loss of one orange signal.

Aberrant Cell (typical results)
Three blue (3B), two green (2G), and one orange (1O) signal resulting from the loss of one orange signal and a trisomy of the blue labeled chromosome.

Aberrant Cell (typical results)
Two blue (2B), three green (3G), and one orange (1O) signal resulting from the presence of ider(20q).

Literature

- Solé et al (2005) Haematologica 90:1168-1178
- Douet-Gilbert et al (2008) Br J Haematol 143:716-720
- Bacher et al (2014) Br J Haematol 164:822-833

Order No:
D-5119-100-OG

Size: **100 µl**

XL del(20q) plus IVD

XL del(20q) plus consists of an orange-labeled probe hybridizing to the PTPRT gene region at 20q12 and a green-labeled probe hybridizing to the MYBL2 gene region at 20q12-13.1.

Myelodysplastic neoplasms (MDS) are a group of hematopoietic stem cell disorders associated with ineffective hematopoiesis and peripheral blood cytopenias. MDS patients have a significant risk of progression to acute myeloid leukemia. In about 50% of de novo MDS, cytogentic aberrations are observed; deletions are predominant, translocations are rare. Recurrent abnormalities are del(5q), monsomy 7, del(7q), del(20q), del(17p) and del(11q).

Del(20q) is a recurrent but rare aberration and is present in about 3-7% of MDS patients. The majority of cases have an interstitial deletion which is flanked by the PTPRT gene and includes the MYBL2 gene. Sole del(20q) is associated with a more favorable outcome.

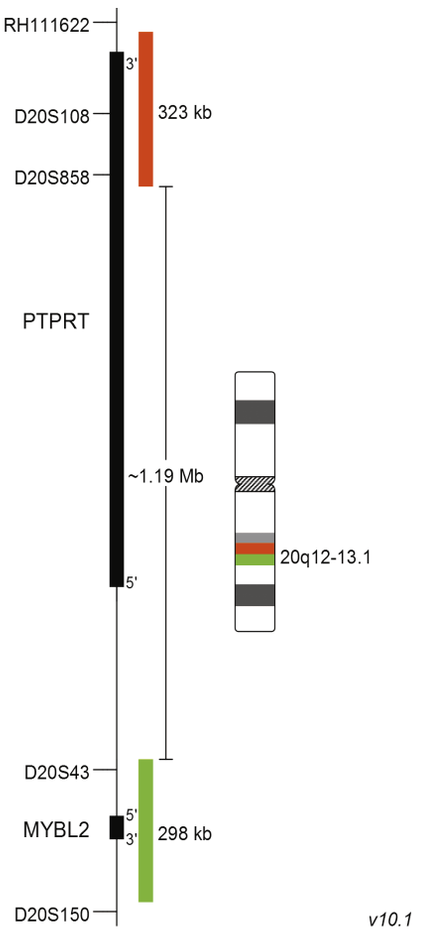
Expected Patterns

Normal Cell
Two green (2G) and two orange (2O) signals.

Aberrant Cell (typical results)
Two green (2G) and one orange (1O) signal resulting from loss of one orange signal.

Aberrant Cell (typical results)
One green (1G) and two orange (2O) signals resulting from loss of one green signal.

Aberrant Cell (typical results)
One green (1G) and one orange (1O) signal resulting from loss of one green and one orange signal.



Literature

- Bench et al (2000) Oncogene 19:3902-3913
- Saunders et al (2005) Cancer Genet Cytogen 156:154-157
- Bacher et al (2014) Brit J Haematol 164:822-833

Order No:
D-5096-100-OG

Size: **100 µl**

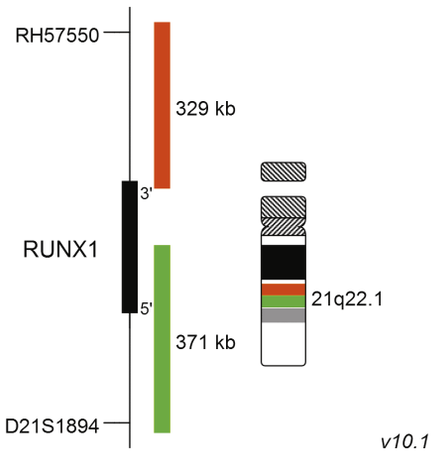
XCyting Locus-Specific Probes
Break Apart Probe XL

IVD XL RUNX1

XL RUNX1 consists of an orange-labeled probe hybridizing proximal to the RUNX1 gene region at 21q22.1 and a green-labeled probe hybridizing distal to the RUNX1 gene region at 21q22.1.

Several recurrent balanced translocations and inversions, and their variants, are recognized in the WHO category acute myeloid leukemia (AML) with recurrent genetic abnormalities. Furthermore, several cytogenetic abnormalities are considered sufficient to establish the WHO diagnosis of AML with myelodysplasia-related features if 20% or more blood or marrow blasts are present.

The RUNX1 gene, located on chromosome 21q22.1, is crucial for the establishment of definite hematopoiesis and the generation of hematopoietic stem cells in the embryo. The most common translocations involving RUNX1 are the t(8;21) RUNX1T1/RUNX1 in AML and t(12;21) ETV6/RUNX1 in acute lymphoblastic leukemia (ALL), both associated with a more favorable diagnosis. More than 40 different translocation partners have currently been identified making the RUNX1 break apart probe a valuable tool in molecular cytogenetics.



Expected Patterns

Normal Cell
Two green-orange (2GO) fusion signals representing the two normal RUNX1 loci.

Aberrant Cell (typical results)
One green (1G), one orange (1O), and one green-orange (1GO) fusion signal, indicating a chromosome break in the RUNX1 locus.

Literature

- Martinez-Ramirez et al (2001) Haematologica 86:1245-1253
- Zhang et al (2002) PNAS 99:3070-3075
- Harrison et al (2014) Leukemia 28:1015-1021

Order No:
D-5117-100-OG

Size: **100 µl**

XL 22q11 IGL BA IVD

XL 22q11 IGL BA consists of an orange-labeled probe hybridizing proximal to the IGL gene region at 22q11.2 and a green-labeled probe hybridizing distal to the IGL gene region at 22q11.2.

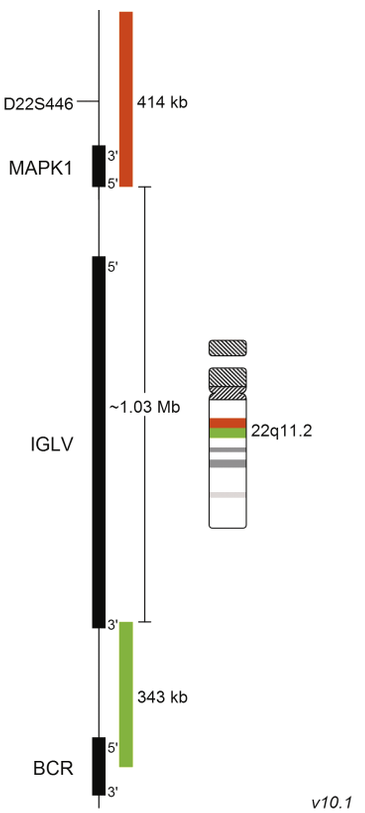
The immunoglobulin (IG) genes for the kappa light chain at 2p12 (IGK), the lambda light chain at 22q11 (IGL) and the heavy chain at 14q32 (IGH) are recurrently involved in the development of non-Hodgkin lymphomas (NHL). By far most frequently involved is IGH with more than 30 partner genes, less frequently IGK and IGL. IG-translocations are leading to juxtaposition of proto-oncogenes with IG enhancer sequences resulting in overexpression of the respective oncogene. Chromosomal translocations involving c-MYC at 8q24 and IG genes frequently occur in Burkitt lymphoma (BL). BL is a rare but fast growing type of NHL which is rapidly fatal if left untreated. About 75% of BL patients are carrying the MYC rearrangement t(8;14) while the remainder show a translocation between MYC and IGK or IGL. MYC-IG rearrangements are also involved in other B-cell malignancies such as atypical Burkitt/Burkitt-like lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma and multiple myeloma. Besides 8q24 (MYC), other translocation partners for IGL, such as chromosomal regions 2p13-14, 3q27 (BCL6), 4q13, 6p25, 16p12, 17p11.2 and 17q21, are known.

FISH break apart assays are valuable tools for the detection of IG light chain rearrangements independent of the translocation partner. Furthermore, double translocations have been described which are difficult to detect by PCR-based methods.

Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.



Literature

- Martin-Subero et al (2002) Int J Cancer 98:470-474
- Einerson et al (2006) Leukemia 10:1790-1799
- Fujimoto et al (2008) Eur J Haematol 80:143-150

Order No:
D-6011-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Break Apart Probe XL

IVD

XL EWSR1 BA

XL EWSR1 BA consists of an orange-labeled probe hybridizing proximal to the EWSR1 gene region at 22q12.1-12.2 and a green-labeled probe hybridizing distal to the EWSR1 gene region at 22q12.2.

Ewing sarcoma (EWS) is a rare and highly aggressive cancer with an incidence of about three in one million Caucasians. The incidence in Africans is significantly lower. EWS is more common among children and young adults than in adults and mostly arises in bones and to lower extend in soft tissue. EWS is typified by chromosomal translocations resulting in fusion genes between the EWS RNA Binding Protein 1 (EWSR1) and a member of the group of ETS transcription factors. t(11;22)(q24;q12) is the most common of these translocations represented by the EWSR1-FLI1 fusion gene with a frequency of about 85%. The EWSR1 part contributes a strong transcriptional domain while FLI1 is providing the ETS family DNA binding domain. The chimeric protein is dysregulating target genes leading to oncogenic transformation and is absolutely required for tumorigenesis in EWS. Other translocation partners are known, but no difference in survival has been observed between different fusion genes. Although complex karyotypes are rare in EWS, gain of chromosome 1q, 8, 12 and loss of 9p21 (CDKN2A) and 16q is observed. The EWSR gene is expressed in several tissues and is involved in other tumor diseases. EWSR1 has manifold functions and is involved in different control mechanisms in the cell. EWS is genetically stable and complex karyotypes are rare.

Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the respective locus.

Literature

- Delattre et al (1992) Nature 359:162-165
- Smith et al (2006) Cancer Cell 9:405-416
- Sannino et al (2017) Future Oncol 13:1207-1211

Order No:
D-5130-100-OG

Size: **100 µl**

XL CRLF2 BA IVD

XL CRLF2 BA consists of an orange-labeled probe hybridizing proximal to the CRLF2 gene region at Xp22.33 and Yp11.32 and a green-labeled probe hybridizing distal to the CRLF2 gene region at Xp22.33 and Yp11.32.

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children (prevalence of approximately 1:1500). Children with Down syndrome have a 10- to 20-fold increased risk of developing acute leukemia. B-Cell dependent BCR-ABL1-like ALL, also known as Philadelphia chromosome (Ph)-like ALL, is a high-risk subset with a gene expression profile which shares significant overlap with that of Ph-positive (Ph+) ALL, but lacking the BCR-ABL1 fusion. In 2017, the WHO recognized BCR-ABL1-like ALL as a new entity.

Chromosomal rearrangements resulting in the overexpression of cytokine receptor like factor 2 (CRLF2) can be found in up to 50% of BCR-ABL1-like ALL cases. The CRLF2 gene is located in the pseudoautosomal region 1 (PAR1) of the X and the Y chromosome. Three genetic key mechanisms regarding CRLF2 and ALL are known. Firstly, the CRLF2 gene is placed under the control of the IGH enhancer. Translocations of the type t(X;14) or t(Y;14) are the genetic basis for this aberration. Secondly, fusion of CRLF2 to CSF2RA, a further PAR1 gene, has been described. Thirdly, cryptic interstitial deletions juxtaposing the initial non-coding exon of the purinergic receptor P2Y8 (P2RY8) and CRLF2 have been shown. The resulting P2RY8-CRLF2 fusion under the control of the P2RY8 promoter is strongly transcribed in lymphoid cells. CRLF2 rearrangements result in increased protein levels, which initiate significantly enhanced JAK/STAT signaling, whereby disproportionate JAK and subsequent STAT5 activation induces strongly enhanced B-cell activation and proliferation.

XL CRLF2 BA detects chromosomal aberrations resulting from CRLF2 gene rearrangements (deletions and translocations).

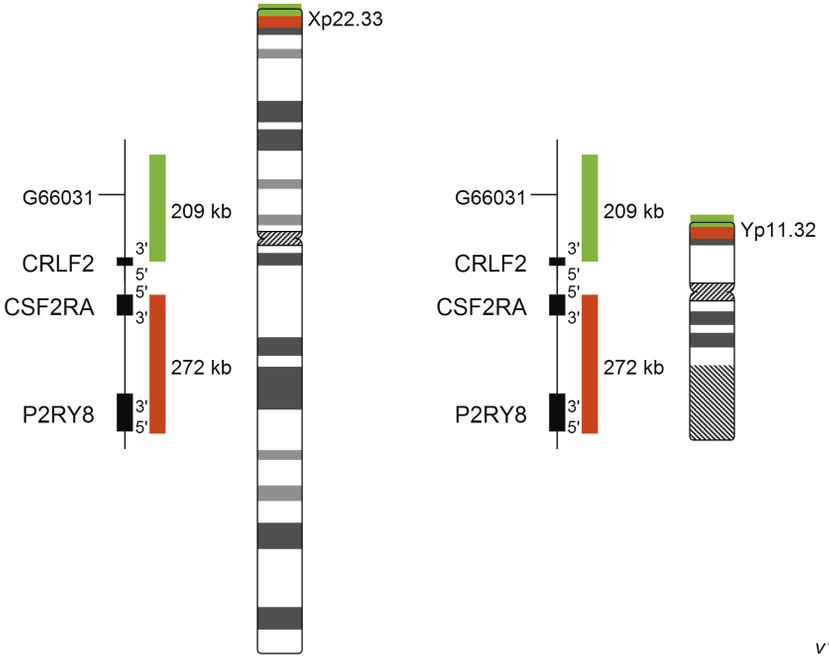
XL P2RY8 del (D-5150-100-OG) can be used as an additional tool in order to detect the presence of the P2RY8-CRLF2 fusion gene.

Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange colocalization/fusion signal (1GO), one separate green (1G) and orange (1O) signal each resulting from a chromosome break in the relevant locus.

Aberrant Cell (typical results)
One green-orange (1GO) colocalization/fusion signal and one green (1G) signal resulting from the loss of one orange signal.



v10.1

Literature

- Roll and Reuther (2010) Cancer Res 70:7347-7352
- Yoda et al (2010) Proc Natl Acad Sci 107:252-257
- Tasian et al (2017) Blood 130:2064-2072

Order No:
D-5150-100-OG

Size: **100 µl**

XCyting Locus-Specific Probes
Deletion Probe
XL

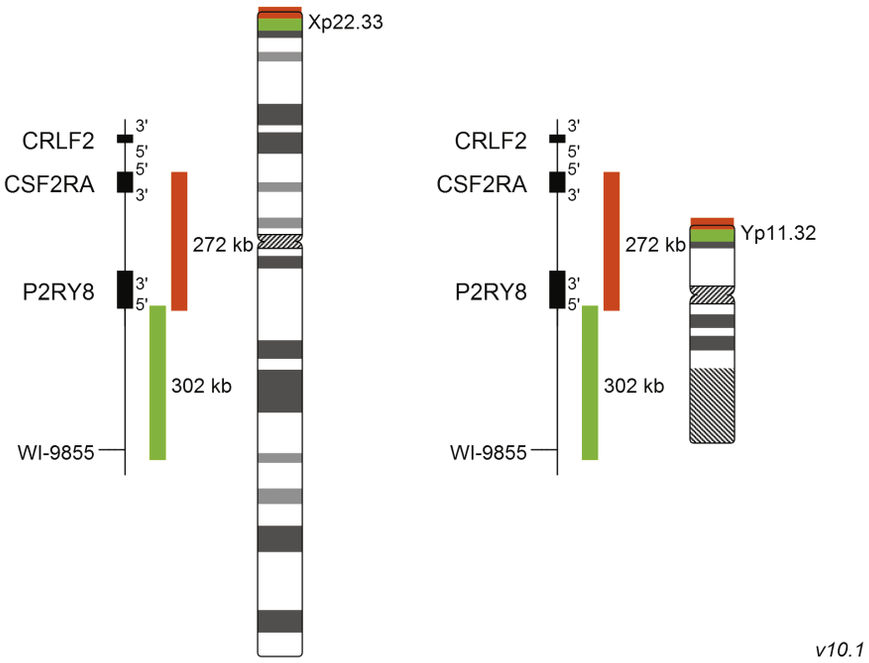
IVD
XL P2RY8 del

XL P2RY8 del consists of an orange-labeled probe hybridizing to P2RY8 and distal to the P2RY8 gene region Xp22.33 and Yp11.32 and a green-labeled probe hybridizing proximal to the P2RY8 gene region at Xp22.33 and Yp11.32.

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children (prevalence of approximately 1:1500). Children with Down syndrome have a 10- to 20-fold increased risk of developing acute leukemia. B-Cell dependent BCR-ABL1-like ALL, also known as Philadelphia chromosome (Ph)-like ALL, is a high-risk subset with a gene expression profile which shares significant overlap with that of Ph-positive (Ph+) ALL, but lacking the BCR-ABL1 fusion. In 2017, the WHO recognized BCR-ABL1-like ALL as new entity.

Chromosomal rearrangements resulting in the overexpression of cytokine receptor like factor 2 (CRLF2) can be found in up to 50% of BCR-ABL1-like ALL cases. The CRLF2 gene is located in the pseudoautosomal region 1 (PAR1) of the X and the Y chromosome. CRLF2 rearrangements result in increased protein levels, which initiate significantly enhanced JAK/STAT signaling, whereby disproportionate JAK and subsequent STAT5 activation induces strongly enhanced B-cell activation and proliferation. One of the genetic mechanisms leading to constitutive overexpression of CRLF2 is a gene fusion of CRLF2 with another PAR1 gene, purinergic receptor P2Y8 (P2RY8). The resulting P2RY8-CRLF2 fusion under the control of the P2RY8 promoter is strongly transcribed in lymphoid cells.

XL P2RY8 del can be used to detect the presence of the P2RY8-CRLF2 fusion gene.



v10.1

Expected Patterns

Normal Cell
Two green-orange colocalization/fusion signals (2GO).

Aberrant Cell (typical results)
One green-orange (1GO) co-localization/fusion signal and one green (1G) signal resulting from the loss of one orange signal.

Literature

- Mullighan et al (2009) Nat Genet 41:1243-1246
- Russell et al (2017) Genes Chromosomes Cancer 56:363-372
- Tasian et al (2017) Blood 130:2064-2072

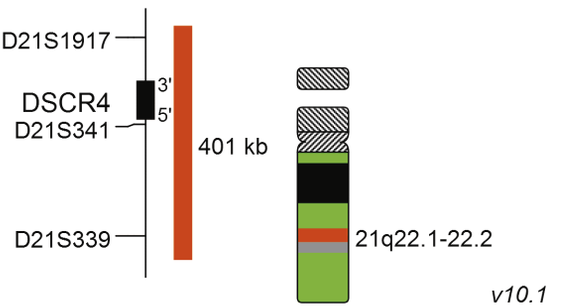
Order No:
D-5441-050-OG

Size: **50 µl**

XL 21q22 / XCP 21 RUO

The XL 21q22/XCP 21 is a combination of a whole chromosome paint 21 in green with an orange labeled locus-specific probe for 21q22. This probe allows analysis of copy numbers and structural aberrations of chromosome 21 on metaphase chromosomes.

Please note that this product is not classified as an IVD product in the EU according to the REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. It is marked as for ´Research Use Only´ (RUO).



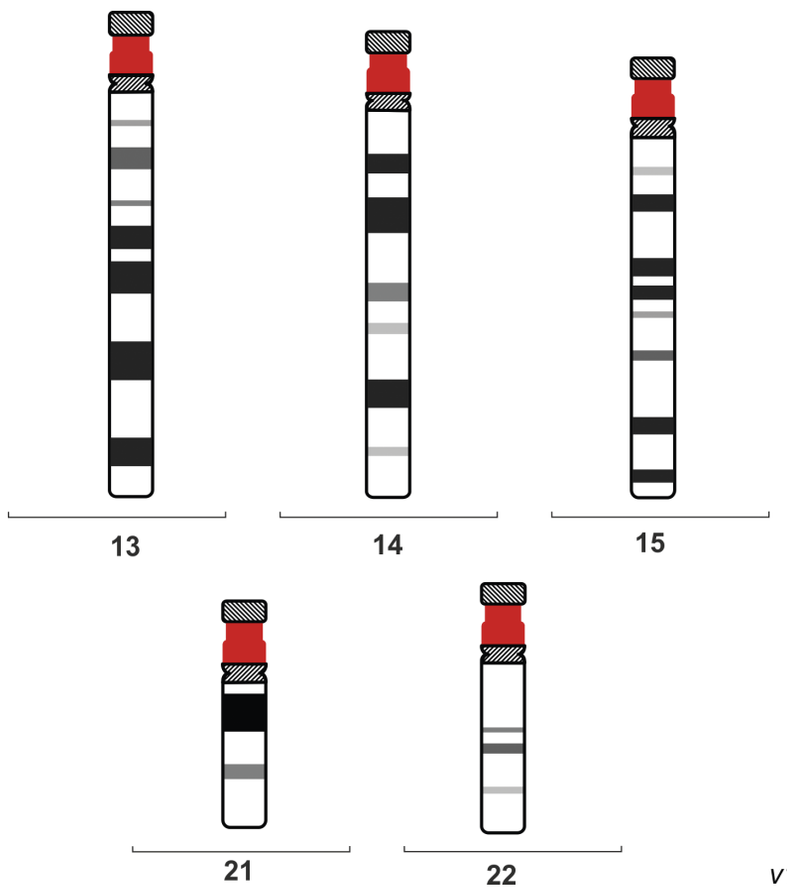
Order No:
D-5440-050-OR

Size: **50 µl**

RUO XL Acro-p

The XL Acro-p probe contains sequences which specifically hybridize to the short (p) arm of all human acrocentric chromosomes. The XL Acro-p FISH probe may replace conventional silver staining used to stain the NOR regions.

Please note that this product is not classified as an IVD product in the EU according to the REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. It is marked as for ´Research Use Only´ (RUO).



v10-a

Notes

Order No:
D-5602-100-OG

Size: **100 µl**

XA 13/21 IVD

The XA 13/21 mix of specific probes allows detecting copy number variations for chromosomes 13 and 21. The green labeled probe hybridizes to a region at 13q14 including the RB1 locus and the orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4).

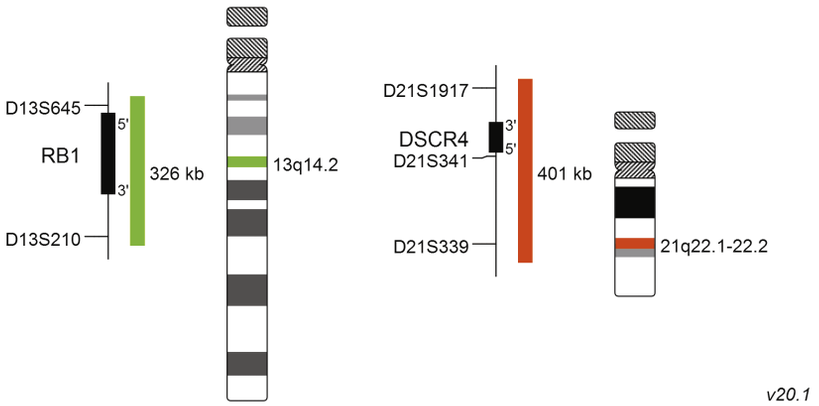
Numerical aberrations of autosomes 13, 18, 21, and sex chromosomes X and Y account for 95% of birth defects in newborns. FISH applied to uncultured amniocytes provides a method to identify those aberrations much faster than conventional chromosome analysis. It has become a standard to provide preliminary results for the detection of anomalies in less than 12 hours.

Duplications of chromosome bands 21q22.13-q22.2 have been shown to define the smallest region implicated in the causation of Down syndrome. Trisomy 13 syndrome is a rare chromosomal disorder in which all or a portion of chromosome 13 appears three times (trisomy). Based on molecular results, a region ranging from 13q14-13qter has been found to be critically involved in Patau syndrome.

Expected Patterns

Normal Cell
Two green (2G), two orange (2O) signals.

Aberrant Cell
Trisomy 13
Three green (3G) and two orange (2O) signals.



v20.1

Aberrant Cell
Trisomy 21
Two green (2G) and three orange (3O) signals.

Literature

- Bryndorf et al (1996) Am J Hum Genet 59:918-926
- Tepperberg et al (2001) Prenat Diagn 21:293-301
- Stumm et al (2006) Cytogenet Genome Res 114:296-301

Order No:
D-5607-100-TC

Size: **100 µl**

IVD XA 13/18/21

The XA 13/18/21 mix of specific probes allows detecting copy number variations of chromosomes 13, 18, and 21. The green labeled probe hybridizes to a region at 13q14 including the RB1 locus, the blue (aqua) labeled probe hybridizes to a locus at 18q21, and the orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4).

Numerical aberrations of autosomes 13, 18, 21, and sex chromosomes X and Y account for 95% of birth defects in newborns. FISH applied to uncultured amniocytes provides a method to identify those aberrations much faster than conventional chromosome analysis. It has become a standard to provide preliminary results for the detection of anomalies in less than 12 hours.

Duplications of chromosome bands 21q22.13-q22.2 have been shown to define the smallest region implicated in the causation of Down syndrome. Trisomy 13 syndrome is a rare chromosomal disorder in which all or a portion of chromosome 13 appears three times (trisomy). Based on molecular results, a region ranging from from 13q14-13qter has been found to be critically involved in Patau syndrome. Most of the features of Edwards syndrome have been shown to be associated with duplication of the region 18q12.3-q22.1. A locus-specific probe for 18q21 gives clearer signals and provides less ambiguous results compared to a centromeric probe for chromosome 18.

Expected Patterns

Normal Cell
Two green (2G), two orange (2O), and two blue (2B) signals.

Aberrant Cell
Trisomy 13
Three green (3G), two orange (2O), and two blue (2B) signals.

Aberrant Cell
Trisomy 21
Two green (2G), three orange (3O), and two blue (2B) signals.

Aberrant Cell
Trisomy 18
Two green (2G), two orange (2O), and three blue (3B) signals.

Literature

- Bryndorf et al (1996) Am J Hum Genet 59:918-926
- Tepperberg et al (2001) Prenat Diagn 21:293-301
- Stumm et al (2006) Cytogenet Genome Res 114:296-301

Order No:
D-5604-100-TC

Size: **2x 100 µl**

XA AneuScore I IVD

The XA AneuScore I Probe Kit contains different probe mix, provided in separate test vials, for assessing chromosomal aneuploidies for chromosomes 13, 18, 21, X, and Y.

XA 13/21 (D-5602-100-OG):

The XA 13/21 mix of specific probes allows detecting copy number variations for chromosomes 13 and 21. The green labeled probe hybridizes to a region at 13q14 including the RB1 locus and the orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4).

XA X/Y/18 (D-5606-100-TC):

The XA X/Y/18 mix of specific probes allows detecting copy number variations for chromosomes X, Y, and 18. The probe mix is composed of repetitive sequences which hybridize to the centromeric region of chromosomes X in green, Y in orange, and 18 in blue (aqua).

Numerical aberrations of autosomes 13, 18, 21, and sex chromosomes X and Y account for 95% of birth defects in newborns. FISH applied to uncultured amniocytes provides a method to identify those aberrations much faster than conventional chromosome analysis. Nowadays, it is widely accepted to provide preliminary results for the detection of anomalies in less than 12 hours.

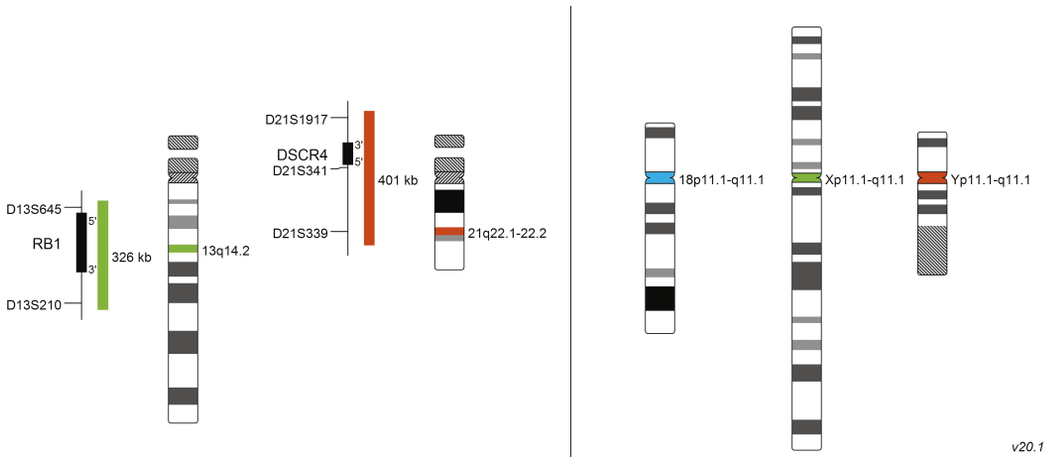
Available in two package sizes:

D-5604-100-TC XA AneuScore I, 10 Tests

D-5604-500-TC XA AneuScore I, 50 Tests

Expected Patterns

For signal patterns please refer to: XA 13/21 (D-5602-100-OG) and XA X/Y/18 (D-5606-100-TC).



Literature

- Bryndorf et al (1996) Am J Hum Genet 59:918-926
- Tepperberg et al (2001) Prenat Diagn 21:293-301
- Stumm et al (2006) Cytogenet Genome Res 114:296-301

Order No:
D-5609-100-TC

Size: **2x 100 µl**

IVD XA AneuScore II

The XA AneuScore II Probe Kit contains different probe mix, provided in separate test vials, for assessing chromosomal aneuploidies for chromosomes 13, 18, 21, X, and Y.

XA 13/18/21 (D-5607-100-TC):

The XA 13/18/21 mix of specific probes allows detecting copy number variations of chromosomes 13, 18, and 21. The green labeled probe hybridizes to a region at 13q14 including the RB1 locus, the blue (aqua) labeled probe hybridizes to a locus at 18q21, and the orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4).

XA X/Y (D-5608-100-OG):

The XA X/Y mix of specific probes allows detecting copy number variations for chromosomes X and Y. The probe mix is composed of repetitive sequences which hybridize to the centromeric region of chromosomes X in green and Y in orange.

Numerical aberrations of autosomes 13, 18, 21, and sex chromosomes X and Y account for 95% of birth defects in newborns. FISH applied to uncultured amniocytes provides a method to identify those aberrations considerably faster than conventional chromosome analysis. Nowadays, it is widely accepted to provide preliminary results for the detection of anomalies in less than 12 hours.

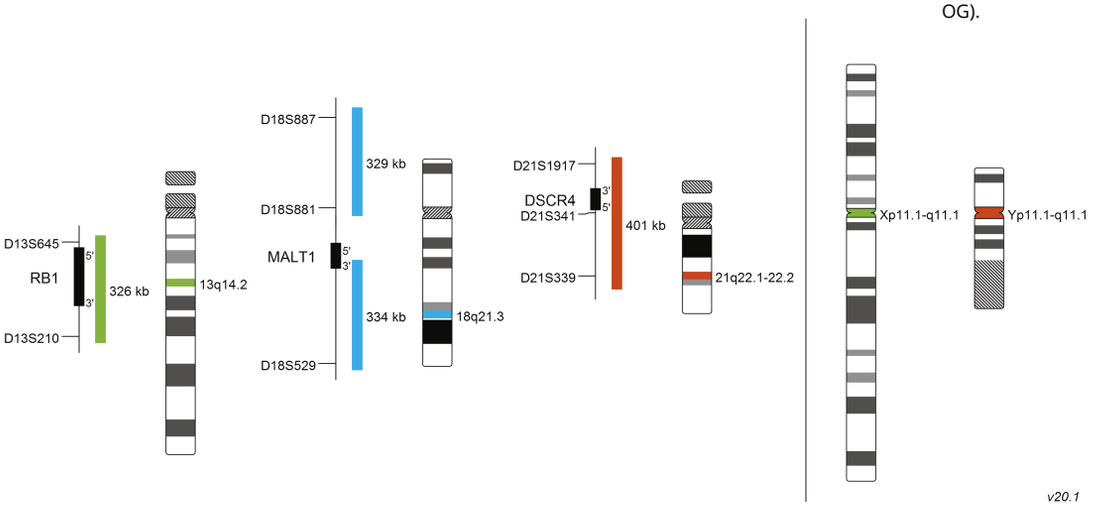
Available in two package sizes:

D-5609-100-TC XA AneuScore II, 10 Tests

D-5609-500-TC XA AneuScore II, 50 Tests

Expected Patterns

For signal patterns please refer to: XA 13/18/21 (D-5607-100-TC) and XA X/Y (D-5608-100-OG).



Literature

- Bryndorf et al (1996) Am J Hum Genet 59:918-926
- Tepperberg et al (2001) Prenat Diagn 21:293-301
- Stumm et al (2006) Cytogenet Genome Res 114:296-301

Order No:
D-5613-100-TC

Size: **2x 100 µl**

XA AneuScore III IVD

The XA AneuScore III Probe Kit contains different probe mixes, provided in separate test vials, for assessing chromosomal aneuploidies for chromosomes 13, 18, 21, X, and Y.

XA 13/18/21 (D-5607-100-TC):

The XA 13/18/21 mix of specific probes allows detecting copy number variations of chromosomes 13, 18, and 21. The green labeled probe hybridizes to a region at 13q14 including the RB1 locus, the blue (aqua) labeled probe hybridizes to a locus at 18q21, and the orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4).

XA X/Y/18 (D-5606-100-TC):

The XA X/Y/18 mix of specific probes allows detecting copy number variations for chromosomes X, Y, and 18. The probe mix is composed of repetitive sequences which hybridize to the centromeric region of chromosomes X in green, Y in orange, and 18 in blue (aqua).

Numerical aberrations of autosomes 13, 18, 21, and sex chromosomes X and Y account for 95% of birth defects in newborns. FISH applied to uncultured amniocytes provides a method to identify those aberrations much faster than conventional chromosome analysis. It has become a standard to provide preliminary results for the detection of anomalies in less than 12 hours.

Duplications of chromosome bands 21q22.13-q22.2 have been shown to define the smallest region implicated in the causation of Down syndrome. Trisomy 13 syndrome is a rare chromosomal disorder in which all or a portion of chromosome 13 appears three times (trisomy). Based on molecular results, a region from 13q14-13qter has been found to be critically involved in Patau syndrome. Most of the features of Edwards syndrome have been shown to be associated with duplication of the region 18q12.3-q22.1. A locus-specific probe for 18q21 gives clearer signals and provides less ambiguous results compared to a centromeric probe for chromosome 18. Repetitive sequences around the centromeric regions of chromosomes X and Y can reliably identify Klinefelter syndrome (47,XXY), Triple-X syndrome (47,XXX), Turner syndrome (45,X0), and 47,XYY.

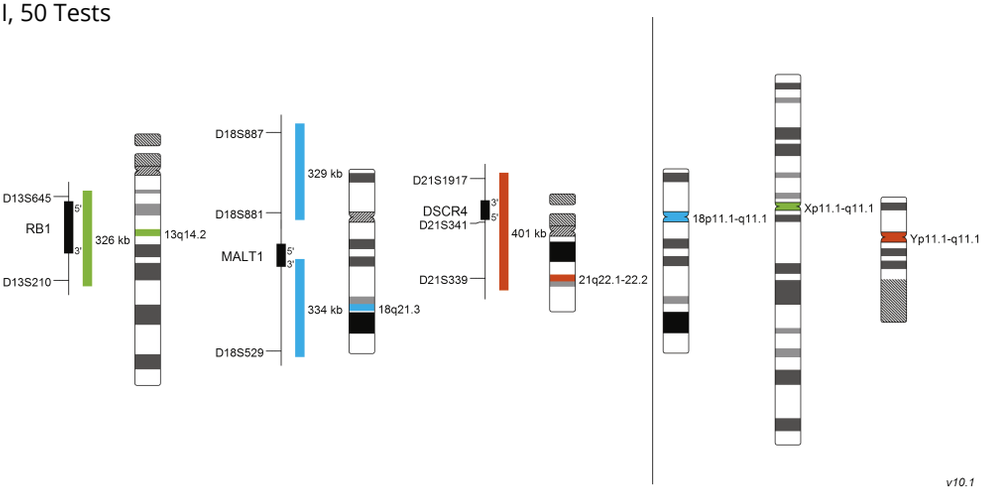
Available in two package sizes:

D-5613-100-TC XA AneuScore III, 10 Tests

D-5613-500-TC XA AneuScore III, 50 Tests

Expected Patterns

For signal patterns please refer to: XA X/Y/18 (D-5606-100-TC) and XA 13/18/21 (D-5607-100-TC).



Literature

- Bryndorf et al (1996) Am J Hum Genet 59:918-926
- Tepperberg et al (2001) Prenat Diagn 21:293-301
- Stumm et al (2006) Cytogenet Genome Res 114:296-301

Order No:
D-5601-100-OR

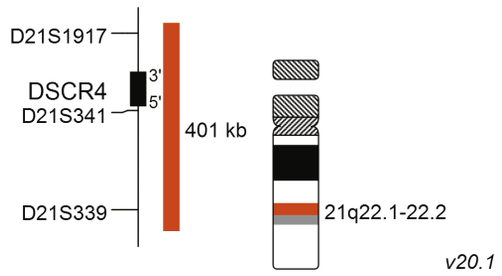
Size: **100 µl**

IVD XA 21q22

The XA 21q22 specific probe allows detecting copy number variations for chromosomes 21. The orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4).

Numerical aberrations of autosomes 13, 18, 21, and sex chromosomes X and Y account for 95% of birth defects in newborns. FISH applied to uncultured amniocytes provides a method to identify those aberrations much faster than conventional chromosome analysis. It has become a standard to provide preliminary results for the detection of anomalies in less than 12 hours.

Duplications of chromosome bands 21q22.13-q22.2 have been shown to define the smallest region implicated in the causation of Down syndrome.



Expected Patterns

Normal Cell
Two orange (2O) signals.

Aberrant Cell
Trisomy 21
Three orange (3O) signals.

Literature

- Tepperberg et al (2001) Prenat Diagn 21:293-301
- Ronan et al (2007) J Med Genet 44:448-451
- Korbel et al (2009) Proc Natl Acad Sci USA 106:12031-12036

Order No:
D-5608-100-OG

Size: **100 µl**

XA X/Y IVD

The XA X/Y mix of specific probes allows detecting copy number variations for chromosomes X and Y. The probe mix is composed of repetitive sequences which hybridize to the centromeric region of chromosomes X in green and Y in orange.

Numerical aberrations of autosomes 13, 18, 21, and sex chromosomes X and Y account for 95% of birth defects in newborns. FISH applied to uncultured amniocytes provides a method to identify those aberrations much faster than conventional chromosome analysis. It has become a standard to provide preliminary results for the detection of anomalies in less than 12 hours.

Repetitive sequences around the centromeric regions of chromosomes X and Y can reliably identify Klinefelter syndrome (47,XXY), Triple-X syndrome (47,XXX), Turner syndrome (45,X0), and 47,XYY.

Expected Patterns

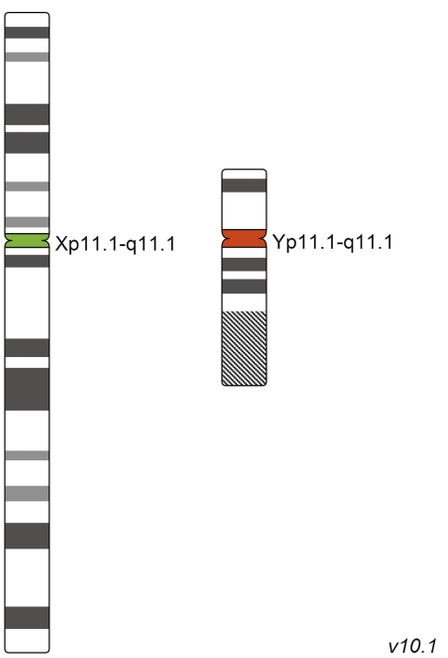
Normal Cell
46,XX
Two green (2G) signals.

Normal Cell
46,XY
One green (1G) and one orange (1O) signal.

Aberrant Cell
45,X0
One green (1G) signal.
Mosaics with 46, XX occur frequently.

Aberrant Cell
47,XXY
Two green (2G) and one orange (1O) signal.
May exist as mosaic with 46, XY or 46, XX.

Aberrant Cell
47,XYY
One green (1G) and two orange (2O) signals.
Additional X-Chromosomes are possible (e.g. 48, XXYY; 52, XXXXXXYY).



Literature

- Bryndorf et al (1996) Am J Hum Genet 59:918-926
- Tepperberg et al (2001) Prenat Diagn 21:293-301
- Stumm et al (2006) Cytogenet Genome Res 114:296-301

Order No:
D-5606-100-TC

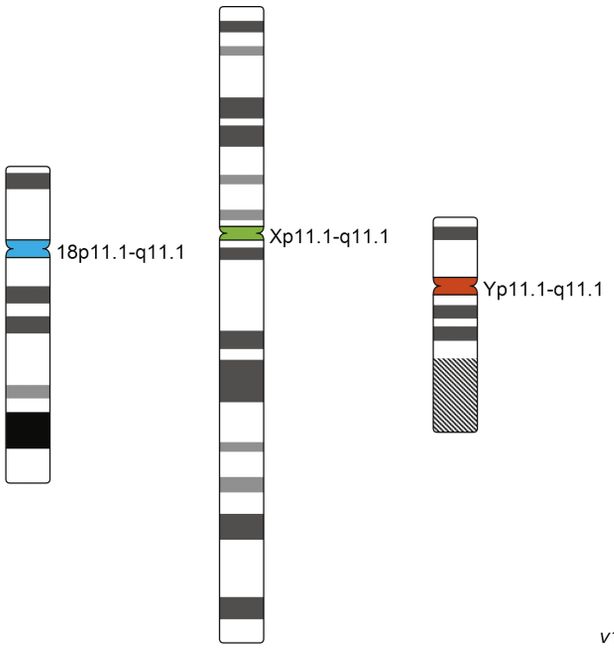
Size: **100 µl**

IVD XA X/Y/18

The XA X/Y/18 mix of specific probes allows detecting copy number variations for chromosomes X, Y, and 18. The probe mix is composed of repetitive sequences which hybridize to the centromeric region of chromosomes X in green, Y in orange, and 18 in blue (aqua).

Numerical aberrations of autosomes 13, 18, 21, and sex chromosomes X and Y account for 95% of birth defects in newborns. FISH applied to uncultured amniocytes provides a method to identify those aberrations much faster than conventional chromosome analysis. It has become a standard to provide preliminary results for the detection of anomalies in less than 12 hours.

Repetitive sequences around the centromeric region of chromosome 18 can reliably determine Edward's syndrome, while chromosome X and Y specifically detect Klinefelter syndrome (47,XXY), Triple-X syndrome (47,XXX), Turner syndrome (45,X0), and 47,XYY.



Expected Patterns

Normal Cell Male:
One green (1G), one orange (1O), and two blue (2B) signals.

Normal Cell Female:
Two green (2G) and two blue (2B) signals.

Aberrant Cell Male:
Trisomy 18
One green (1G), one orange (1O), and three blue (3B) signals.

Aberrant Cell Female:
Trisomy 18
Two green (2G) and three blue (3B) signals.

Aberrant Cell Male:
Klinefelter (47,XXY)
Two green (2G), one orange (1O), and two blue (2B) signals.

Aberrant Cell Female:
Turner (45,X0)
One green (1G) and two blue (2B) signals.

Literature

- Trepperberg et al (2001) Prenat Diagn 21:293-301
- Stumm et al (2006) Cytogenet Genome Res 114:296-301

Order No:
D-5603-100-TC

Size: **100 µl**

XA TriScore (X/Y/21) IVD

The XA TriScore (X/Y/21) mix of specific probes allows detecting copy number variations for chromosomes X, Y, and 21. The probe mix is composed of repetitive sequences which hybridize to the centromeric region of chromosomes X in blue (aqua) and Y in green. The orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4).

Numerical aberrations of autosomes 13, 18, 21, and sex chromosomes X and Y account for 95% of birth defects in newborns. FISH applied to uncultured amniocytes provides a method to identify those aberrations much faster than conventional chromosome analysis. It has become a standard to provide preliminary results for the detection of anomalies in less than 12 hours.

Duplications of chromosome bands 21q22.13-q22.2 have been shown to define the smallest region implicated in the causation of Down syndrome. Repetitive sequences around the centromeric region of the X and Y chromosomes can reliably determine Klinefelter syndrome (47,XXY), Triple-X syndrome (47,XXX), Turner syndrome (45,X0), and 47,XYY. This probe also allows to differentiate male fetal cells from maternal cells in blood contaminated amniocyte samples.

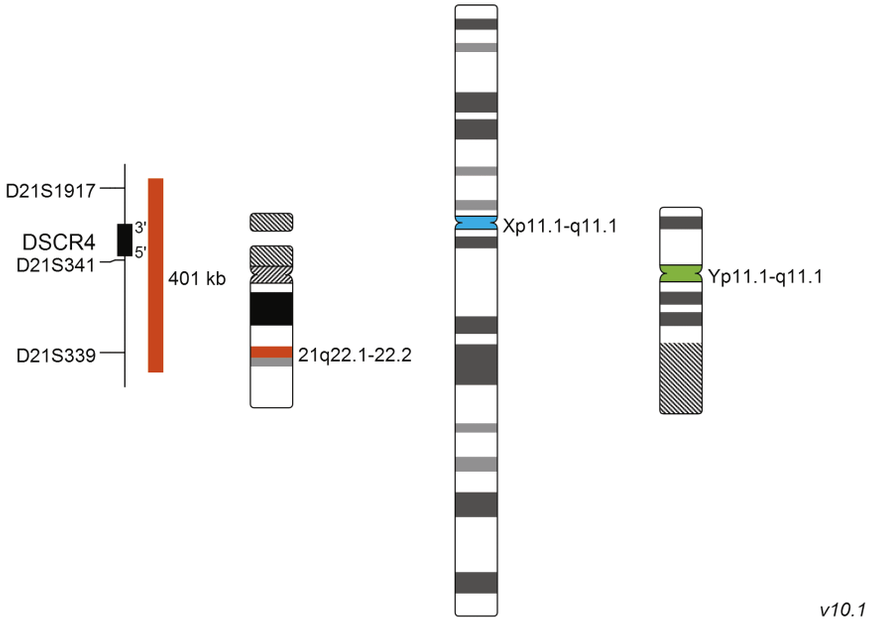
Expected Patterns

Normal Cell Male:
One green (1G), two orange (2O), and one blue (1B) signal.

Normal Cell Female:
No green (0G), two orange (2O), and two blue (2B) signals.

Aberrant Cell Male:
Trisomy 21
One green (1G), three orange (3O), and one blue (1B) signal.

Aberrant Cell Female:
Trisomy 21
No green (0G), three orange (3O), and two blue (2B) signals.



v10.1

Literature

- Bryndorf et al (1996) Am J Hum Genet 59:918-926
- Tepperberg et al (2001) Prenat Diagn 21:293-301
- Stumm et al (2006) Cytogenet Genome Res 114:296-301

AneuScore-Table

Numerical aberrations of autosomes 13, 18, 21, and sex chromosomes X and Y account for 95% of birth defects in newborns. FISH applied to uncultured amniocytes provides a method to identify those aberrations much faster than conventional chromosome analysis. Nowadays, it is widely accepted to provide preliminary results for the detection of anomalies in less than 12 hours.

Product	Order No.	Package Size	Product Details
XA 21q22	D-5601-100-OR	100 µl	The XA 21q22 specific probe allows detecting copy number variations for chromosomes 21. The orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4).
XA 13/21	D-5602-100-OG	100 µl	The XA 13/21 mix of specific probes allows detecting copy number variations for chromosomes 13 and 21. The green labeled probe hybridizes to a region at 13q14 including the RB1 locus and the orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4).
XA X/Y/21 TriScore	D-5603-100-TC	100 µl	The XA TriScore (X/Y/21) mix of specific probes allows detecting copy number variations for chromosomes X, Y, and 21. The probe mix is composed of repetitive sequences which hybridize to the centromeric region of chromosomes X in blue (aqua) and Y in green. The orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4).
XA X/Y/18	D-5606-100-TC	100 µl	The XA X/Y/18 mix of specific probes allows detecting copy number variations for chromosomes X, Y, and 18. The probe mix is composed of repetitive sequences which hybridize to the centromeric region of chromosomes X in green, Y in orange, and 18 in blue (aqua).
XA 13/18/21	D-5607-100-TC	100 µl	The XA 13/18/21 mix of specific probes allows detecting copy number variations of chromosomes 13, 18, and 21. The green labeled probe hybridizes to a region at 13q14 including the RB1 locus, the blue (aqua) labeled probe hybridizes to a locus at 18q21, and the orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4).
XA X/Y	D-5608-100-OG	100 µl	The XA X/Y mix of specific probes allows detecting copy number variations for chromosomes X and Y. The probe mix is composed of repetitive sequences which hybridize to the centromeric region of chromosomes X in green and Y in orange.
XA AneuScore I (XA 13/21 + XA X/Y/18)	D-5604-100-TC D-5604-500-TC	2×100 µl 10×100 µl	The XA AneuScore I Probe Kit contains different probe mix, provided in separate test vials, for assessing chromosomal aneuploidies for Chromosomes 13, 18, 21, X, and Y. XA 13/21 (D-5602-100-OG): The XA 13/21 mix of specific probes allows detecting copy number variations for chromosomes 13 and 21. The green labeled probe hybridizes to a region at 13q14 including the RB1 locus and the orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4). XA X/Y/18 (D-5606-100-TC): The XA X/Y/18 mix of specific probes allows detecting copy number variations for chromosomes X, Y, and 18. The probe mix is composed of repetitive sequences which hybridize to the centromeric region of chromosomes X in green, Y in orange, and 18 in blue (aqua).
XA AneuScore II (XA 13/18/21 + XA X/Y)	D-5609-100-TC D-5609-500-TC	2×100 µl 10×100 µl	The XA AneuScore II Probe Kit contains different probe mix, provided in separate tests vials, for assessing chromosomal aneuploidies for Chromosomes 13, 18, 21, X, and Y. XA 13/18/21 (D-5607-100-TC): The XA 13/18/21 mix of specific probes allows detecting copy number variations of chromosomes 13, 18, and 21. The green labeled probe hybridizes to a region at 13q14 including the RB1 locus, the blue (aqua) labeled probe hybridizes to a locus at 18q21, and the orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4). XA X/Y (D-5608-100-OG): The XA X/Y mix of specific probes allows detecting copy number variations for chromosomes X and Y. The probe mix is composed of repetitive sequences which hybridize to the centromeric region of chromosomes X in green and Y in orange.
XA AneuScore III (XA 13/18/21 + XA X/Y/18)	D-5613-100-TC D-5613-500-TC	2×100 µl 10×100 µl	The XA AneuScore III Probe Kit contains different probe mix, provided in separate tests vials, for assessing chromosomal aneuploidies for chromosomes 13, 18, 21, X, and Y. XA 13/18/21 (D-5607-100-TC): The XA 13/18/21 mix of specific probes allows detecting copy number variations of chromosomes 13, 18, and 21. The green labeled probe hybridizes to a region at 13q14 including the RB1 locus, the blue (aqua) labeled probe hybridizes to a locus at 18q21, and the orange labeled probe hybridizes to a region at 21q22 including the DSCR4 (Down syndrome critical region 4). XA X/Y/18 (D-5606-100-TC): The XA X/Y/18 mix of specific probes allows detecting copy number variations for chromosomes X, Y, and 18. The probe mix is composed of repetitive sequences which hybridize to the centromeric region of chromosomes X in green, Y in orange, and 18 in blue (aqua).

Notes

Order No:
D-5416-050-OG

Size: **50 µl**

XL Wolf-Hirschhorn IVD

XL Wolf-Hirschhorn consists of an orange-labeled probe hybridizing to the NSD2/NELFA gene region at 4p16.3 and a green-labeled probe hybridizing to a region at 4q12.

Wolf-Hirschhorn syndrome (WHS) is a rare genetic disorder characterized by a range of problems including the minimal diagnostic criteria: distinctive facial features (Greek warrior helmet appearance), congenital hypotonia, intellectual disabilities, delayed development and seizures.

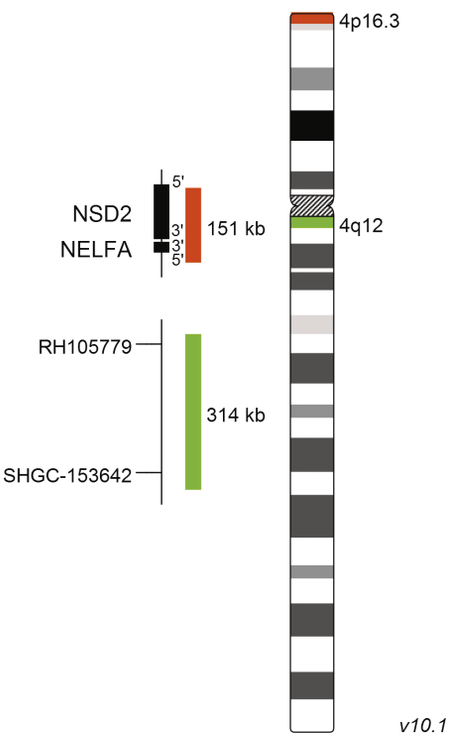
The association of partial 4p16 deletions with WHS was first described by Cooper and Hirschhorn in 1961. Most 4p16 deletions in WHS occur de novo, only in the minority of cases the rearranged chromosome is inherited. WHS is a contiguous gene syndrome associated with haploinsufficiency of several closely linked genes. The severity of clinical manifestation depends on the amount of genetic material affected.

Two WHS critical regions (WHSCR) have been identified. The classical WHSCR1, spanning 165 kb on chromosomal location 4p16.3, includes the genes NSD2 (nuclear receptor binding SET domain protein 2) and NELFA (negative elongation factor complex member A). WHSCR2 was defined based on the identification of patients with atypical forms of WHS, showing no deletion of WHSCR1. WHSCR2 is located distally to WHSCR1 partially including the gene NSD2, but excluding NELFA.

Expected Patterns

Normal Signal Pattern:
Two green (2G) and two orange (2O) signals.

Aberrant Signal Pattern:
Two green (2G) and one orange (1O) signal resulting from loss of one orange signal.



Literature

- Wright et al (1997) Hum Mol Gen 6:317-324
- Zollino (2003) Am J Hum Genet 72:590-597
- Buggenhout (2004) J Med Genet 41:691-698

Order No:
D-5417-050-OG

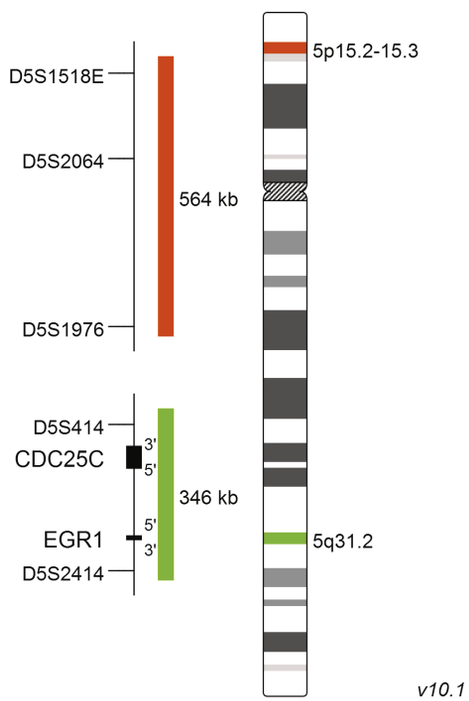
Size: **50 µl**

IVD XL Cri-Du-Chat

XL Cri-Du-Chat consists of an orange-labeled probe hybridizing to a region at 5p15.2-15.3 including the markers D5S1976, D5S2064 and D5S1518E and a green-labeled probe hybridizing to a region at 5q31.2.

Cri-du-Chat syndrome (CdCS), or 5p-minus syndrome, was first described by Lejeune et al in 1963, a French pediatrician and geneticist. The name refers to the main clinical feature of the syndrome, a characteristic cat-like cry in early childhood. The severity of further symptoms as microcephaly, mental retardation, delayed development, craniofacial manifestations, and other anomalies may vary strongly among individuals.

CdCS is a rather frequent microdeletion syndrome with an incidence of about 1:15.000 to 1:50.000 live births. The majority of patients carry a terminal deletion of the short arm of chromosome 5 with breakpoints ranging from 5p13 to 5p15.2 with a size of up to 40Mb. Most 5p deletions occur de novo, probably during spermatogenesis. Breakpoints are not well defined and differ between CdCS cases. Only a few patients have an interstitial deletion, translocations or other less common aberrations. Patient studies established a link between the size of the deleted region and the CdCS phenotype and identified regions 5p15.2 and 5p15.3 responsible for dysmorphism, mental retardation, and the cat-like cry.



Expected Patterns

Normal Signal Pattern:
Two green (2G) and two orange (2O) signals.

Aberrant Signal Pattern:
Two green (2G) and one orange (1O) signal resulting from loss of one orange signal.

Literature

- Lejeune et al (1963) C R Hebd Seances Acad Sci 257:3098-3102
- Mainarid et al (2001) J Med Genet 38:151-158
- Nguyen et al (2015) Am J Med Genet C Semin Med Genet 169c:224-238

Order No:
D-5418-050-OG

Size: **50 µl**

XL Williams-Beuren IVD

XL Williams-Beuren consists of an orange-labeled probe hybridizing to the ELN/LIMK1 gene region at 7q11.23 and a green-labeled probe hybridizing to a region at 7p11.2.

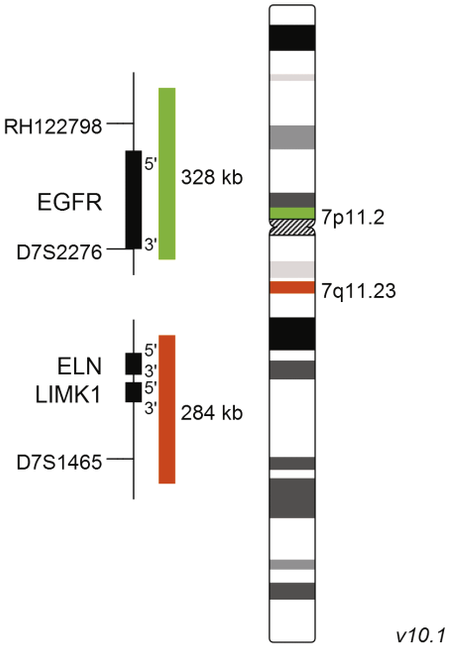
Williams-Beuren syndrome (WBS) is a contiguous gene deletion syndrome with an estimated prevalence of 1:7.500 to 1:25.000 newborns. WBS phenotype is complex, age-dependent and varies between individuals. Newborns have characteristic ´elfin-like´ facial features with full cheeks, small head, flat nasal bridge, broad forehead, prominent open mouth, broad nose and puffiness around eyes and lips. Patients have a wide spectrum of features affecting the cardiovascular system, development and cognition, teeth, endocrine system, gastrointestinal tract, acoustic perception, nose and throat. One of the most fatal and characteristic complications is supravalvular aortic stenosis (SVAS).

WBS is associated with a chromosomal microdeletion in region 7q11.23. The common critical region is about 1.6Mb in size and contains more than 20 genes, including ELN (elastin) and LIMK1 (LIM domain kinase 1). Haploinsufficiency of ELN correlates with cardiovascular problems and is responsible for the SVAS phenotype of WBS patients. Deletions in region 7q11.23 are a consequence of non-allelic homologous recombination between low copy repeat elements flanking the WBS deleted region. Most WBS cases are sporadic, only few cases are transmitted vertically.

Expected Patterns

Normal Signal Pattern:
Two green (2G) and two orange (2O) signals.

Aberrant Signal Pattern:
Two green (2G) and one orange (1O) signal resulting from loss of one orange signal.



Literature

- Wu et al (1998) Am J Med Genet 78:82-89
- Bayés et al (2003) Am J Hum Genet 73:131-151
- Jurado (2003) Horm Res 59 (suppl 1):106-113

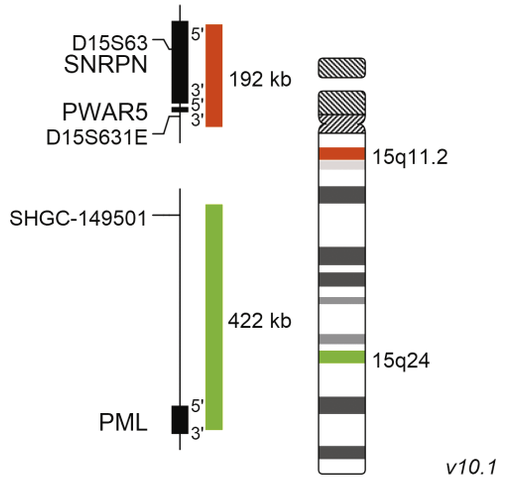
Order No:
D-5421-050-OG

Size: **50 µl**

IVD XL Prader-Willi/Angelman

XL Prader-Willi/Angelman consists of an orange-labeled probe hybridizing to the SNRPN/PWAR5 gene region at 15q11.2 and a green-labeled probe hybridizing to the PML gene region at 15q24.

Prader-Willi syndrome (PWS), first described by Prader, Labhart and Willi in 1956, and Angelman syndrome (AS) initially reported by Angelman in 1963, are complex neurodevelopmental disorders caused by chromosomal deletion of genes in the 15q11-q13 region. In most cases, the corresponding genes are silenced on the sister chromosome via genetic imprinting. The deletion of the paternal segment 15q11-q13 leads to the development of PWS, while patients carrying the maternal deletion of this segment suffer from AS. The clinical manifestation of PWS is characterized by muscular hypotony (´floppy infants´), hypogonadism, developmental and cognitive delays, hyperphagia and obesity. Furthermore, learning disabilities and obsessive-compulsive disorder can be observed. Typical AS indications observed are a small head, severe intellectual disability and developmental retardation. Speaking, sleep, balance and movement problems, as well as seizure disorder are further symptoms. The most common genetic cause for PWS is the deletion of the paternal 15q11-q13 copy. Maternal uniparental disomy of 15q11-q13 (genes are silenced via genetic imprinting) or translocations with breaks in the 15q11-q13 region are further mechanisms leading to PWS. Genes located in this region, especially SNRPN (small nuclear ribonucleoprotein polypeptide N) and NDN (necdin), are considered to be crucial for disease development. The absence of the maternal UBE3A (ubiquitin-protein ligase E3A) gene copy located in this segment is crucial for the development of AS.



Expected Patterns

Normal Signal Pattern:
Two green (2G) and two orange (2O) signals.

Aberrant Signal Pattern:
Two green (2G) and one orange (1O) signal resulting from loss of one orange signal.

Literature

- Clayton-Smith and Pembrey (1992) Med Genet 29:412-415
- Butler (2011) Curr Genomics 12(3):204-215
- Kalsner and Chamberlain (2015) Pediatr Clin North Am 62(3):587-606

Order No:
D-5422-050-OG

Size: **50 µl**

XL Smith-Magenis/ Miller-Dieker

IVD

XL Smith-Magenis/Miller-Dieker consists of a green-labeled probe hybridizing to the RAI1 gene region at 17p11.2 and an orange-labeled probe hybridizing to the PAFAH1B1 gene region at 17p13.

First described in 1982 by Ann C. M. Smith and her colleagues, Smith-Magenis syndrome (SMS) has an estimated prevalence of 1:25.000 newborns. While interstitial deletions in the segment 17p11.2 are the genetic basis of Smith-Magenis syndrome (SMS), deletions of the more distal part 17p13.3 lead to Miller-Dieker syndrome (MDS). SMS is characterized by relatively mild craniofacial and skeletal abnormalities, delay in psycho-motoric development, and specific behavioural disorders. In addition to neuro-behavioural problems, often including self-injurious pattern, SMS patients suffer from a disturbed sleep cycle, as the day and night melatonin secretion cycle is reversed.

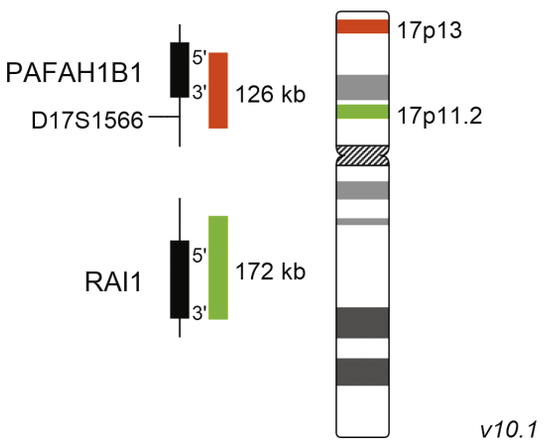
MDS patients show a neuro-developmental and structural disorder of the brain, called lissencephaly. The typical walnut structure of the brain containing fissures and gyri is hardly recognizable. Craniofacial dysmorphism, decreased head circumference, delay in psychomotor development and seizures are further symptoms of this syndrome. The SMS inducing deletions of 17p11.2 have no preferential breakpoints, but most patients analyzed show deletions smaller than 4Mb. The key gene responsible for the manifestation of the clinical symptoms of SMS is RAI1 (retinoic acid induced 1), coding for a transcription factor. One of the crucial genes involved in the development of Miller-Dieker lissencephaly and craniofacial dysmorphism is the PAFAH1B1 gene encoding the regulatory subunit of the platelet activating factor acetylhydrolase 1b.

Expected Patterns

Normal Signal Pattern:
Two green (2G) and two orange (2O) signals.

Aberrant Signal Pattern:
Two green (2G) and one orange (1O) signal resulting from loss of one orange signal.

Aberrant Signal Pattern:
One green (1G) and two orange (2O) signal resulting from loss of one green signal.



Literature

- Elsea (2008) Eur J Hum Genet 16:412-421
- Blazejewski et al (2018) Front Genet 9:8:doi:10.3389/fgene.2018.00080
- Falco et al (2017) Appl Clin Genet 10:85-94

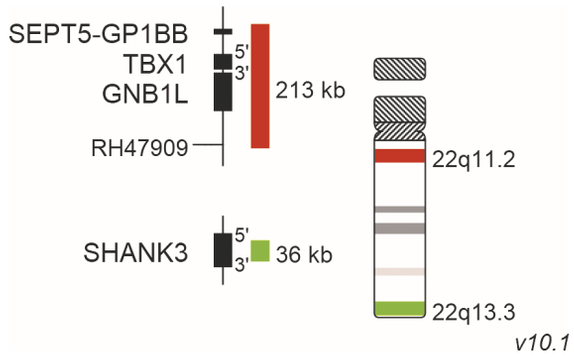
Order No:
D-5415-050-OG

Size: **50 µl**

IVD XL DiGeorge TBX1

XL DiGeorge TBX1 consists of an orange-labeled probe hybridizing to the TBX1 gene region at 22q11.2 and a green-labeled probe hybridizing to the SHANK3 gene region at 22q13.3.

22q11.2 deletion syndrome (22q11.2DS) includes the DiGeorge- and Velo-cardio-facial syndrome and is the most common microdeletion syndrome. The prevalence is estimated to be 1:3.000 to 1:6.000 live births. The features of 22q11.2DS vary widely and may include, but are not limited to, immunodeficiency, hypoparathyroidism, congenital heart disease, cleft palate, developmental disabilities, and schizophrenia. Up to 95% of the deletions identified occur de novo and are not inherited. 22q11.2DS related de novo deletions are mediated by non-allelic inter- and intrachromosomal homologous recombination between low copy number repeats on chromosome 22. A deletion of 3 Mb overlapping about 90 genes is detected in the vast majority of 22q11.2DS cases, whereas a smaller fraction is identified with a nested deletion of about 1.5Mb overlapping with about 55 genes. One of the most thoroughly investigated genes in this region is the T-box transcription factor 1 (TBX1). TBX1 is phylogenetically conserved and has manifold functions during embryonic development. Studies using mouse as a model organism have shown that TBX1 is a key determinant in 22q11.2DS.



Expected Patterns

Normal Signal Pattern:
Two green (2G) and two orange (2O) signals.

Aberrant Signal Pattern:
Two green (2G) and one orange (1O) signal resulting from loss of one orange signal.

Aberrant Signal Pattern:
One green (1G) and two orange (2O) signal resulting from loss of one green signal.

Literature

- Edelmann et al (1999) Am J Hum Genet 64:1076-1086
- Jerome and Papaioannou (2001) Nature Genet 27:286-291
- McDonald-McGinn et al (2015) Nat Rev Dis Primers 1:1-19

Notes

XCE Table IVD RUO

The XCE DNA probes hybridize to human highly repetitive sequences (also called Satellite DNA) located at and around the centromeric region of chromosomes. The XCE probes produce sharp and bright signals allowing for rapid and precise identification and enumeration of human chromosomes in metaphase and interphase cells on various sample types.

XCE probes are provided premixed in hybridization buffer. They are directly labeled with either blue (aqua), green, or orange fluorochromes.

MetaSystems XCE probes are optimized for 1 hour hybridization.

Chromosome	Product	Package Size	Localization	D_Z_	IVD/RUO	Order No. / Label		
						Green	*Orange*	*Blue*
1	XCE 1	50 µl	1q12	D1Z1	RUO	D-0801-050-FI	D-0801-050-OR	-
2	XCE 2	50 µl	2p11.1-q11.1	D2Z2	RUO	D-0802-050-FI	D-0802-050-OR	-
3	XCE 3	50 µl	3p11.1-q11.1	D3Z1	RUO	D-0803-050-FI	D-0803-050-OR	-
4	XCE 4	50 µl	4p11-q11	n.a.[1]	RUO	D-0804-050-FI	D-0804-050-OR	-
5/19	XCE 5/19	50 µl	5p11-q11.1 19p11-q11	D5Z1 D19Z2	RUO	D-0805-050-FI	D-0805-050-OR	-
6	XCE 6	50 µl	6p11.1-q11	D6Z1	RUO	D-0806-050-FI	D-0806-050-OR	D-0806-050-BL
7	XCE 7	50 µl	7p11.1-q11.1	n.a.[1]	RUO	D-0807-050-FI	D-0807-050-OR	D-0807-050-BL
8	XCE 8	50 µl	8p11.1-q11.1	n.a.[1]	IVD	D-0808-050-FI	D-0808-050-OR	D-0808-050-BL
9	XCE 9	50 µl	9p11-q11	D9Z4	RUO	D-0809-050-FI	D-0809-050-OR	-
10	XCE 10	50 µl	10p11.1-q11.1	D10Z1	RUO	D-0810-050-FI	D-0810-050-OR	-
11	XCE 11	50 µl	11p11.11-q11	D11Z1	RUO	D-0811-050-FI	D-0811-050-OR	D-0811-050-BL
12	XCE 12	50 µl	12p11.1-q11	D12Z3	IVD	D-0812-050-FI	D-0812-050-OR	D-0812-050-BL
15	XCE 15	50 µl	15p11.1-q11.1	D15Z4	RUO	D-0815-050-FI	D-0815-050-OR	-
17	XCE 17	50 µl	17p11.1-q11.1	n.a.[1]	RUO	D-0817-050-FI	D-0817-050-OR	-
18	XCE 18	50 µl	18p11.1-q11.1	D18Z1	RUO	D-0818-050-FI	D-0818-050-OR	D-0818-050-BL
20	XCE 20	50 µl	20p11.1-q11.1	D20Z1	RUO	D-0820-050-FI	D-0820-050-OR	-
X	XCE X	50 µl	Xp11.1-q11.1	DXZ1	RUO	D-0823-050-FI	D-0823-050-OR	-
Y	XCE Y	50 µl	Yp11.1-q11.1	DYZ3	RUO	D-0824-050-FI	D-0824-050-OR	D-0824-050-BL

1: No specific data available

Chromosomes	Product	Package Size	IVD/RUO	Order No. / Label	
X/Y	XCE X/Y	50 µl	RUO	D-0825-050-OG	Green / Orange
X/Y	XCE X/Y	4×50 µl	RUO	D-0825-200-OG	Green / Orange
7/8	XCE 7/8	50 µl	RUO	D-0826-050-OG	Orange / Green
3/7/17	XCE 3/7/17	50 µl	RUO	D-0829-050-TC	Orange / Green / Blue
4/10/17	XCE 4/10/17	50 µl	RUO	D-0830-050-TC	Orange / Green / Blue

For centromeric localization details of combined XCE products, see table above.
MetaSystems' XA and relevant XL products contain the same centromeric probes described in the table above.

Order No:
D-0832-050-OG

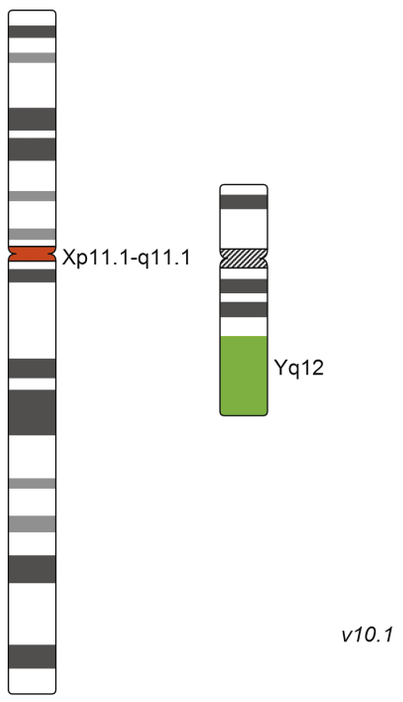
Size: **50 µl**

XCyting Centromere Enumeration Probes **XCE**

RUO **XCE X/Yqh**

The XCE X/Yqh DNA probe contains a mix of repetitive sequences specific for the chromosome X centromeric region in orange and chromosome Yqh in green which is located in the heterochromatic region at Yq12.

Please note that this product is not classified as an IVD product in the EU according to the REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. It is marked as for ´Research Use Only´ (RUO).



Expected Patterns

Normal Cell Female:
46, XX
Two orange (2O) signals.

Normal Cell Male:
46, XY
One green (1G) and one orange (1O) signal.

Aberrant Cell Female:
Turner (45,X0)
One orange (1O) signal.

Aberrant Cell Male:
Klinefelter (47,XXY)
One green (1G) and two orange (2O) signals.

Literature

- Dewald et al (1993) Bone Marrow Trans 12:149-154
- Najfeld et al (1997) Bone Marrow Trans 19:829-834

XCE

XCyting Centromere Enumeration Probes

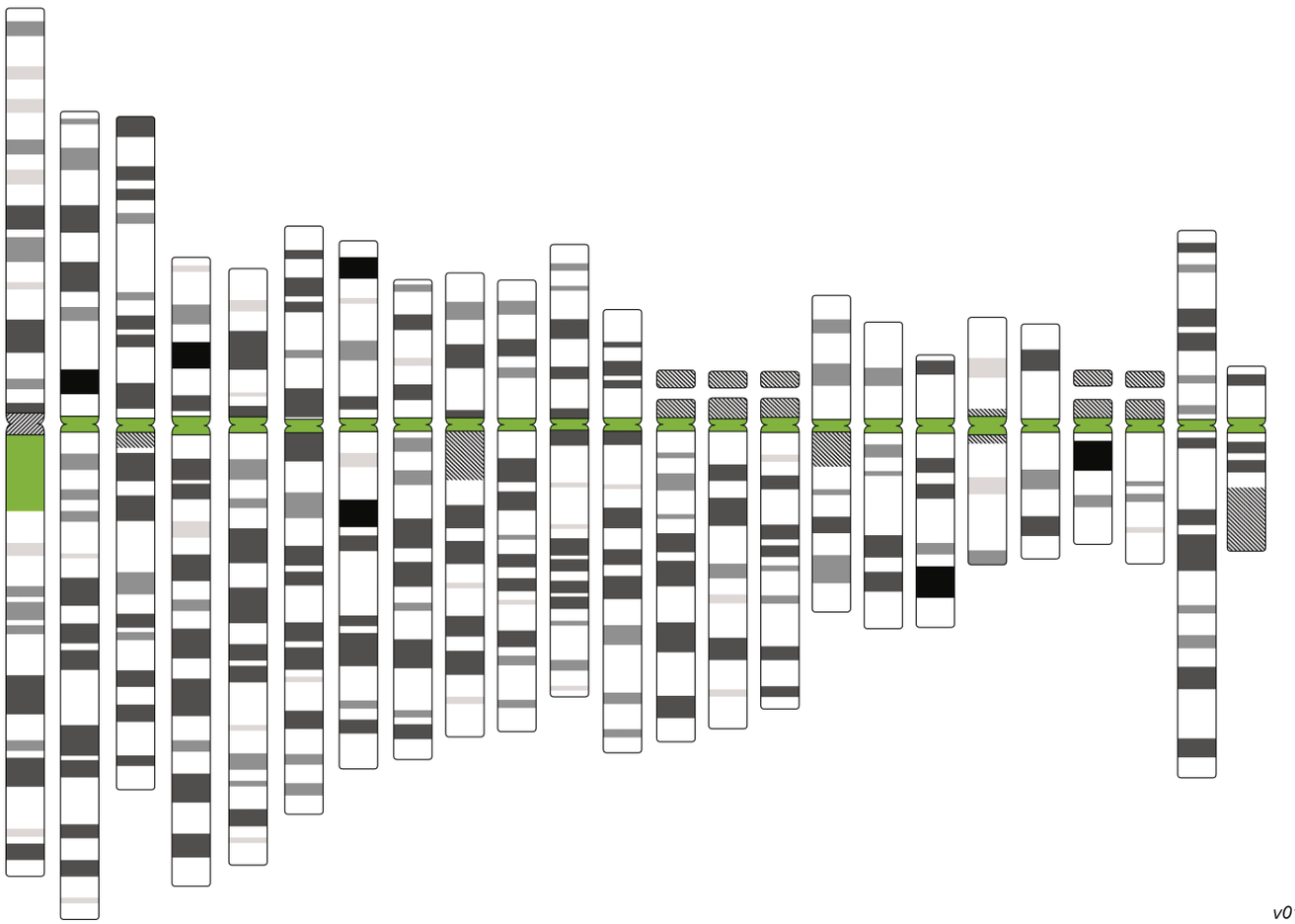
Order No:
D-0836-050-FI

Size: **50 µl**

XCE pan-cen RUO

XCE pan-cen is composed of green labeled repetitive sequences specific for human centromeres except for chromosome 1 which is identified by repetitive sequences specific for the heterochromatic region 1q12. The product is also available labeled in orange (D-0836-050-OR).

Please note that this product is not classified as an IVD product in the EU according to the REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. It is marked as for ´Research Use Only´ (RUO).



v01.1

Literature

- Wojcik et al (2000) Genet Mol Biol 23:1083-1085
- Formian et al (2000) Int J Radiat Biol 76:807-813
- Lindberg et al (2008) Mutagenesis 23:371-376

Notes

Notes

XCP Green Table RUO

XCyting Chromosome Paints are chromosome-specific and cover the entire chromosome. These XCPs are labeled in green.

Chromosomes	Product	Package Size / Order No.			
1	XCP 1 Green	50 µl	D-0301-050-FI	2×50 µl	D-0301-100-FI
2	XCP 2 Green	50 µl	D-0302-050-FI	2×50 µl	D-0302-100-FI
3	XCP 3 Green	50 µl	D-0303-050-FI	2×50 µl	D-0303-100-FI
4	XCP 4 Green	50 µl	D-0304-050-FI	2×50 µl	D-0304-100-FI
5	XCP 5 Green	50 µl	D-0305-050-FI	2×50 µl	D-0305-100-FI
6	XCP 6 Green	50 µl	D-0306-050-FI	2×50 µl	D-0306-100-FI
7	XCP 7 Green	50 µl	D-0307-050-FI	2×50 µl	D-0307-100-FI
8	XCP 8 Green	50 µl	D-0308-050-FI	2×50 µl	D-0308-100-FI
9	XCP 9 Green	50 µl	D-0309-050-FI	2×50 µl	D-0309-100-FI
10	XCP 10 Green	50 µl	D-0310-050-FI	2×50 µl	D-0310-100-FI
11	XCP 11 Green	50 µl	D-0311-050-FI	2×50 µl	D-0311-100-FI
12	XCP 12 Green	50 µl	D-0312-050-FI	2×50 µl	D-0312-100-FI
13	XCP 13 Green	50 µl	D-0313-050-FI	2×50 µl	D-0313-100-FI
14	XCP 14 Green	50 µl	D-0314-050-FI	2×50 µl	D-0314-100-FI
15	XCP 15 Green	50 µl	D-0315-050-FI	2×50 µl	D-0315-100-FI
16	XCP 16 Green	50 µl	D-0316-050-FI	2×50 µl	D-0316-100-FI
17	XCP 17 Green	50 µl	D-0317-050-FI	2×50 µl	D-0317-100-FI
18	XCP 18 Green	50 µl	D-0318-050-FI	2×50 µl	D-0318-100-FI
19	XCP 19 Green	50 µl	D-0319-050-FI	2×50 µl	D-0319-100-FI
20	XCP 20 Green	50 µl	D-0320-050-FI	2×50 µl	D-0320-100-FI
21	XCP 21 Green	50 µl	D-0321-050-FI	2×50 µl	D-0321-100-FI
22	XCP 22 Green	50 µl	D-0322-050-FI	2×50 µl	D-0322-100-FI
X	XCP X Green	50 µl	D-0323-050-FI	2×50 µl	D-0323-100-FI
Y	XCP Y Green	50 µl	D-0324-050-FI	2×50 µl	D-0324-100-FI

Chromosomes	Product	Package Size / Order No.	
1–22, X, Y	Kit with 24 XCPs Green	24×50µl	D-0325-050-FI
1–12	Kit with 12 XCPs Green	12×50µl	D-0326-050-FI
13–22, X, Y	Kit with 12 XCPs Green	12×50µl	D-0327-050-FI

RUO XCP Orange Table

XCyting Chromosome Paints are chromosome-specific and cover the entire chromosome. These XCPs are labeled in orange.

Chromosomes	Product	Package Size / Order No.			
1	XCP 1 Orange	50 µl	D-0301-050-OR	2×50 µl	D-0301-100-OR
2	XCP 2 Orange	50 µl	D-0302-050-OR	2×50 µl	D-0302-100-OR
3	XCP 3 Orange	50 µl	D-0303-050-OR	2×50 µl	D-0303-100-OR
4	XCP 4 Orange	50 µl	D-0304-050-OR	2×50 µl	D-0304-100-OR
5	XCP 5 Orange	50 µl	D-0305-050-OR	2×50 µl	D-0305-100-OR
6	XCP 6 Orange	50 µl	D-0306-050-OR	2×50 µl	D-0306-100-OR
7	XCP 7 Orange	50 µl	D-0307-050-OR	2×50 µl	D-0307-100-OR
8	XCP 8 Orange	50 µl	D-0308-050-OR	2×50 µl	D-0308-100-OR
9	XCP 9 Orange	50 µl	D-0309-050-OR	2×50 µl	D-0309-100-OR
10	XCP 10 Orange	50 µl	D-0310-050-OR	2×50 µl	D-0310-100-OR
11	XCP 11 Orange	50 µl	D-0311-050-OR	2×50 µl	D-0311-100-OR
12	XCP 12 Orange	50 µl	D-0312-050-OR	2×50 µl	D-0312-100-OR
13	XCP 13 Orange	50 µl	D-0313-050-OR	2×50 µl	D-0313-100-OR
14	XCP 14 Orange	50 µl	D-0314-050-OR	2×50 µl	D-0314-100-OR
15	XCP 15 Orange	50 µl	D-0315-050-OR	2×50 µl	D-0315-100-OR
16	XCP 16 Orange	50 µl	D-0316-050-OR	2×50 µl	D-0316-100-OR
17	XCP 17 Orange	50 µl	D-0317-050-OR	2×50 µl	D-0317-100-OR
18	XCP 18 Orange	50 µl	D-0318-050-OR	2×50 µl	D-0318-100-OR
19	XCP 19 Orange	50 µl	D-0319-050-OR	2×50 µl	D-0319-100-OR
20	XCP 20 Orange	50 µl	D-0320-050-OR	2×50 µl	D-0320-100-OR
21	XCP 21 Orange	50 µl	D-0321-050-OR	2×50 µl	D-0321-100-OR
22	XCP 22 Orange	50 µl	D-0322-050-OR	2×50 µl	D-0322-100-OR
X	XCP X Orange	50 µl	D-0323-050-OR	2×50 µl	D-0323-100-OR
Y	XCP Y Orange	50 µl	D-0324-050-OR	2×50 µl	D-0324-100-OR

Chromosomes	Product	Package Size / Order No.	
1-22, X, Y	Kit with 24 XCPs Orange	24×50µl	D-0325-050-OR
1-12	Kit with 12 XCPs Orange	12×50µl	D-0326-050-OR
13-22, X, Y	Kit with 12 XCPs Orange	12×50µl	D-0327-050-OR

XCP

XCyting Chromosome Paints

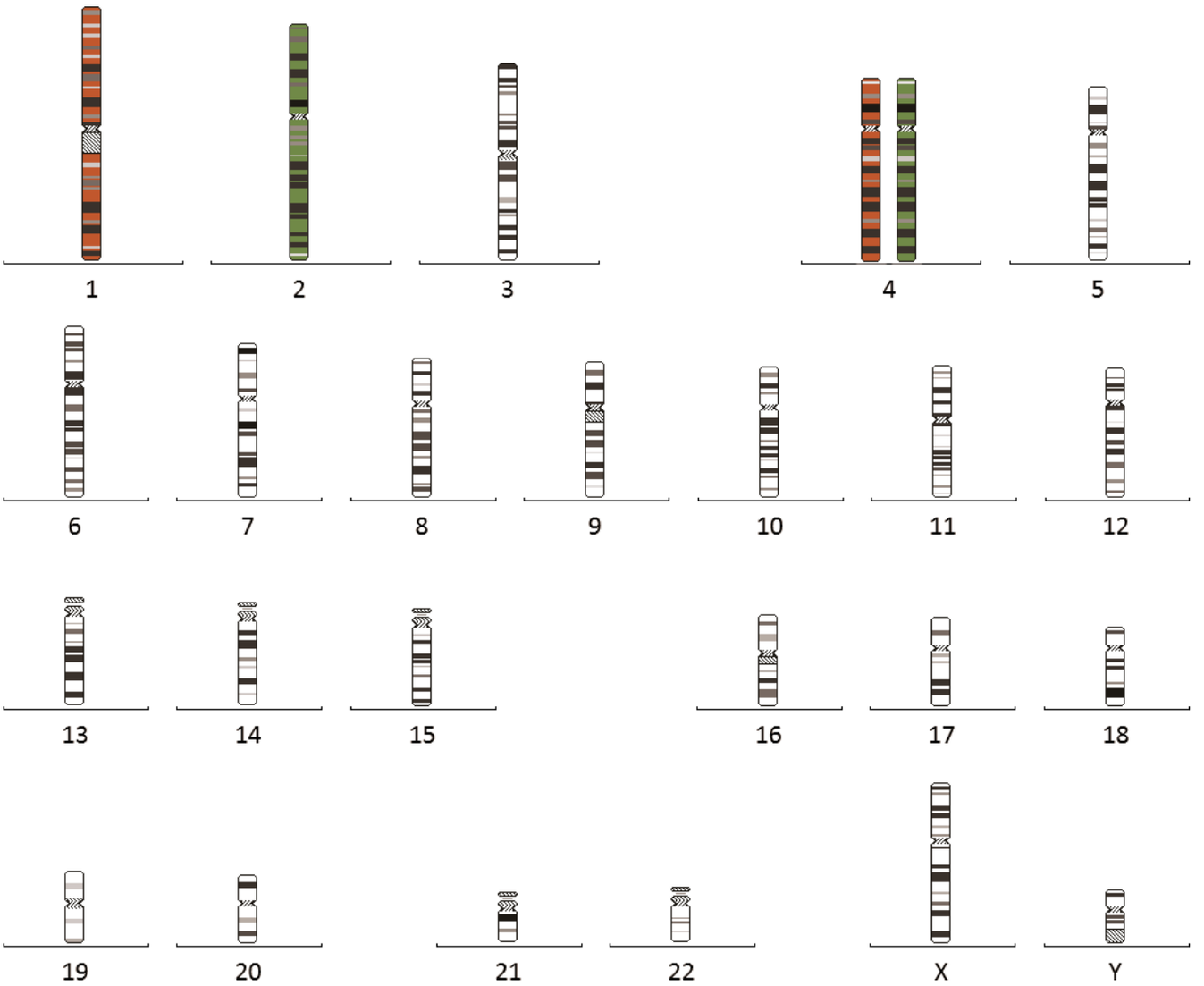
Order No:
D-0328-200-MC

Size: **200 µl**

XCP-Mix #1O-#2G-#4GO RUO

Probe mix containing whole chromosome paints (XCP) specific for chromosome 1 labeled with an orange emitting fluorophore, chromosome 2 with a green emitting fluorophore, and chromosome 4 with a combination of the 2 fluorophores.

Please note that this product is not classified as an IVD product in the EU according to the REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. It is marked as for ´Research Use Only´ (RUO).



Literature

- Terzoudi et al (2006) Radiat Prot Disom 122:513-520
- Pouzoulet et al (2007) J Radiat Res 48:425-434
- Huber et al (2011) Radiat Oncol 6:doi:10.1186/1748-717X-6-32

RUO XCP-Mix Customized

XCyting Chromosome Paints are chromosome-specific and cover the entire chromosome.

Please note that these products are not classified as IVD products in the EU according to the REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. They are marked as for ´Research Use Only´ (RUO).

Product	Available Labels	Note	Package Size	Order No.
XCP-Mix, Customized Green	Green	This probe mix contains 3 green labeled XCPs of your choice. Please specify chromosome classes when ordering.	10×200 µl	D-1100-200-FI
XCP-Mix, Customized Orange	Orange	This probe mix contains 3 orange labeled XCPs of your choice. Please specify chromosome classes when ordering.	10×200 µl	D-1100-200-OR
XCP-Mix, Customized 3 Colors	1st XCP: Green 2nd XCP: Orange 3rd XCP: Green + Orange	This probe mix contains 3 specific XCPs of your choice. Please specify chromosome classes and labels when ordering.	10×200 µl	D-1100-202-MC
XCP-Mix, Customized 5 Colors	1st XCP: Aqua (Blue) 2nd XCP: Green 3rd XCP: Gold/Orange 4th XCP: Orange/Red 5th XCP: Near Infrared (Far Red)	This probe mix contains 5 specific XCPs of your choice. Please specify chromosome classes and labels when ordering.	10×200 µl	D-1100-200-MC

Notes

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Order No:
D-0125-060-DI

Size: **60 µl**

XCyting Multicolor FISH Probes
Human Multicolor FISH Probe

mFISH

RUO 24XCyte

24 painting probes specific for the 24 different human chromosomes, labeled with different fluorochromes. The excitation/ emission spectra are comparable to the common aqua, green, orange, red and near infrared fluorochromes.

Also available as 120µl (2x60µl) D-0125-120-DI and as 600µl (10x60µl) D-0125-600-DI.

The principle of mFISH is based on combinatorial labeling of whole chromosome paints. For each chromosome, the different fluorochromes are mixed resulting in a unique color combination (see labeling scheme). The analysis is carried out after capturing grey scale images of each fluorochrome. For best separation of the different colors the filter sets used need to be highly selective assuring that crosstalk is reduced to a minimum. Multicolor FISH Analysis with MetaSystems' Isis supports the analysis by applying appropriate algorithms which leads to pseudo coloring of the different chromosome classes (color combinations). Each chromosome class will be displayed in a unique color. Translocations show up as color changes on individual chromosomes.

Please note that this product is not classified as an IVD product in the EU according to the REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. It is marked as for ´Research Use Only´ (RUO).

Literature

- Speicher MR et al (1996) Nat Genet 12:368-375
- Fauth C and Speicher MR (2001) Cytogenet Cell Genet 93:1-10
- Schoch C et al (2002) Genes Chromosomes Cancer 35:20-29

Notes

Notes

RUO XCyte mBAND Table

The mBAND technique is based on a series of partial chromosome paints for sequential partially overlapping chromosome regions of a single chromosome. For labeling the same 5 fluorochromes as in the 24XCyte probe are used. The characteristic multicolor banding pattern of mBAND is generated by quantifying the fluorescence intensity ratios along the chromosome. These ratios are unique and visualized as band-specific pseudo colors. mBAND provides information that allows for a precise analysis of even highly complex inter- and intrachromosomal aberrations.

Please note that this product is not classified as an IVD product in the EU according to the REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. It is marked as for ´Research Use Only´ (RUO).

Chromosome	Product	Package Size / Order No.					
1	XCyte 1	30 µl	D-0201-030-DI	2×30 µl	D-0201-060-DI	4×30 µl	D-0201-120-DI
2	XCyte 2	30 µl	D-0202-030-DI	2×30 µl	D-0202-060-DI	4×30 µl	D-0202-120-DI
3	XCyte 3	30 µl	D-0203-030-DI	2×30 µl	D-0203-060-DI	4×30 µl	D-0203-120-DI
4	XCyte 4	30 µl	D-0204-030-DI	2×30 µl	D-0204-060-DI	4×30 µl	D-0204-120-DI
5	XCyte 5	30 µl	D-0205-030-DI	2×30 µl	D-0205-060-DI	4×30 µl	D-0205-120-DI
6	XCyte 6	30 µl	D-0206-030-DI	2×30 µl	D-0206-060-DI	4×30 µl	D-0206-120-DI
7	XCyte 7	30 µl	D-0207-030-DI	2×30 µl	D-0207-060-DI	4×30 µl	D-0207-120-DI
8	XCyte 8	30 µl	D-0208-030-DI	2×30 µl	D-0208-060-DI	4×30 µl	D-0208-120-DI
9	XCyte 9	30 µl	D-0209-030-DI	2×30 µl	D-0209-060-DI	4×30 µl	D-0209-120-DI
10	XCyte10	30 µl	D-0210-030-DI	2×30 µl	D-0210-060-DI	4×30 µl	D-0210-120-DI
11	XCyte 11	30 µl	D-0211-030-DI	2×30 µl	D-0211-060-DI	4×30 µl	D-0211-120-DI
12	XCyte 12	30 µl	D-0212-030-DI	2×30 µl	D-0212-060-DI	4×30 µl	D-0212-120-DI
13	XCyte 13	30 µl	D-0213-030-DI	2×30 µl	D-0213-060-DI	4×30 µl	D-0213-120-DI
14	XCyte 14	30 µl	D-0214-030-DI	2×30 µl	D-0214-060-DI	4×30 µl	D-0214-120-DI
15	XCyte 15	30 µl	D-0215-030-DI	2×30 µl	D-0215-060-DI	4×30 µl	D-0215-120-DI
16	XCyte 16	30 µl	D-0216-030-DI	2×30 µl	D-0216-060-DI	4×30 µl	D-0216-120-DI
17	XCyte 17	30 µl	D-0217-030-DI	2×30 µl	D-0217-060-DI	4×30 µl	D-0217-120-DI
18	XCyte 18	30 µl	D-0218-030-DI	2×30 µl	D-0218-060-DI	4×30 µl	D-0218-120-DI
19	XCyte 19	30 µl	D-0219-030-DI	2×30 µl	D-0219-060-DI	4×30 µl	D-0219-120-DI
20	XCyte 20	30 µl	D-0220-030-DI	2×30 µl	D-0220-060-DI	4×30 µl	D-0220-120-DI
21	XCyte 21	30 µl	D-0221-030-DI	2×30 µl	D-0221-060-DI	4×30 µl	D-0221-120-DI
22	XCyte 22	30 µl	D-0222-030-DI	2×30 µl	D-0222-060-DI	4×30 µl	D-0222-120-DI
X	XCyte X	30 µl	D-0223-030-DI	2×30 µl	D-0223-060-DI	4×30 µl	D-0223-120-DI
Y	XCyte Y	30 µl	D-0224-030-DI	2×30 µl	D-0224-060-DI	4×30 µl	D-0224-120-DI

Literature

- Chudoba I et al (1999) Cytogenet Cell Genet 84:156-160
- Johannes C et al (1999) Chromosome Res 7:625-633
- MacKinnon RN and Campbell LJ (2005) Cancer Genet Cytogenet 163:176-179

Notes

XMP Table RUO

XMP are chromosome-specific and comprise mouse whole chromosome painting probes which are directly labeled with a green or orange emitting fluorochrome, respectively.

Mouse Chromosome	Product	Package Size	Order No. / Label	
			Green	*Orange*
1	XMP 1	50 µl	D-1401-050-FI	D-1401-050-OR
2	XMP 2	50 µl	D-1402-050-FI	D-1402-050-OR
3	XMP 3	50 µl	D-1403-050-FI	D-1403-050-OR
4	XMP 4	50 µl	D-1404-050-FI	D-1404-050-OR
5	XMP 5	50 µl	D-1405-050-FI	D-1405-050-OR
6	XMP 6	50 µl	D-1406-050-FI	D-1406-050-OR
7	XMP 7	50 µl	D-1407-050-FI	D-1407-050-OR
8	XMP 8	50 µl	D-1408-050-FI	D-1408-050-OR
9	XMP 9	50 µl	D-1409-050-FI	D-1409-050-OR
10	XMP 10	50 µl	D-1410-050-FI	D-1410-050-OR
11	XMP 11	50 µl	D-1411-050-FI	D-1411-050-OR
12	XMP 12	50 µl	D-1412-050-FI	D-1412-050-OR
13	XMP 13	50 µl	D-1413-050-FI	D-1413-050-OR
14	XMP 14	50 µl	D-1414-050-FI	D-1414-050-OR
15	XMP 15	50 µl	D-1415-050-FI	D-1415-050-OR
16	XMP 16	50 µl	D-1416-050-FI	D-1416-050-OR
17	XMP 17	50 µl	D-1417-050-FI	D-1417-050-OR
18	XMP 18	50 µl	D-1418-050-FI	D-1418-050-OR
19	XMP 19	50 µl	D-1419-050-FI	D-1419-050-OR
X	XMP X	50 µl	D-1420-050-FI	D-1420-050-OR
Y	XMP Y	50 µl	D-1421-050-FI	D-1421-050-OR

RUO XRP Table

XRP are chromosome-specific and comprise rat whole chromosome painting probes which are directly labeled with a green or orange emitting fluorochrome, respectively.

Rat Chromosome	Product	Package Size	Order No. / Label	
			Green	*Orange*
1	XRP 1	50 µl	please inquire	
2	XRP 2	50 µl	please inquire	
3	XRP 3	50 µl	please inquire	
4	XRP 4	50 µl	please inquire	
5	XRP 5	50 µl	please inquire	
6	XRP 6	50 µl	please inquire	
7	XRP 7	50 µl	please inquire	
8	XRP 8	50 µl	please inquire	
9	XRP 9	50 µl	please inquire	
10	XRP 10	50 µl	please inquire	
12	XRP 12	50 µl	please inquire	
13	XRP 13	50 µl	please inquire	
16	XRP 16	50 µl	please inquire	
17	XRP 17	50 µl	please inquire	
18	XRP 18	50 µl	please inquire	
19	XRP 19	50 µl	please inquire	
20	XRP 20	50 µl	please inquire	
X	XRP X	50 µl	D-1521-050-FI	D-1521-050-OR
Y	XRP Y	50 µl	D-1522-050-FI	D-1522-050-OR

mFISH-Non-Human RUO

mFISH probes are comprised of whole chromosome painting probes which are labeled with a total of five fluorochromes. The combinations of the fluorochromes for the different chromosomal paints result in an individual color signature for each chromosome class. The excitation/emission spectra are comparable to the common aqua, green, orange, red and near infrared fluorochromes.

Beside the human mFISH probes, MetaSystems offers additional specific mFISH probes for three different species: Mouse, Rat, and Chinese Hamster.

Probe Kit Family	Product	Package Size / Order No.			
Multicolor FISH Probe Kit for Mouse Chromosomes	21XMouse	60 µl	D-0425-060-DI	2×60 µl	D-0425-120-DI
Multicolor FISH Probe Kit for Rat Chromosomes	22XRat*	60 µl	D-1525-060-DI	2×60 µl	D-1525-120-DI
Multicolor FISH Probe Kit for Chinese Hamster Chromosomes	12XCHamster	60 µl	D-1526-060-DI	–	–

*Chromosomes 13 and 14 show an identical labeling scheme and are not distinguishable with 22XRat.

Notes

Notes

Order No:
R-0101-020-OR

Size: **200 µl**

XRNA SARS-CoV-2, orange RUO

The XRNA SARS-CoV-2 probe kit comprises 96 oligos detecting the spike glycoprotein mRNA of SARS-CoV-2 and a portion of the viral ORF1 mRNA. We are using the proprietary HuluFISH enzymatic multi fluorophore labeling technique enabling the detection of RNA at the single-cell, single-molecule level in cell and tissue samples. The probe kit is labeled in orange (Atto565).

For Research Use Only (RUO). Not for diagnostic procedures.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel human-pathogenic coronavirus causing coronavirus disease 2019 (COVID-19), was first reported in December 2019. The virus spread quickly, leading to the global COVID-19 pandemic. SARS-CoV-2 primarily causes respiratory infections but is also known to affect other organ systems. While most patients show mild clinical symptoms, severe COVID-19 is characterized by viral pneumonia and acute respiratory distress syndrome. In addition to respiratory symptoms, systemic inflammation and cytokine storm can lead to multiorgan failure and death.

Coronavirus particles consist of four structural proteins called spike (S), envelope (E), membrane (M) and nucleocapsid (N) protein. The SARS-CoV-2 genome is approximately 30kb in size and consists of a positive-sense, single-stranded RNA. It functions not only as viral genome but also as mRNA. The genome contains 10 open reading frames (ORFs) which encode 24-27 genes.

A well-studied cell entry mechanism of SARS-CoV-2 is mediated by the viral S protein, which uses angiotensin-converting-enzyme (ACE2) on the surface of host cells as an attachment receptor. After viral attachment, the S protein is cleaved by the host transmembrane serine protease TMPRSS2 leading to membrane fusion and the release of the viral genome into the cytoplasm. The first viral proteins translated are the polyproteins pp1a and pp1ab which are then cleaved into non-structural proteins by viral proteases. One of them is the RNA-dependent RNA polymerase (RdRP), which replicates the viral genome. After replication, the viral RNA and N proteins are assembled into nucleocapsids within the cytoplasm. Budding of new particles takes place at the membrane of the endoplasmic reticulum–Golgi intermediate compartment. Finally, the new viral particles are assembled and released via exocytosis.

The viral replication machinery uses the genomic positive-sense RNA as a template to synthesize a negative-sense antigenomic RNA. This negative-sense RNA then serves as a matrix for genomic RNA synthesis. Therefore, the presence of minus-strand RNA indicates viral RNA replication. RNA in situ hybridization and multiplex FISH analysis have shown differential distribution of the positive- and negative strand RNA within the cell. The positive-sense RNA showed distribution in the cytoplasm, while the negative-sense RNA was detected in perinuclear inclusion bodies, corresponding to the localization of the viral RNA replicase-transcriptase complex.

XRNA SARS-CoV-2 opens up manyfold possibilities for COVID-19 research:

Semi-quantitative virus identification on a cellular level, application in pre-clinical studies for vaccines and therapeutics and analysis of cell-, tissue-, and organ-tropism are some examples of the possible applications. And the list goes on: analysis of the cell response to infection, analysis of sub-cellular RNA distribution, analysis of the end of infectivity and more!

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Literature

- Nishiga et al (2020) Nat Rev Cardiol 17:543-558
- Liu et al (2020) JCI Insight 5:e139042
- Khailany et al (2020) Gene Rep 19:100682

Order No:
R-0201-020-FI

Size: **200 µl**

XCyting RNA Probes
Human RNA FISH **XRNA**

RUO XRNA ACE2, green

The XRNA ACE2 probe kit comprises 96 oligos detecting the human ACE2 mRNA. We are using the proprietary HuluFISH enzymatic multi fluorophore labeling technique enabling the detection of RNA at the single-cell, single-molecule level in cell and tissue samples. The probe kit is labeled in green (Atto488).

For Research Use Only (RUO). Not for diagnostic procedures.

Novel coronavirus SARS-CoV-2 primarily causes severe respiratory infections which can progress to diverse clinical manifestations affecting multiple organs. The broad tissue tropism of the virus is attributed to the cell entry mechanism employed by SARS-CoV-2:

The viral spike (S) protein binds to the cellular angiotensin-converting enzyme 2 (ACE2) receptor facilitating attachment of the virus to the host cell. In a second step, the viral S protein is primed by the cellular transmembrane serine protease TMPRSS2, enabling membrane fusion and thereby cell entry. Both ACE2 and TMPRSS2 are pleiotropically expressed, including but not limited to the lung, gastrointestinal tissue, testes, and kidneys. There is histological evidence of SARS-CoV-2 infecting respiratory- and non-respiratory organs such as the heart, brain, liver, and kidneys. Endothelial cells, which are an essential component of every organ system, show a high level of ACE2 expression. ACE2 is known to play an important regulatory role in the immune- and cardiovascular system and was shown to be involved in the development of hypertension, heart failure and diabetes.

SARS-CoV, the coronavirus responsible for the SARS outbreak in 2002, utilizes the same cell entry mechanism as SARS-CoV-2. Studies have shown that SARS-CoV entry into the cell is followed by downregulation of ACE2, a mechanism which is now being suspected to apply to SARS-CoV-2 as well. Given the cardio- and lung-protective role of ACE2, this could be a cause of cardiac dysfunction and exacerbated lung damage in COVID-19 patients. Within the cell, ACE2 is part of the renin-angiotensin-aldosterone system and inactivates angiotensin II by converting it to angiotensin (1-7).

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Literature

- Nishiga et al (2020) Nature Reviews Cardiology 17:543–558
- Baughn et al (2020) Mayo Clin Proc 95:1989–1999
- Hoffmann et al (2020) Cell 181:271–280

Order No:
R-0202-020-BL

Size: **200 µl**

XRNA TMPRSS2, aqua RUO

The XRNA TMPRSS2 probe kit comprises 96 oligos detecting the human TMPRSS2 mRNA. We are using the proprietary HuluFISH enzymatic multi fluorophore labeling technique enabling the detection of RNA at the single-cell, single-molecule level in cell and tissue samples. The probe kit is labeled in aqua (Atto425).

For Research Use Only (RUO). Not for diagnostic procedures.

Novel coronavirus SARS-CoV-2 causes severe respiratory infections which can progress to diverse clinical manifestations. The pleiotropic effects of SARS-CoV-2 infection are partly attributed to the two-step cell entry mechanism utilized by SARS-CoV-2, which is equal to the mechanism used by the related coronavirus SARS-CoV in its main features:

Binding of the viral spike (S) protein to the cellular angiotensin-converting enzyme 2 (ACE2) receptor facilitates attachment of the virus to the host cell. The cellular transmembrane protease serine 2 (TMPRSS2) then primes the viral S protein for entry, by cleavage of the S protein at the S1/S2 and S2 sites. S protein priming by TMPRSS2 is necessary for fusion of viral and cellular membranes, and therefore cell entry. Hence, TMPRSS2 activity is essential for viral spread and pathogenesis in the infected host. This makes TMPRSS2 expression and activity interesting candidates for targeted COVID-19 therapies. Inhibition of TMPRSS2 with a clinically proven inhibitor was already shown to be efficient against SARS-CoV-2 host cell entry in vitro.

Both ACE2 and TMPRSS2 are pleiotropically expressed, including but not limited to the lungs, gastrointestinal tract, testes, kidneys and skin. In a study analysing the tissue- and gender-specific expression level of TMPRSS2, it was found that the highest TMPRSS2 expression is located in the prostate. TMPRSS2 is a member of the type II transmembrane protease family and is positively regulated by androgen signalling. TMPRSS2 expression previously gained interest in cancer research, as it shows high expression in prostate cancers, as well as subcellular protein mislocalization in advanced prostate cancer and is associated with tumor cell differentiation.

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Literature

- Baughn et al (2020) Mayo Clin Proc 95:1989–1999
- Lucas et al (2008) J Pathol 215:118–125
- Hoffmann et al (2020) Cell 181:271–280

Order No:
R-0203-020-FI

Size: **200 µl**

RUO XRNA PD-L1, green

The XRNA PD-L1 probe kit comprises 96 oligos detecting the human PD-L1 mRNA. We are using the proprietary HuluFISH enzymatic multi fluorophore labeling technique enabling the detection of RNA at the single-cell, single-molecule level in cell and tissue samples. The probe kit is labeled in green (Atto488).

For Research Use Only (RUO). Not for diagnostic procedures.

Programmed death ligand 1 (PD-L1) is the main ligand of the programmed cell death 1 (PD-1) receptor. PD-1 functions as coinhibitory receptor which can be constitutively expressed or induced on myeloid, lymphoid, normal epithelial and cancer cells. PD-L1 is encoded by the PDCDL1 gene located on chromosome 9p24.1. The resulting type I transmembrane protein is known to be constitutively expressed at low levels on resting lymphocytes and antigen-presenting cells, but also other cell types such as Langerhans' islet cells, where it plays a part in tissue homeostasis in proinflammatory response. Furthermore, the 'immune privileged' status of tissues such as testis, placenta and the anterior chamber of the eye is mediated by PD-L1, which prevents induction of the inflammatory response after exposure to exogenous antigens. In the course of infection and/or inflammation, PD-L1 plays a key role as suppressive signal on haematopoietic, epithelial, and endothelial cells. The expression of PD-L1 is influenced by multiple signalling pathways including toll-like receptor and IFN-γ receptor 1 and 2 mediated signal transduction.

In carcinogenesis, multiple oncogenic mechanisms lead to elevated PD-L1 expression levels via different dysregulated signalling pathways, causing the gain of an immune evasion mechanism in cancer cells. As a result, various types of cancer cells, including non-small cell lung cancer cells, show elevated PD-L1 levels on their surface. PD-1/PD-L1 is considered as an immune checkpoint, which can inhibit immune surveillance and promote tumor growth under oncogenic pathological conditions. Modern immunotherapy methods (immune checkpoint inhibitors) use monoclonal antibodies targeting PD-1 or PD-L1 to reestablish the anti-tumor immune response and suppress tumor growth. Meanwhile, several PD-1/PD-L1 immune checkpoint inhibitors have been approved or are currently being evaluated in clinical studies, as PD-L1 is a well-established immune-based biomarker in carcinogenesis.

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Literature

- Kythreotou et al (2018) Clin Pathol 71:189-194
- Pawelczyk et al (2019) J Mol Sci 20:824
- Davis and Patel (2019) J. Immunotherapy Cancer 7:278

Order No:
R-0204-020-IR

Size: **200 µl**

XRNA PGK1, near infrared RUO

The XRNA PGK1 probe kit comprises 96 oligos detecting the human PGK1 mRNA. We are using the proprietary HuluFISH enzymatic multi fluorophore labeling technique enabling the detection of RNA at the single-cell, single-molecule level in cell and tissue samples. The probe kit is labeled in near infrared (Atto647N).

For Research Use Only (RUO). Not for diagnostic procedures.

Phosphoglycerate kinase 1 (PGK1) is encoded by the X-chromosomal PGK1 gene and is ubiquitously expressed. The resulting polypeptide is a central enzyme of aerobic glycolysis and essential for the formation of adenosine triphosphate (ATP), which is referred to as the molecular unit of intracellular energy currency. Countless metabolic processes and enzymatic reactions are linked to the hydrolysis of ATP. PGK1 catalyzes the reversible formation of 3-phosphoglycerate and ATP by transferring a phosphate group from 1,3-bisphosphoglycerate to adenosine diphosphate (ADP). On top of maintaining cell metabolism, PGK1 has additional functions, depending also on its localization within the cell.

PGK1 is a commonly used housekeeping gene utilized in gene expression analyses, for example in real-time reverse transcription PCR assays. Housekeeping genes are used to normalize expression values of analyzed genes in gene expression assays. However, it has become clear that the expression levels of housekeeping genes can show considerable variation, depending on the experimental conditions and analyzed tissue. PGK1 has been shown to be a stably expressed housekeeping gene for performing expression studies of leukocytes.

Powered by HuluFISH technology from PixelBiotech

Literature

- Fu and Yu (2020) Life Sci 256:117863
- Vega-Sanchez et al (2015) Placenta 36:240-245
- Abruzzo et al (2005) Biotechniques 38:785-792

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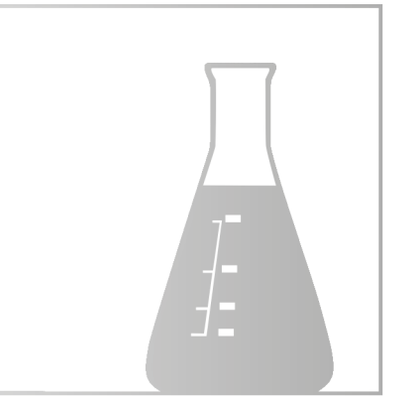
General Reagents



General Reagents

DAPI/Antifade

Order No:
D-0902-500-DA

Size: **500 µl**

Chromosome counterstain in a buffer containing anti-photobleaching (antifade) reagent (250ng/ml, 500µl).

MetaSystems DAPI/Antifade contains a blue fluorescent stain with a concentration of 250ng/ml which intercalates into the minor groove of double stranded DNA. It is mixed with an anti-photobleaching, non-hardening solution. DAPI/Antifade is intended for use on cytogenetic preparations and on formalin-fixed paraffin embedded tissue sections suitable for FISH.

Order No:
D-0905-025-TF

General Reagents

TissueFISH Pretreatment Kit

The MetaSystems' TissueFISH Pretreatment Kit contains reagents and solutions to process formalin-fixed paraffin-embedded tissue sections for FISH assays. Reagents provided are: 5x 5 ml 10x Pretreatment Buffer, 200 ml Protease Buffer, 500 µl Protease Stock Solution.

The MetaSystems' TissueFISH Pretreatment Kit provides reagents which help to unmask formalin-fixed paraffin-embedded tissue cells to allow FISH. The first step is permeabilization which is thought to reverse protein cross-linking caused by formalin fixation. In a second step cells are digested by a protease to facilitate penetration of the fluorescent probe. Processing tissue slides using the MetaSystems' TissueFISH Pretreatment Kit will take less than 90 minutes.

The kit comes in two parts:

Part 1: Pretreatment reagents, stored at room temperature

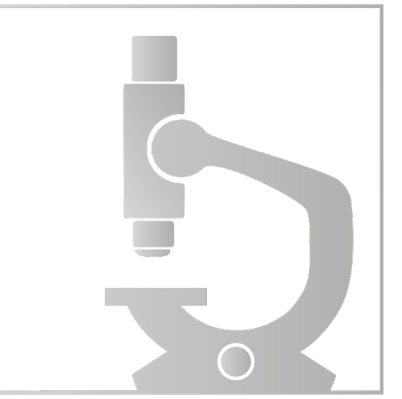
Part 2: Protease, to be stored at 2°C to 8°C upon arrival

Literature

- Fioretos et al (1999) Blood 94:225-232
- Srinivasan et al (2002) Am J Pathol 161:1961-1971
- Chin et al (2003) Mol Pathol 56:275-279

Notes

MetaSystems
Imaging Solutions

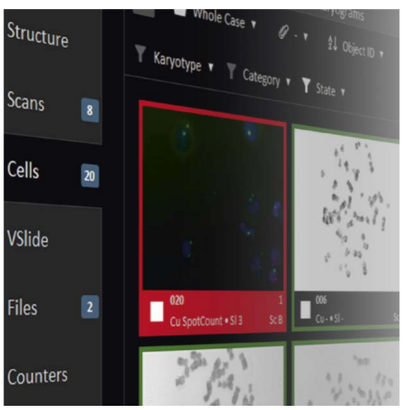


Case and Image Management
Metafer Slide Scanning
Rapid FISH Spot Workflow
TissueFISH

MetaSystems Automated Imaging Solutions

Efficient FISH Imaging Workflows

For more than 35 years, microscope-based imaging solutions from MetaSystems, the sister company of MetaSystems Probes, have been known for their outstanding quality and performance. MetaSystems' debut was the 1986 launch of Metafer for automated slide scanning and detection of metaphases, nuclei, or cells. In the following decades, Metafer evolved into a highly versatile and flexible high-throughput scanning software for microscope-based imaging of various application areas. Dedicated solutions for FISH, karyotyping and remote analysis complemented the product portfolio. To date, MetaSystems develops complete solutions for laboratories in cytogenetics, pathology, microbiology, toxicology, radiation biology, forensics, and other fields. Our installations help users in more than 2,690 laboratories in 101 countries optimize and streamline their imaging work.



Case and Image Management

In modern laboratories, digital microscope-based workflows do not end with acquisition. Every image relates to respective case data, external files, metadata, and other sources of information. Therefore, all MetaSystems imaging software licenses integrate the case and image management technology Neon. It collects information from any given source, prepares data in a convenient and transparent manner, and manages the lab-specific workflow in the most effective way. Sensitive case data are safely processed, and information is selectively provided to users with the respective authorization. Every processing step is stored in the case history file, and powerful statistics engines allow for summarizing the activities in large case databases. Neon does not require changing existing routines; the software easily adapts to existing workflows and structures. Programmable gateways for automated import and export of case data and images allow for comprehensive integration in larger settings.

Metafer Slide Scanning

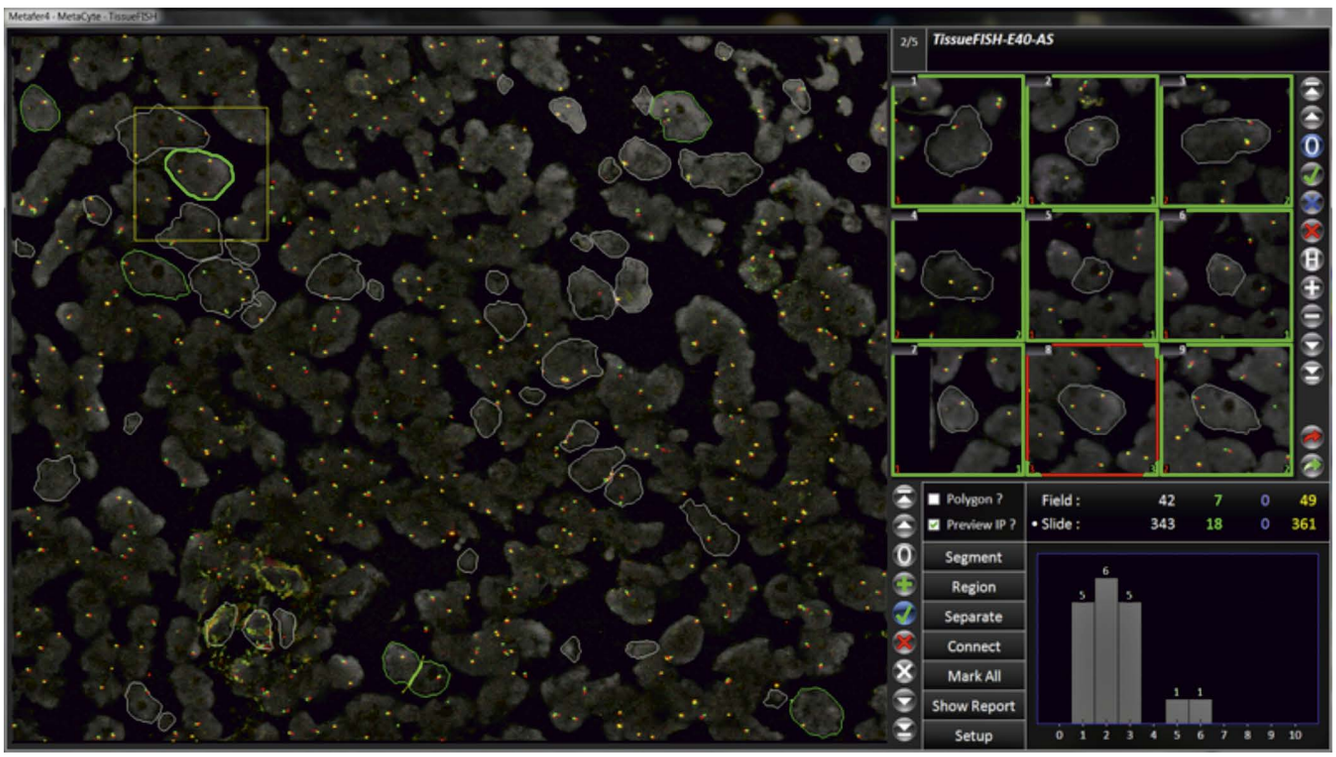
Growing case numbers and limited resources are well-known obstacles in many clinical laboratories. Therefore, reliable automation of slide scanning is an important asset for every FISH-based analysis workflow. While automated approaches usually score all cells irrespectively of the actual signal pattern, human scorers are often biased by certain expectations in the results. Therefore, labs often work with very low, abnormal cut off values for positivity. As a result of this discrepancy, technologists often spend significant time to correct and/or reject automated spot counts.

The Rapid FISH Spot Workflow

With Metafer, it is different: MetaSystems invented RapidScore, an outstandingly fast method of analyzing, reviewing, and confirming FISH signal patterns in cell nuclei. Every Metafer software running the application package for FISH analysis comes with a complete set of parameter files, and report templates for every probes layout. FISH signal patterns are obtained automatically, precisely, and reproducibly using the Metafer software scanning tools. A comprehensive gallery displays the nuclei, the signal patterns, and the obtained spot counts. Automated spot patterns are summarized in convenient graphs and tables. Immediately after automated assessment, the experts can begin reviewing and confirming or correcting the automated proposals. Spot pattern categories are assigned to each cell using the dynamic RapidScore keypad with key layouts that change with the probe analyzed. An enlarged, unprocessed image of the selected nuclei with single focus plane images facilitates evaluation of the signal pattern. New, unexpected categories can be added on the fly.

TissueFISH

By combining sophisticated software tools and outstanding imaging and scanning hardware, the Rapid FISH Spot Workflow is a swift way of analyzing and confirming FISH signal patterns. Together with Metafer's dedicated tools for imaging and analyzing FISH in tissue sections (TissueFISH), Metafer and the Rapid FISH Spot application package are fast and efficient solutions for high-throughput interpretation of FISH signals.



Notes

MetaSystems XCyting probes are directly labeled with bright fluorophores:

	Label		Abs. max. [nm]	Em. max. [nm]
	AQUA	spectrally equivalent to DEAC/ SpectrumAqua™	426	480
	GREEN	spectrally equivalent to FITC/ SpectrumGreen™	505	530
	ORANGE	spectrally equivalent to TRITC/ SpectrumOrange™	552	576
	RED	spectrally equivalent to TexasRed®/ SpectrumRed™	595	615
	NEAR INFRARED	spectrally equivalent to Cy™5/ SpectrumFRed™	644	669

For appropriate analysis the following filter sets are recommended:

	Label	Filter	Recommended for
	MetaSystems DAPI	Hard coated narrow-band filter set for DAPI Catalog No. C-3010-001-MS	XL, XA, XCE, XCP, 24XCyte, XCyte mBAND, XMP, XRP, 21XMouse, 22XRat, 12XCHamster
	MetaSystems AQUA	Hard coated narrow-band filter set for AQUA Catalog No. C-3010-004-MS	XL (tricolor probes), XA, XCE, 24XCyte, XCyte mBAND, 21XMouse, 22XRat, 12XCHamster, XRNA
	MetaSystems GREEN	Hard coated narrow-band filter set for GREEN Catalog No. C-3010-002-MS	XL, XA, XCE, XCP, 24XCyte, XCyte mBAND, XMP, XRP, 21XMouse, 22XRat, 12XCHamster, XRNA
	MetaSystems ORANGE	Hard coated narrow-band filter set for ORANGE Catalog No. C-3010-003-MS	XL, XA, XCE, XCP, 24XCyte, XCyte mBAND, XMP, XRP, 21XMouse, 22XRat, 12XCHamster, XRNA
	MetaSystems RED	Hard coated narrow-band filter set for RED Catalog No. C-3010-010-MS	24XCyte, XCyte mBAND, 21XMouse, 22XRat, 12XCHamster
	MetaSystems NEAR INFRARED	Hard coated narrow-band filter set for NEAR INFRARED Catalog No. C-3010-006-MS	24XCyte, XCyte mBAND, 21XMouse, 22XRat, 12XCHamster, XRNA

For viewing only the following multi-pass filter sets are recommended:

	Label	Filter	Recommended for
	MetaSystems GO	Dual band filter set GREEN/ORANGE Catalog No. C-3010-007-MS	XL, XA, XCE, XCP, XMP, XRP
	MetaSystems DGO	Triple band filter set DAPI/GREEN/ORANGE Catalog No. C-3010-013-MS	XL, XA, XCE, XCP, XMP, XRP
	MetaSystems AGO	Triple band filter set AQUA/GREEN/ORANGE Catalog No. C-3010-008-MS	XL, XA, XCE
	MetaSystems DAGO	Quad band filter set DAPI/AQUA/GREEN/ORANGE Catalog No. C-3010-012-MS	XL, XA, XCE

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D-5607-100-TC	XA 13/18/21	Aneusomy Probe	–	121
D-5608-100-OG	XA X/Y	Aneusomy Probe	–	126
D-5609-100-TC	XA AneuScore II	Aneusomy Probe	–	123
D-5613-100-TC	XA AneuScore III	Aneusomy Probe	–	124
D-56NN-NNN-NN	AneuScore-Table	XCyting Aneusomy Probe	–	129
D-6001-100-OG	XL ALK BA	Break Apart Probe	•	13
D-6005-100-OG	XL EGFR amp	Amplification Probe	•	45
D-6008-100-OG	XL MYC amp	Amplification Probe	•	48
D-6010-100-OG	XL ERBB2 (HER2/NEU) amp	Amplification Probe	•	98
D-6011-100-OG	XL EWSR1 BA	Break Apart Probe	•	113
D-6015-100-OG	XL MALT1 BA	Break Apart Probe	•	104
D-6016-100-OG	XL BCL6 BA	Break Apart Probe	•	15
D-6018-100-OG	XL BCL2 BA	Break Apart Probe	•	103
D-6019-100-OG	XL 19p/19q del	Deletion Probe	•	106
D-6020-100-OG	XL t(14;18) IGH/MALT1 DF	Translocation/Dual Fusion Probe	•	91
D-6021-100-OG	XL 1p36/1q25 del	Deletion Probe	•	9
D-6023-100-OG	XL MYC BA	Break Apart Probe	•	49
D-6029-100-OG	XL ROS1-GOPC BA	Break Apart Probe	•	37
D-6030-100-TC	XL MYC BA triple-color	Break Apart Probe - Triple Color	•	50
D-6031-100-OG	XL MYCN amp	Amplification Probe	•	14
D-6032-100-OG	XL DDIT3 BA	Break Apart Probe	•	76
D-6033-100-OG	XL SS18 BA	Break Apart Probe	•	105
D-6034-100-OG	XL FOXO1 BA	Break Apart Probe	•	81
D-6035-100-OG	XL FUS BA	Break Apart Probe	•	97
D-6040-100-OG	XL IRF4 BA	Break Apart Probe	•	36
R-0101-020-OR	XRNA SARS-CoV-2, orange	Virus RNA FISH	–	166
R-0201-020-FI	XRNA ACE2, green	Human RNA FISH	–	167
R-0202-020-BL	XRNA TMPRSS2, aqua	Human RNA FISH	–	168
R-0203-020-FI	XRNA PD-L1, green	Human RNA FISH	–	169
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DSCR4	21q22.13	D-5155-100-OG	XL 5p15/21q22	Deletion/Enumeration Probe		33
	21q22.13	D-5441-050-OG	XL 21q22 / XCP 21		–	116
	21q22.13	D-5601-100-OR	XA 21q22	Aneusomy Probe	–	125
	21q22.13	D-5602-100-OG	XA 13/21	Aneusomy Probe		120
	21q22.13	D-5603-100-TC	XA TriScore (X/Y/21)	Aneusomy Probe		128
	21q22.13	D-5604-100-TC	XA AneuScore I	Aneusomy Probe		122
	21q22.13	D-5607-100-TC	XA 13/18/21	Aneusomy Probe		121
	21q22.13	D-5609-100-TC	XA AneuScore II	Aneusomy Probe		123
	21q22.13	D-5613-100-TC	XA AneuScore III	Aneusomy Probe		124
EGFR	7p11.2	D-5418-050-OG	XL Williams-Beuren	Deletion Probe	–	134
	7p11.2	D-6005-100-OG	XL EGFR amp	Amplification Probe	•	45
EGR1	5q31.2	D-5042-100-OG	XL 5q31/5q33	Deletion Probe	–	27
	5q31.2	D-5081-100-TC	XL 5q31/5q33/5p15	Deletion Probe	–	30
	5q31.2	D-5085-100-OG	XL del(5)(q31)	Deletion Probe	–	28
	5q31.2	D-5417-050-OG	XL Cri-Du-Chat	Deletion Probe	–	133
ELL	19p13.1	D-5135-100-OG	XL t(11;19) KMT2A/ELL DF	Translocation/Dual Fusion Probe		73
ELN	7q11.23	D-5418-050-OG	XL Williams-Beuren	Deletion Probe	–	134
ERBB2 (HER2/NEU)	17q12	D-6010-100-OG	XL ERBB2 (HER2/NEU) amp	Amplification Probe	•	98
ETV6	12p13.2	D-5139-100-OG	XL ETV6 BA	Break Apart Probe	–	78
	12p13.2	D-5073-100-OG	XL ETV6	Break Apart Probe	–	77
	12p13.2	D-5101-100-OG	XL t(7;12) MNX1/ETV6	Translocation/Dual Fusion Probe		46
	12p13.2	D-5115-100-OG	XL t(12;21) ETV6/RUNX1 DF	Translocation/Dual Fusion Probe	–	80
EWSR1	22q12.2	D-6011-100-OG	XL EWSR1 BA	Break Apart Probe	•	113
FGFR1	8p11.2	D-5041-100-OG	XL FGFR1	Break Apart Probe	–	47
FGFR3	4p16.3	D-5108-100-OG	XL t(4;14) FGFR3/IGH DF	Translocation/Dual Fusion Probe	–	23
FIP1L1	4q12	D-5063-100-TC	XL 4q12	Translocation/Deletion Probe	–	18
	4q12	D-5123-100-OG	XL 4q12 DC	Translocation/Deletion Probe	–	19

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TP53	17p13	D-5044-100-TC	XL CLL Probe Kit (XL DLEU/ LAMP/12cen + XL ATM/TP53)	Deletion/Enumeration Probe		75
	17p13	D-5046-100-OG	XL ATM/TP53	Deletion Probe		72
	17p13	D-5048-100-OG	XL Iso(17q)	Amplification/Deletion Probe	–	100
	17p13	D-5067-100-OG	XL DLEU/TP53	Deletion Probe		85
	17p13	D-5089-100-OG	XL TP53/NF1	Deletion Probe	–	102
	17p13	D-5103-100-OG	XL TP53/17cen	Deletion Probe	–	101
WWOX	16q23	D-5112-100-OG	XL t(14;16) IGH/MAF DF	Translocation/Dual Fusion Probe		89
ZNF443	19p13.2	D-6019	XL 19p/19q del	Deletion Probe	•	106

Notes

MetaSystems Probes

XCyting FISH Probes

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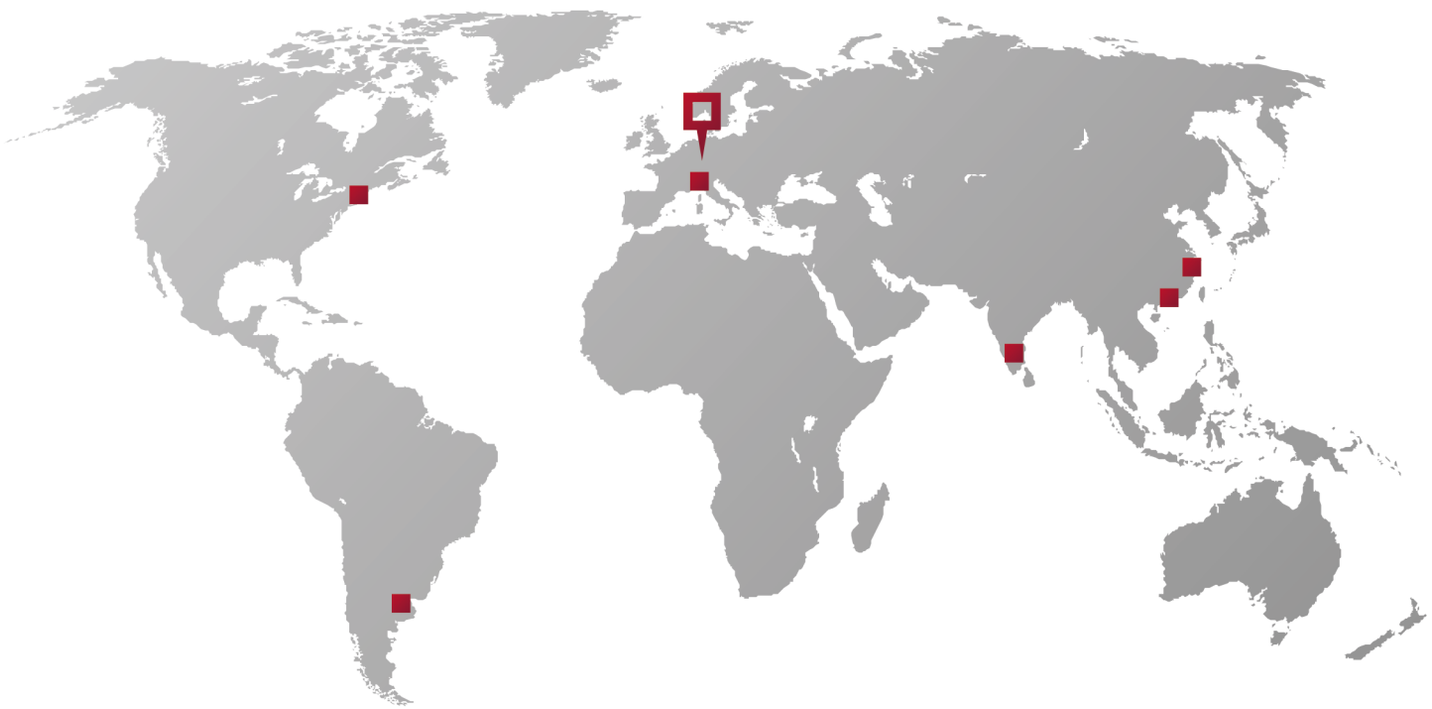

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