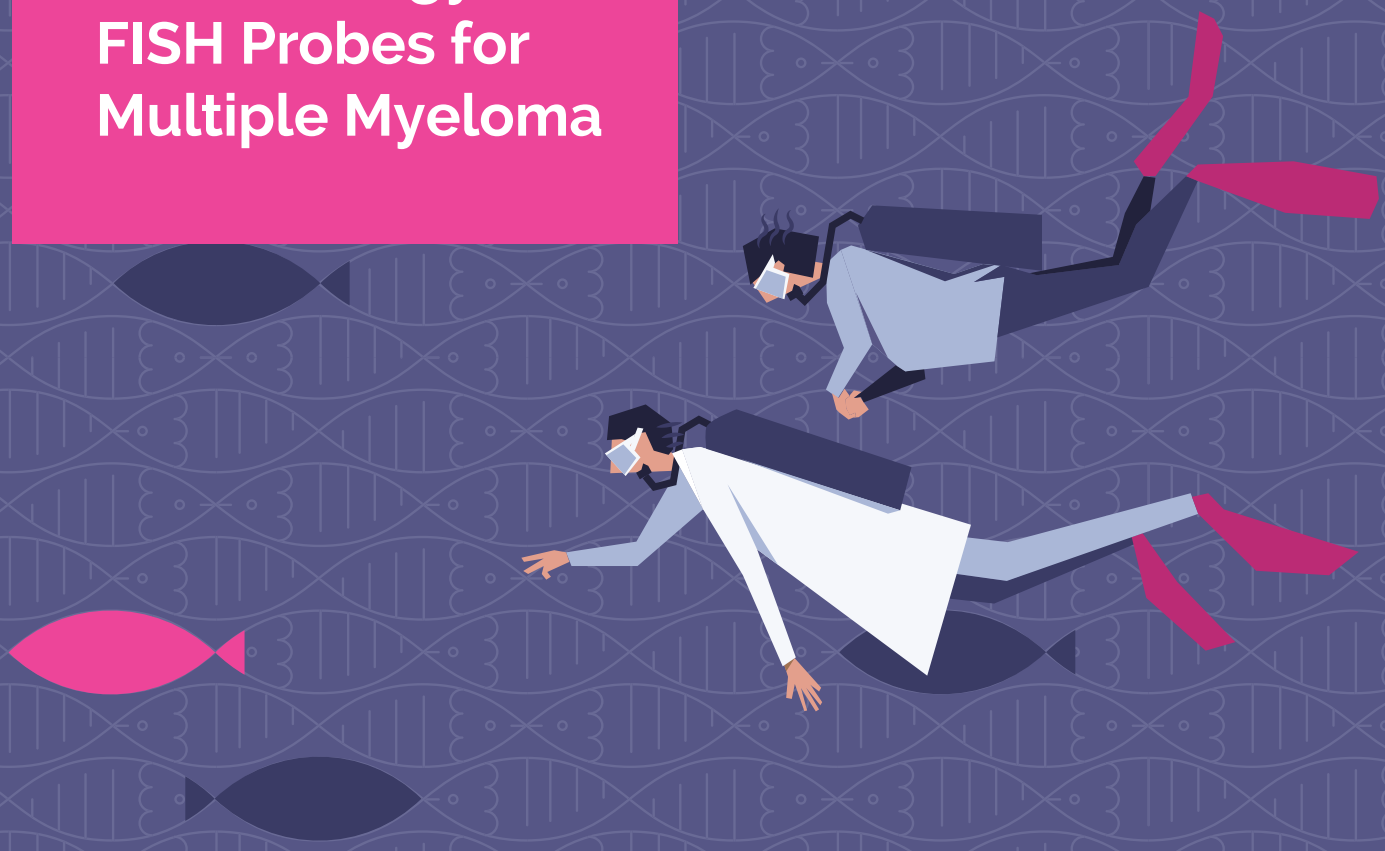
CytoCell

ogt

A Sysmex Group Company

Haematology FISH Probes for Multiple Myeloma



Features

- Improve confidence in result interpretation with high intensity signals and minimal background
- Enhance detection and scoring accuracy with robust, easy-to-analyse probes
- Save time and minimise mixing errors with easy-to-use, pre-mixed probes
- Optimise stock levels and minimise wastage with flexible pack sizes to meet your needs

Multiple Myeloma

Multiple myeloma (MM) is a plasma cell neoplasm characterised by the accumulation of clonal plasma cells in the bone marrow and very complex cytogenetic and molecular genetic aberrations. The modal chromosome number in newly diagnosed symptomatic patients is usually either hyperdiploid, with multiple trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19 and 21, or hypodiploid with immunoglobulin heavy chain (Ig) translocations. At disease progression, several genetic progression factors have been identified as deletions of 13q, deletions of 17p and deletion of 1p and/or amplification of 1q[1,2,3].

Cytogenetic abnormalities are detected by conventional cytogenetics in about one third of the cases, but FISH increases the proportion of chromosomal abnormality detection to >90%[4].

References

1. Fonseca, *et al*. Leukemia. 2009;23(12):2210-2221.
2. Sawyer. Cancer Genetics. 2011;204(1):3-12.
3. Morgan, *et al*. Nat Rev Cancer. 2012;12(5):335-348.
4. Swerdlow, *et al*. Editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC:2008

The OGT Partnership

Behind every sample is a life that can be improved through the right care decisions.
The OGT partnership approach is key to providing the highest level of service, working closely with you to understand your unique challenges, customising our approach to meet your exact needs. Choose CytoCell® probes for your FISH analysis; our effective, accurate and simple to use products help clinical decision makers to reach the right decisions for each patient.

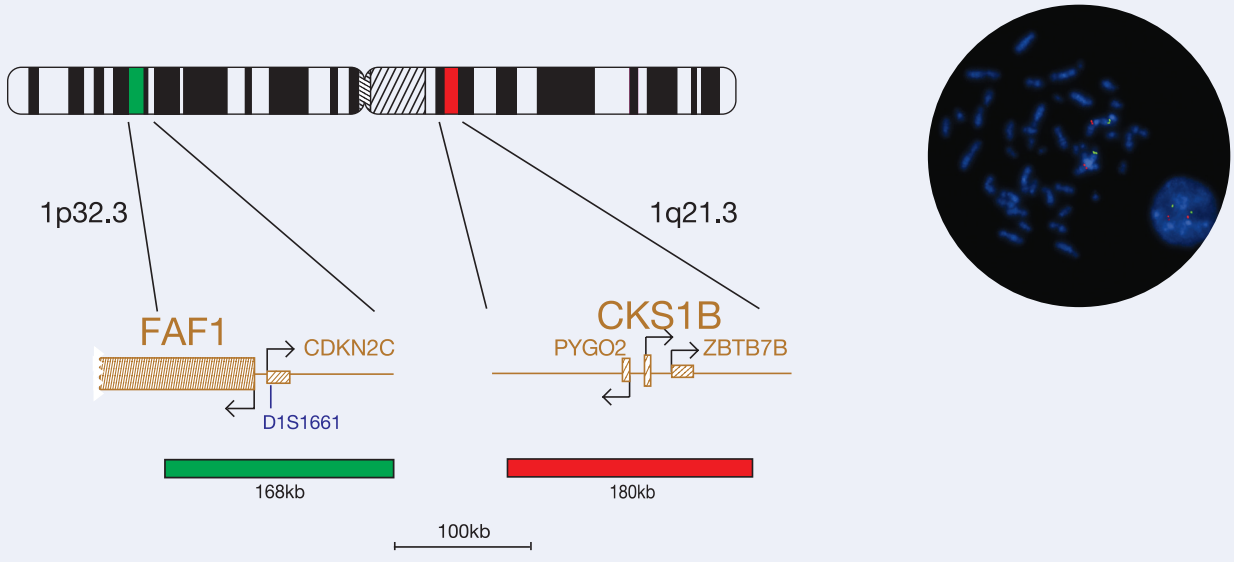
CKS1B/CDKN2C (P18) Amplification/Deletion

Cat. No. **LPH 039-S** (5 tests) | Cat. No. **LPH 039** (10 tests)

The CKS1B *(CDC28 protein kinase regulatory subunit 1B)* gene is located at 1q21.3 and the CDKN2C *(cyclin dependent kinase inhibitor 2C)* gene is located at 1p32.3.

Gain of the 1q21 region including CKS1B is one of the most frequently-occurring chromosomal aberrations seen in multiple myeloma[1]. Over-expression of the CKS1B gene up-regulates cell cycle progression, resulting in a more proliferative disease[2]. This is related to the advanced phenotype of multiple myeloma and may therefore be associated with poor prognosis and disease progression[1,2,3]. Gain of 1q21 has been linked to inferior survival and further amplification is observed in disease relapse. Complete gains of the long arm of chromosome 1 are also common in multiple myeloma and can occur as isochromosomes, duplications or jumping translocations and are frequently associated with disease progression[4].

CDKN2C is a tumour suppressor gene responsible for inducing apoptotic cell death and DNA fragmentation[5]. It is up-regulated by the expression of the cytokine IL-6 in multiple myeloma and homozygous deletion of the gene is associated with a more proliferative disease[5]. Although CDKN2C deletions have been reported to be rare in human malignancy, cytogenetic analyses have shown that abnormalities of 1p32-36 occur in around 16% of human multiple myeloma and are associated with worse overall survival[2,3,5,6].



CMP H013 V002

References

1. Hanamura I. Blood. 2006;108(5):1724-32.
2. Fonseca R, *et al.* Leukemia. 2009;23(12):2210-2221.
3. Sawyer JR. Cancer Genetics. 2011;204(1):3-12.
4. Fonseca R, *et al.* Leukemia. 2006;20(11):2034-40.
5. Leone PE, *et al.* Clin Cancer Res. 2008;14(19):6033-41.
6. Kulkarni MS, *et al.* Leukemia. 2002;16:127-34.

P53 (TP53) Deletion

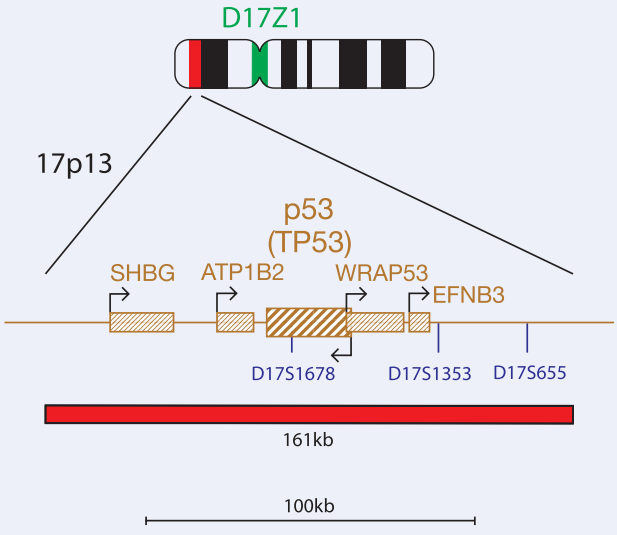
Cat. No. **LPH 017-S** (5 tests) | Cat. No. **LPH 017** (10 tests)

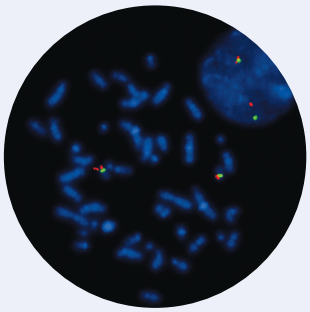
The TP53 *(tumor protein p53)* gene at 17p13 is a tumour-suppressor gene that has been shown to be deleted in a wide range of human malignancies.

The TP53 gene is one of most important tumour suppressor genes; it acts as a potent transcription factor with fundamental role in the maintenance of genetic stability. Screening for TP53 loss is important, as deletions or losses of the short arm of chromosome 17; which includes the TP53 region, are reported in many cancers and are often associated with disease progression, inferior response to treatment and/or a poor prognosis.

In particular, loss of TP53 is reported in 10% of patients with chronic lymphocytic leukaemia (CLL), and is considered to be the poorest prognostic marker in that disease[1,2]. In acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL), TP53 loss is associated with a poor outcome and is often seen as a marker of disease progression or secondary disease[3-5].

TP53 loss in patients with multiple myeloma is a late event, where it is seen as a marker of disease progression and is associated with a very poor prognosis[6,7].





CMP H039 V006

References

1. Rossi D, *et al.* Blood. 2013 Feb 21;121(8):1403-12.
2. Baliakas P, *et al.* Leukemia. 2014;(April):1-8.
3. Grimwade D, *et al.* Br J Haematol. 2010; (3):17.
4. Seifert H, *et al.* Leukemia. 2009;23(4):656-63.
5. Stengel A, *et al.* Blood. 2014;124(2):251-8.
6. Palumbo A, *et al.* J Clin Oncol. 2015 Sep 10;33(26):2863-9.
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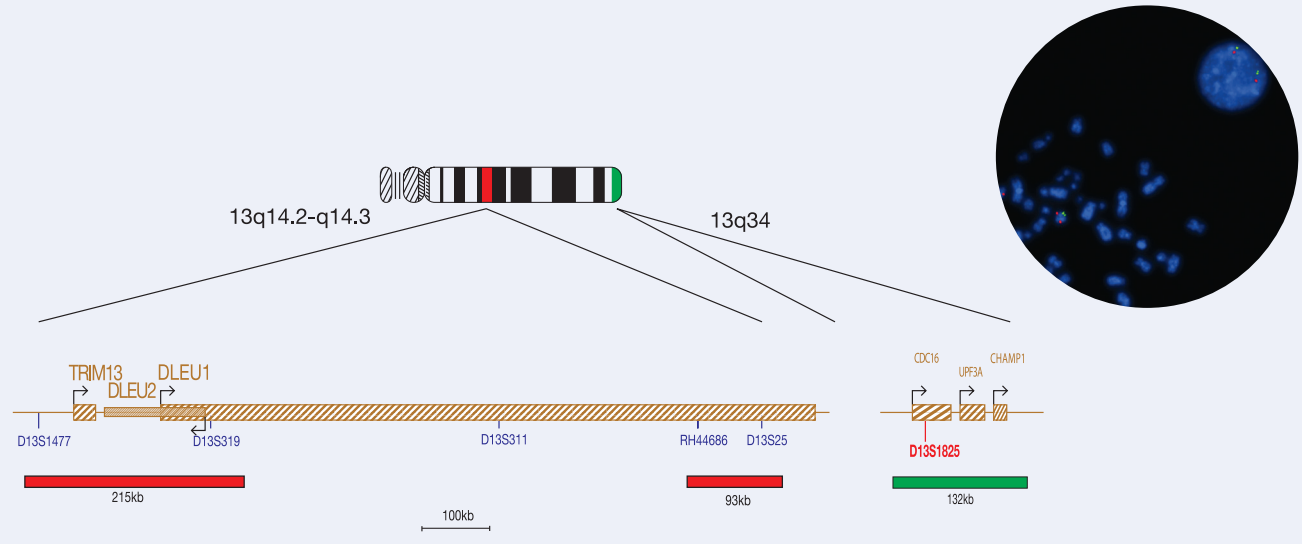
13q Deletion Probes

Chromosome 13q aberrations occur in 16–40% of MM cases – most of them being complete monosomy 13 (85%), whilst the remaining 15% constitute deletion of 13q[1,2,3]. A case study of MM patients narrowed down the critical deleted region to 13q14[4]. Historically, deletions of 13q have been associated with poor prognosis in MM, but now it is believed that its prognostic relevance may be related to its association with other concurrent genetic lesions[3,5].

13q14.3 Deletion

Cat. No. **LPH 006-S** (5 tests) | Cat. No. **LPH 006** (10 tests)

The 13q14.3 Deletion probe, labelled in red, covers the D13S319 and D13S25 markers. The 13qter subtelomere specific probe (clone 163C9), labelled in green, allows identification of chromosome 13 and acts as a control probe.



CMP H001 V3

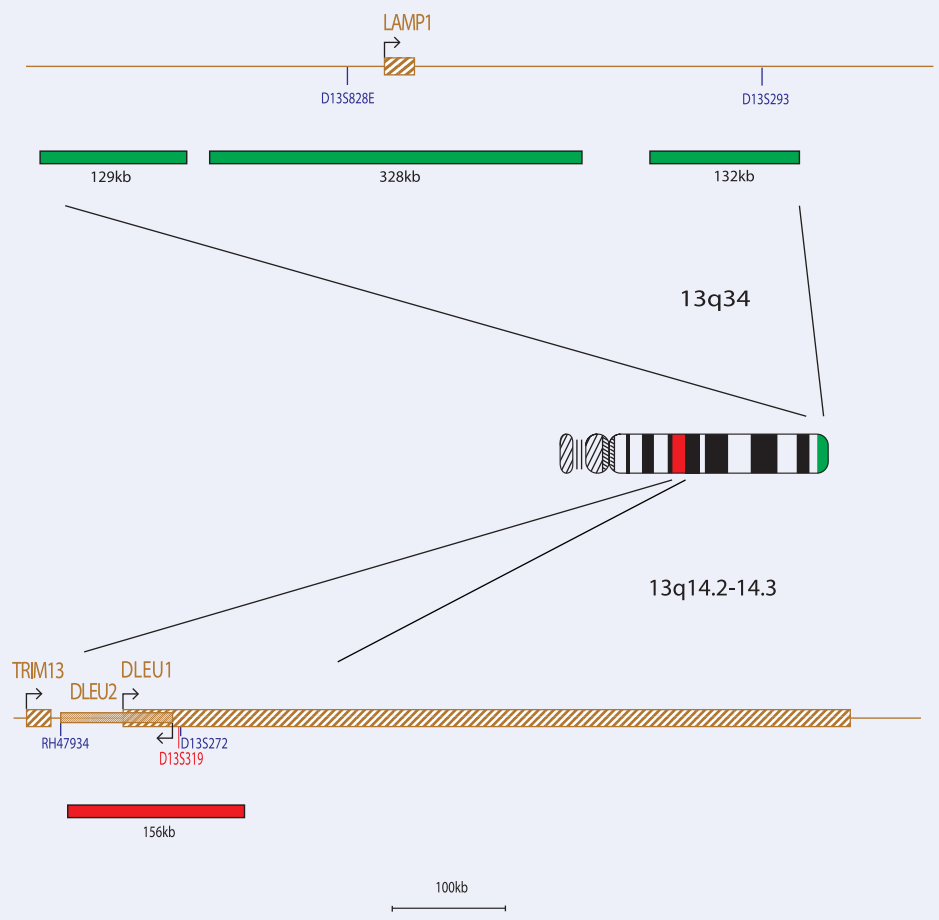
References

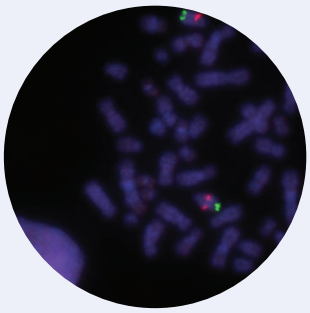
1. Bullrich, *et al.* Cancer Res. 2001;61:6640–8.
2. Zojer, *et al.* Blood. 2000;95(6):1925–1930.
3. Sawyer JR. Cancer Genetics. 2011;204:3–12.
4. Shaughnessy J, *et al.* Blood. 2000;96:1505–11.
5. Fonseca R, *et al.* Leukemia. 2009;23:2210–2221.

D13S319 *Plus* Deletion

Cat. No. **LPH 068-S** (5 tests) | Cat. No. **LPH 068** (10 tests)

The D13S319 probe, labelled in red, covers a 156kb region including the entire DLEU1 and most of the DLEU2 genes and the D13S319, D13S272 and RH47934 markers. The 13qter subtelomere specific probe, labelled in green, allows identification of chromosome 13 and acts as a control probe.



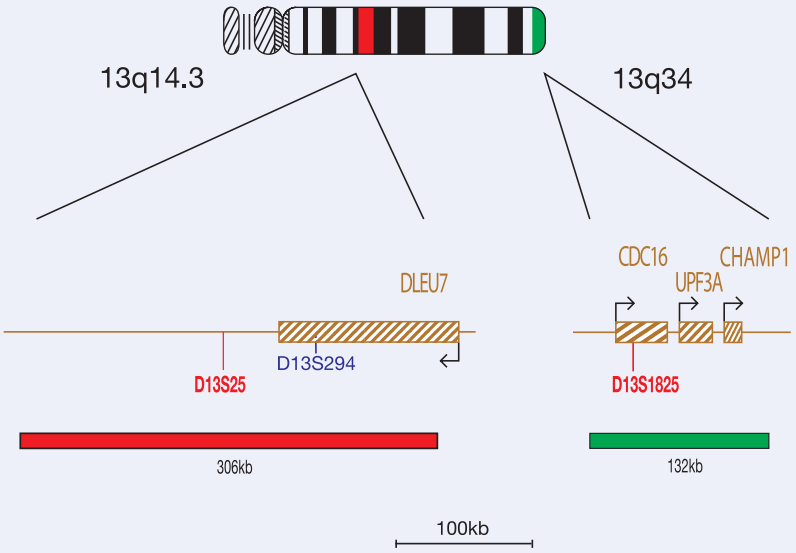


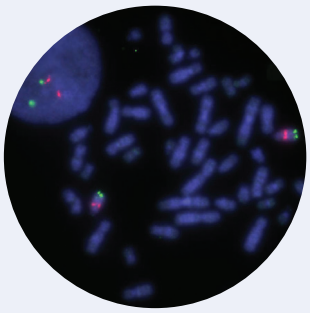
CMP H079 V004

D13S25 Deletion

Cat. No. **LPH 043-S** (5 tests) | Cat. No. **LPH 043** (10 tests)

The D13S25 probe, labelled in red, covers a 306kb region including most of the DLEU7 gene and the D13S25 marker. The 13qter subtelomere specific probe (clone 163C9), labelled in green, allows identification of chromosome 13 and acts as a control probe.





CMP H016 V004.00

IGH Breakapart and IGH *Plus* Breakapart

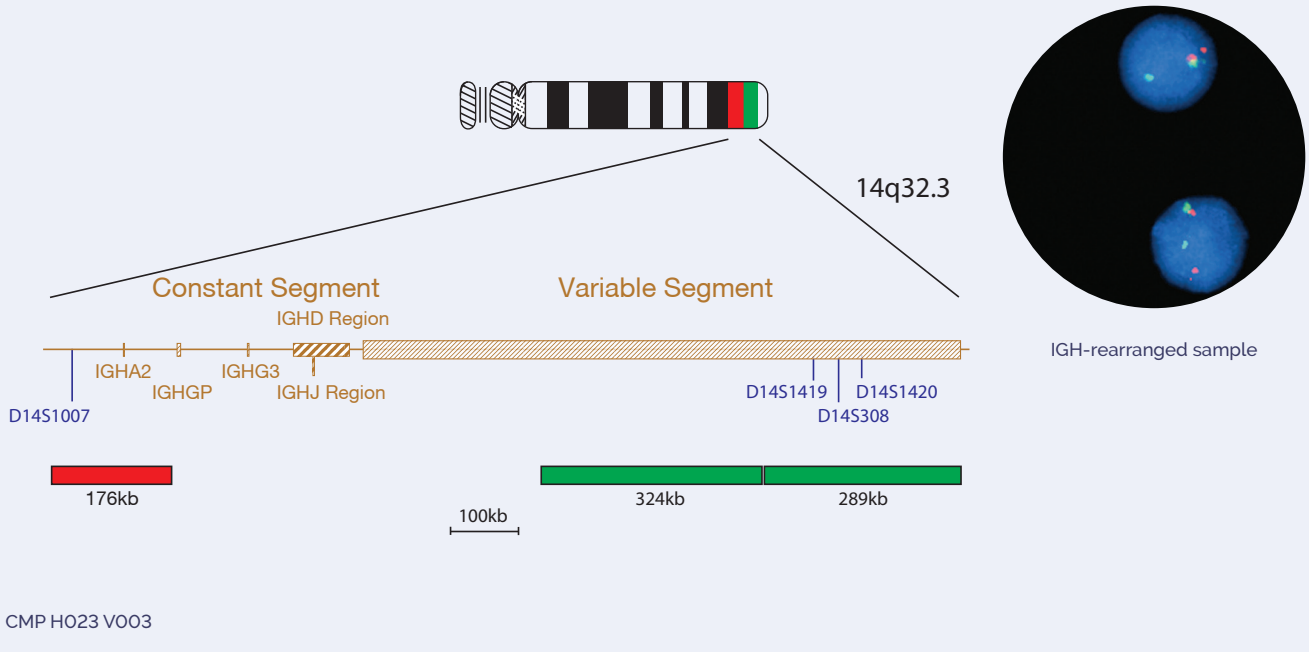
IGH rearrangements with a number of different gene partners are a frequent finding in patients with multiple myeloma, including: t(4;14)(p16;q32) translocations involving IGH with FGFR3 and NSD2, t(6;14)(p21;q32) translocations involving IGH and CCND3, t(11;14)(q13;q32) translocations involving IGH and CCND1, t(14;16)(q32;q23) translocations involving IGH and MAF, and t(14;20)(q32;q12) translocations involving IGH and MAFB[1,2].

OGT provides two different IGH Breakapart probe designs to suit your needs:

IGH Breakapart

Cat. No. **LPH 014-S** (5 tests) | Cat. No. **LPH 014** (10 tests)

The IGH probe mix consists of a 176kb probe, labelled in red, covering part of the Constant region of the gene and two green probes (324kb and 289kb), covering part of the Variable segment of the gene.



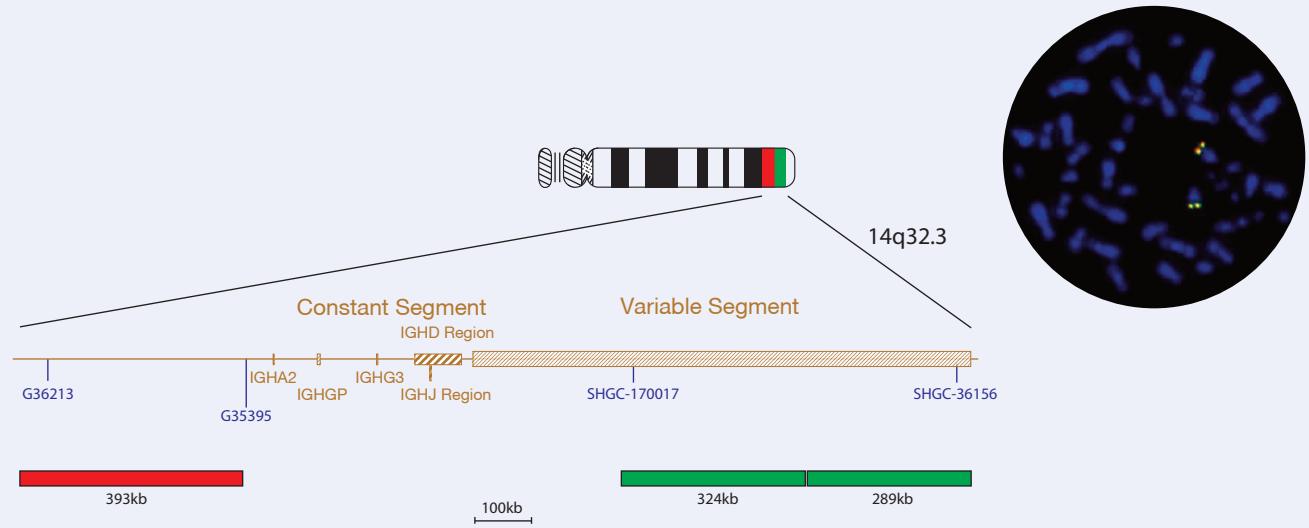
References

1. Bergsagel, *et al.* Proc Natl Acad Sci USA. 1996 Nov 26;93(24):13931-6.
2. Sawyer JR. Cancer Genet. 2011 Jan;204(1):3-12.

IGH *Plus* Breakapart

IVDR Cat. No. **CE-LPH 070-S** (5 tests) | Cat. No. **CE-LPH 070** (10 tests)

The IGH probe mix consists of a 393kb probe, labelled in red, centromeric to the Constant region of the gene and two green probes (324kb and 289kb), within the Variable segment of the gene.



CMP H075 V002

IGH Translocation, Dual Fusion Probes

Approximately 50-60% of MM cases are associated with translocations involving IGH and one of several partners including CCND1, NSD2 (WHSC1) and FGFR3, CCND3, MAF or MAFB[1].

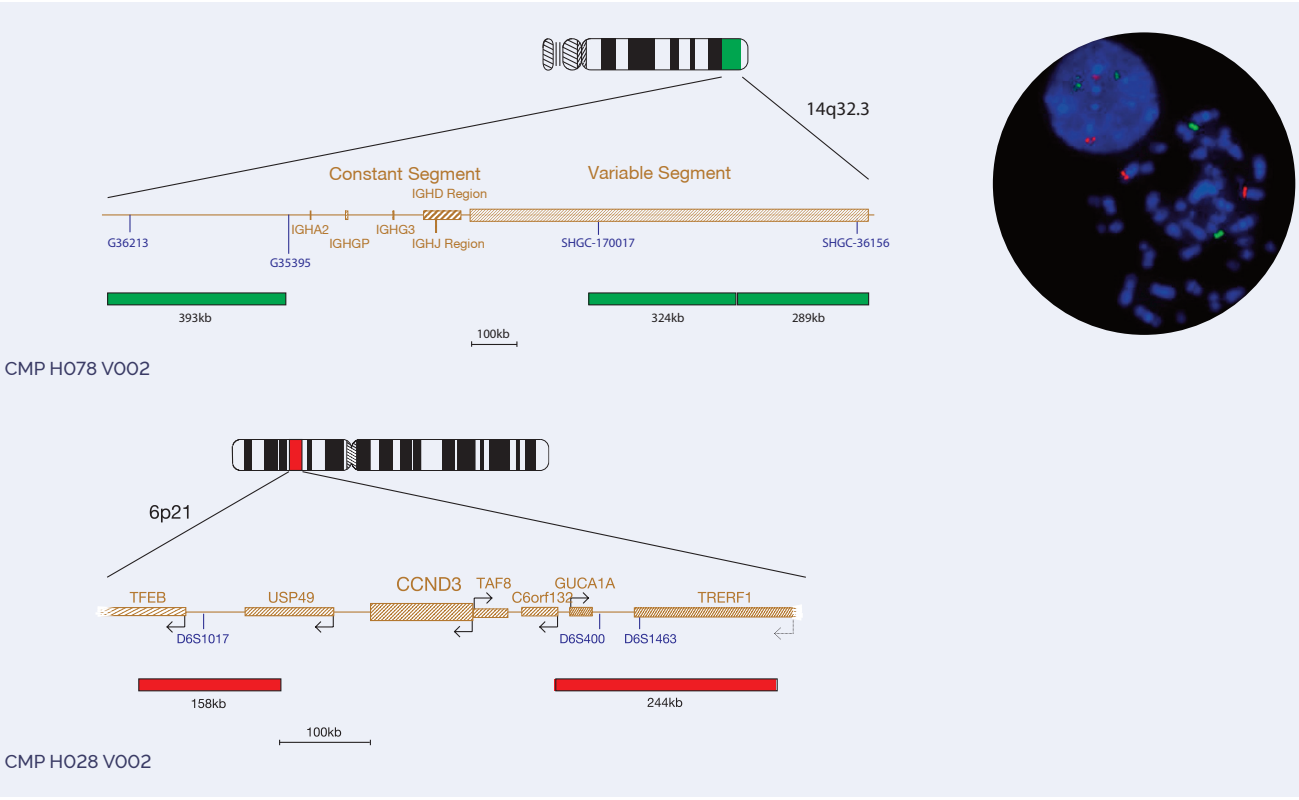
Our IGH Translocation, Dual Fusion probes all consist of two green probes that cover the IGH region, positioned proximal to the constant region and within the Variable segment. The second part of the probe, labelled in red, covers the gene associated with the respective translocation.

IGH/CCND3 *Plus* Translocation, Dual Fusion

Cat. No. **LPH 075-S** (5 tests) | Cat. No. **LPH 075** (10 tests)

The CCND3 (*cyclin D3*) gene is located at 6p21.1 and IGH (*immunoglobulin heavy locus*) at 14q32.3.

The t(6;14)(p21;q32) translocation is a recurrent translocation seen in 4% of cases of MM[2]. CCND3 has been identified as a putative oncogene that is dysregulated as a consequence of the t(6;14)(p21;q32) translocation[2].



References

1. Fonseca R, *et al.* Cancer Res. 2004;64:1546-58.
2. Shaughnessy J, *et al.* Blood. 2001;98(1):217-23.

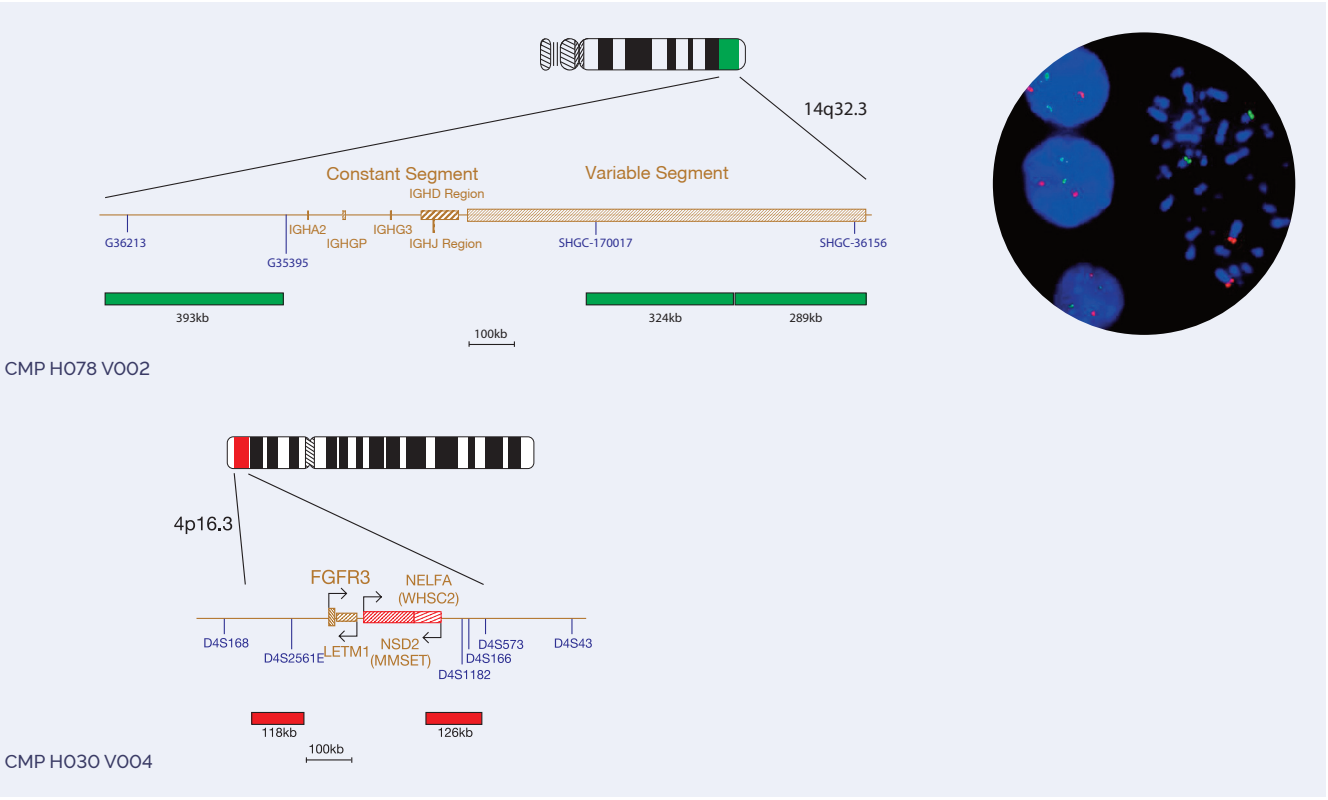
IGH/FGFR3 *Plus* Translocation, Dual Fusion

IVDR Cat. No. **CE-LPH 074-S** (5 tests) | Cat. No. **CE-LPH 074** (10 tests)

The FGFR3 *(fibroblast growth factor receptor 3)* gene is located at 4p16.3 and IGH *(immunoglobulin heavy locus)* at 14q32.3.

The t(4;14)(p16.3;q32.3) translocation is a recurrent translocation seen in 15% of MMs[1,2]. The translocation results in the dysregulation of two genes at 4p16; WHSC1 *(Wolf-Hirschhorn syndrome candidate 1)* and FGFR3. The consequence of the translocation is increased expression of FGFR3 and WHSC1. The translocation can be unbalanced, with 25% of cases losing the derivative chromosome 14, associated with the loss of FGFR3 expression[1,2].

The majority of the breakpoints on chromosome 4 occur between FGFR3 and WHSC1. The breakpoint on chromosome 14 is almost exclusively in the switch region of constant genes. For the overexpression of both FGFR3 and WHSC1 the breakpoint on chromosome 14 must be located between the µ enhancer and the 3' IGH enhancers and between FGFR3 and WHSC1. As a consequence, both derivative chromosomes contain an enhancer juxtaposed to an oncogene[3]. This t(4;14) translocation is often cytogenetically cryptic and was poorly described before the advent of FISH techniques. The translocation has been associated with poorer survival in MM patients[1,2].



References

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2. Sawyer JR. Cancer Genetics. 2011;204(1):3-12.
3. Walker, *et al.* Blood. 2013;121(17);3413-3419.

IGH/MAF *Plus* v2 Translocation, Dual Fusion

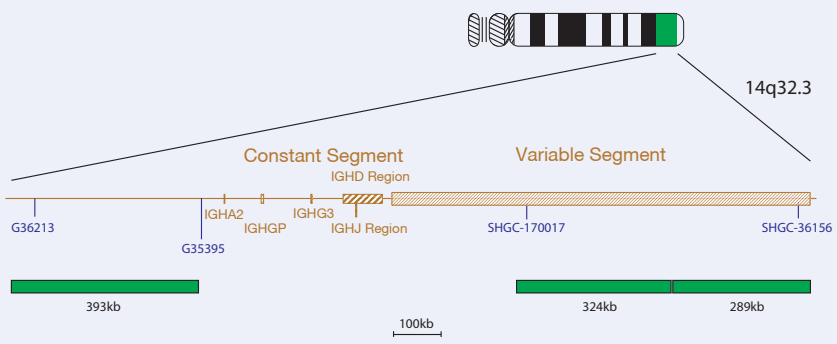
Cat. No. **LPH 108-S** (5 tests) | Cat. No. **LPH 108** (10 tests)

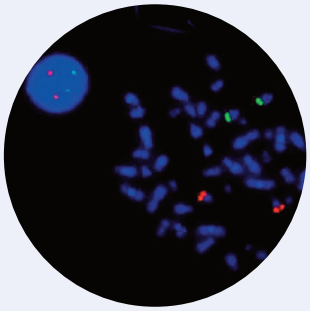
MAF *(MAF bZIP transcription factor)* gene is located at 16q23 and IGH *(immunoglobulin heavy locus)* at 14q32.3.

The t(14;16)(q32.3;q23) translocation is a recurrent translocation seen in 2-10% of MMs[1].

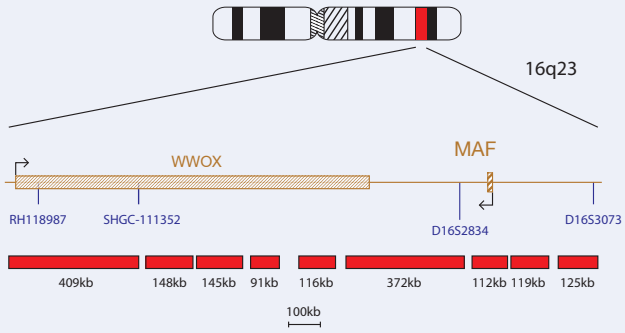
The majority of the breakpoints occur within the last intron of WWOX *(WW domain containing oxidoreductase)*, centromeric to MAF. These breakpoints have a dual impact of positioning the IGH enhancer near MAF and disrupting the WWOX gene[2]. Gene expression profiling of myeloma cell lines revealed that MAF caused transactivation of cyclin D2 (a promoter of cell cycle progression), thus enhancing proliferation of myeloma cells[3].

According to the literature, MM patients harbouring the t(14;16) appear to have a more aggressive clinical outcome[4,5].





CMP H078 V002



CMP H139 v001

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2. Walker, *et al.* Blood. 2013;121(17);3413-3419.
3. Chang H, *et al.* Leukemia. 2007;21:1572-1574.
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5. Sawyer JR. Cancer Genetics. 2011;204(1):3-12.

IGH/MAFB *Plus* Translocation, Dual Fusion

Cat. No. **LPH 077-S** (5 tests) | Cat. No. **LPH 077** (10 tests)

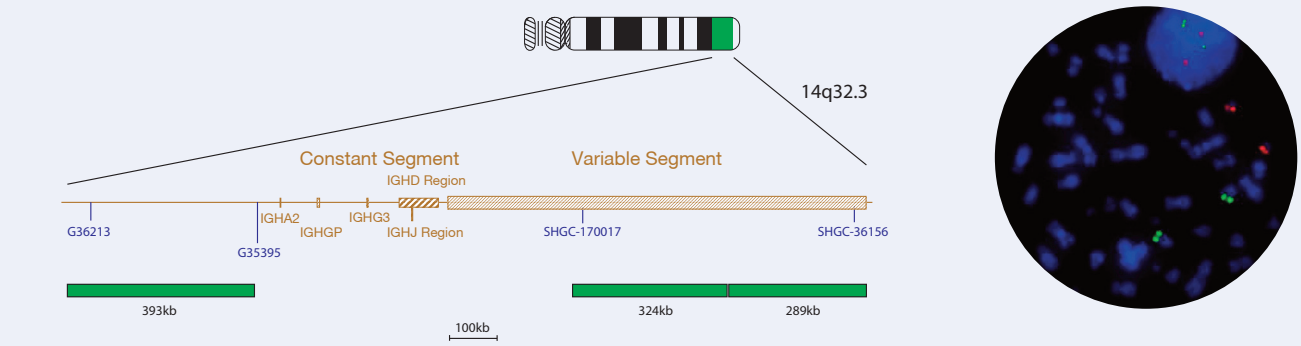
The MAFB *(MAF bZIP transcription factor B)* gene is located at 20q12 and IGH *(immunoglobulin heavy locus)* at 14q32.3.

The t(14;20)(14q32;q12) translocation is a recurrent translocation seen in around 2% of MMs[1,2].

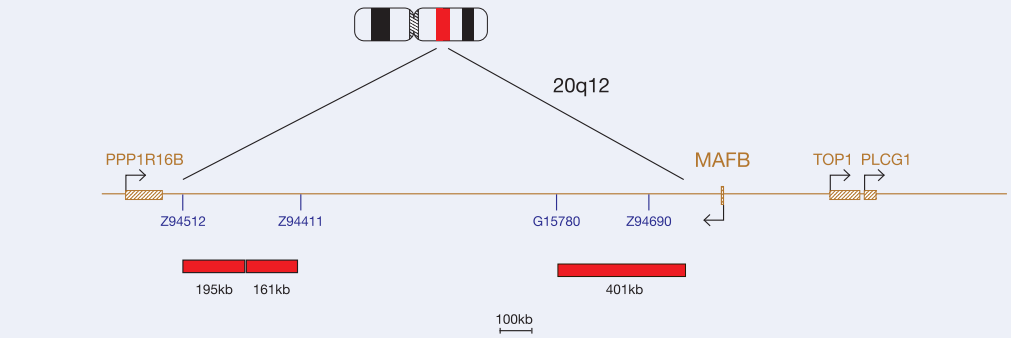
The reciprocal rearrangement brings a truncated form of the IGH µ-enhancer (Eµ, located between the joining (J) segments and the constant region of the IGH gene) in close contact with the MAFB gene[3].

The resultant fusion and the up-regulated transcription product has been shown to cause dysregulation of cyclin D21.

The prognostic outcome of t(14;20)(14q32;q12) is assumed to be the same as the t(14;16)(q32;q23)[2].



CMP H078 V002



CMP H032 V004

References

1. Fonseca R, *et al.* Leukemia. 2009;23(12):2210-2221.
2. Sawyer JR. Cancer Genetics. 2011;204(1):3-12.
3. Boersma-Vreugdenhil, *et al.* Br J Haematol. 2004;126:355-63.

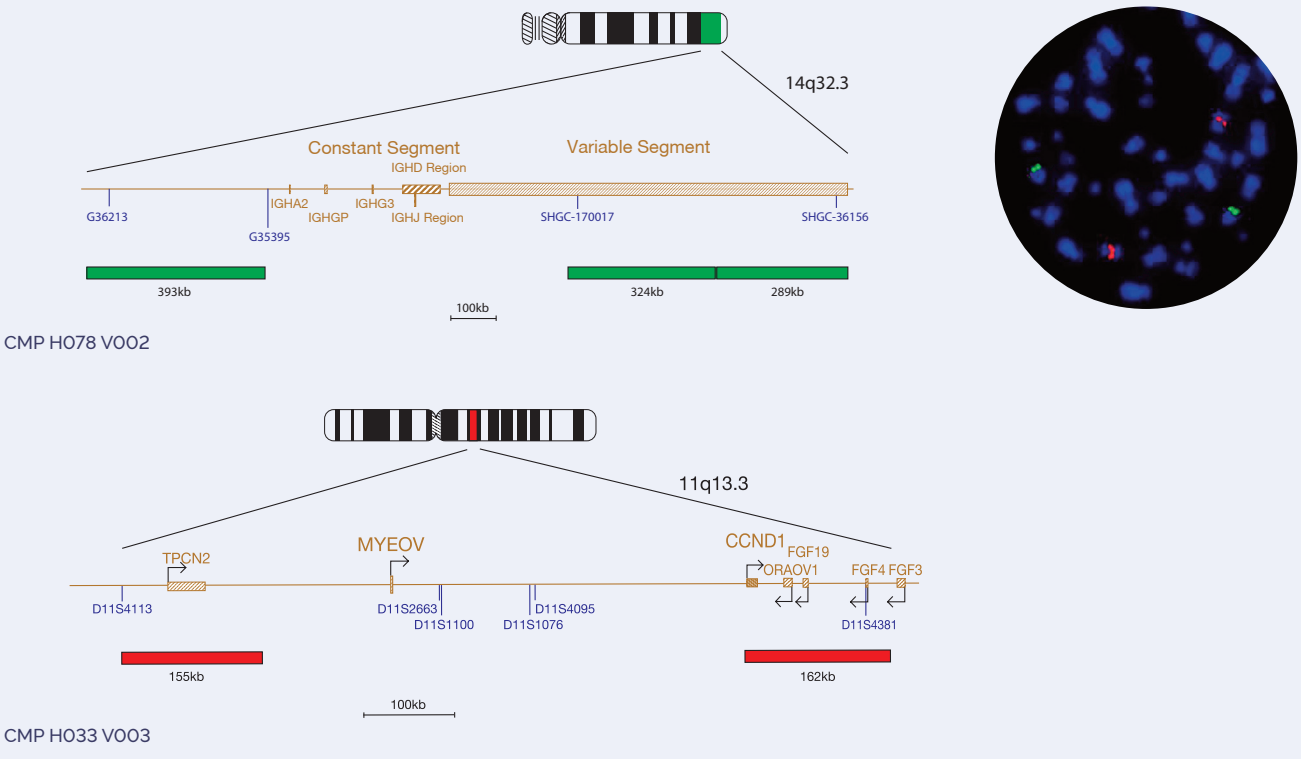
IGH/MYEOV *Plus* Translocation, Dual Fusion

IVDR Cat. No. **CE-LPH 078-S** (5 tests) | Cat. No. **CE-LPH 078** (10 tests)

The MYEOV *(myeloma overexpressed)* gene is located at 11q13.3 and IGH *(immunoglobulin heavy locus)* at 14q32.3.

The t(11;14)(q13;q32.3) translocation is the most common translocation in MM, where it is seen in approximately 15% of cases[1,2]. Unlike mantle cell lymphoma (MCL), where the breakpoints are clustered in a 1kb region that is 120kb centromeric to the CCND1 gene[3], the breakpoints in MM cases are dispersed within a 360kb region between CCND1 and MYEOV at 11q13[4]. MYEOV is a putative oncogene, located 360kb centromeric to CCND1, which is thought to be activated in the translocation by becoming closely associated with IGH enhancers. In contrast to IGH rearrangements in other neoplasms, those found in MM have IGH breakpoints predominantly in the C/J region, which, in the case of MYEOV, brings the MYEOV gene under the control of the 3' Eα1 enhancer[4]. In CCND1 translocations by contrast, the Eμ enhancer controls CCND1 expression. MYEOV overexpression is a possible prognostic factor in MM[5].

The t(11;14)(q13;q32.3) is associated with a favourable outcome in most series and therefore is regarded as neutral with regard to prognosis[2].



References

1. Fonseca R, *et al.* Leukemia. 2009;23(12):2210-2221.
2. Sawyer JR. Cancer Genetics. 2011;204(1):3-12.
3. Ronchetti, *et al.* Blood. 1999 93(4):1330-1337.
4. Janssen, *et al.* Blood. 2000 15;95(8):2691-2698.
5. Moreaux, *et al.* Exp Haematol. 2010;38(12):1189-1198.

Haematology FISH Probes for Multiple Myeloma

Multiple Myeloma Probe Range

Probe Name	Chromosome Region	Probe Type	Control Probe	No. Tests	Cat. No.*
13q14.3 Deletion	13q14.2-q14.3	Deletion	D13S1825	5 or 10	LPH 006
CKS1B/CDKN2C (P18) Amplification/Deletion	1q21.3/1p32.3	Amplification/Deletion	-	5 or 10	LPH 039
D13S319 *Plus* Deletion	13q14.2-14.3	Deletion	LAMP1	5 or 10	LPH 068
D13S25 Deletion	13q14.3	Deletion	D13S1825	5 or 10	LPH 043
IGH Breakapart	14q32.3	Breakapart	-	5 or 10	LPH 014
IVDR IGH *Plus* Breakapart	14q32.3	Breakapart	-	5 or 10	CE-LPH 070
IGH/CCND3 *Plus* Translocation, Dual Fusion	14q32.3/6p21	Translocation	-	5 or 10	LPH 075
IVDR IGH/FGFR3 *Plus* Translocation, Dual Fusion	14q32.3/4p16.3	Translocation	-	5 or 10	CE-LPH 074
IGH/MAF *Plus* v2 Translocation, Dual Fusion	14q32.3/16q23	Translocation	-	5 or 10	LPH 108
IGH/MAFB *Plus* Translocation, Dual Fusion	14q32.3/20q12	Translocation	-	5 or 10	LPH 077
IVDR IGH/MYEOV *Plus* Translocation, Dual Fusion	14q32.3/11q13.3	Translocation	-	5 or 10	CE-LPH 078
P53 (TP53) Deletion	17p13	Deletion	D17Z1	5 or 10	LPH 017

*For 5 test kit add -S to catalogue number, e.g: LPH ###-S.

Haematology FISH Probes for Multiple Myeloma

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What binds us, makes us.

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