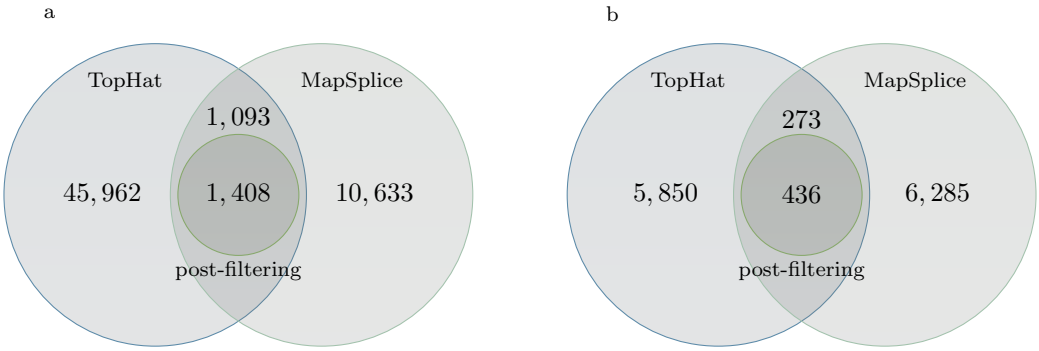
File name: Supplementary Information
Description: Supplementary Figures and Supplementary Tables

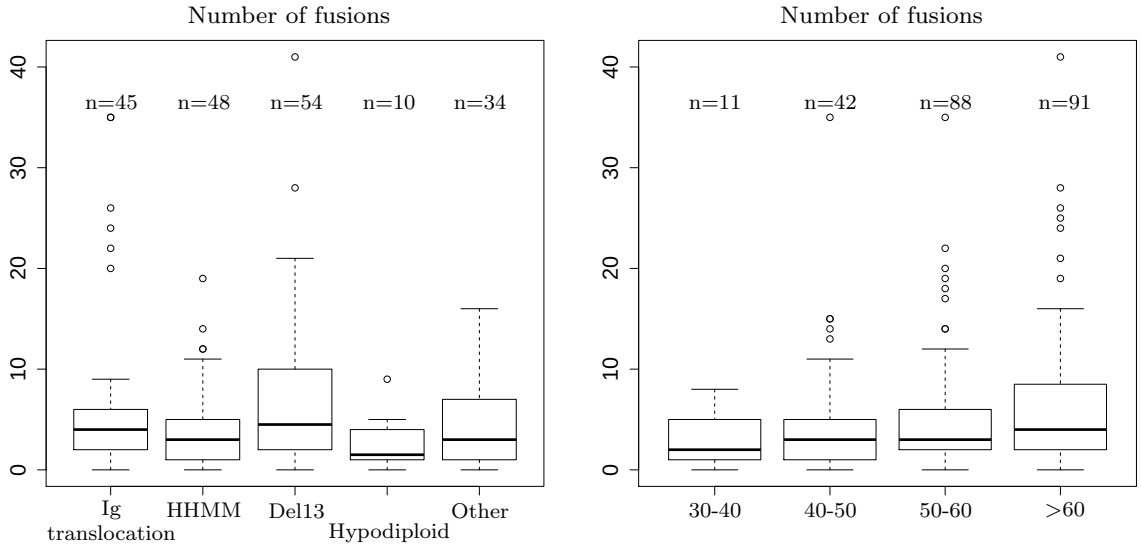
File name: Supplementary Data 1
Description: Fusion list in MM cohort

File name: Supplementary Data 1
Description: Commands used for data analysis

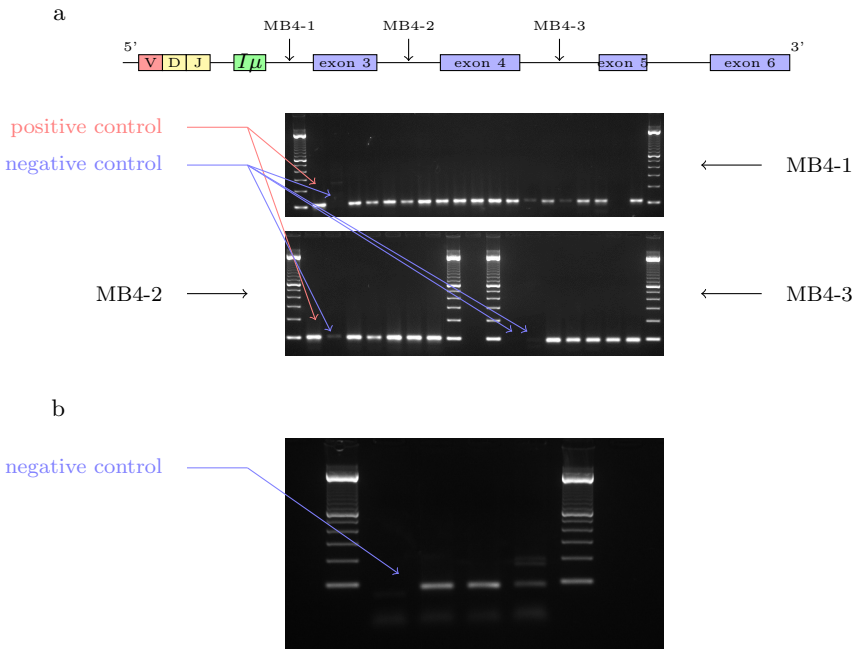
File name: Peer Review File
Description:



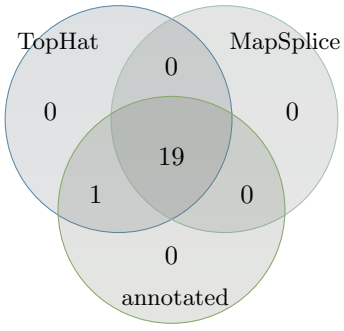
Supplementary Figure 1 – Number of fusions predicted by each algorithm, number found by both algorithms, and number of fusions retained post-filtering. In the IFM cohort (a) and in the cell-lines (b).



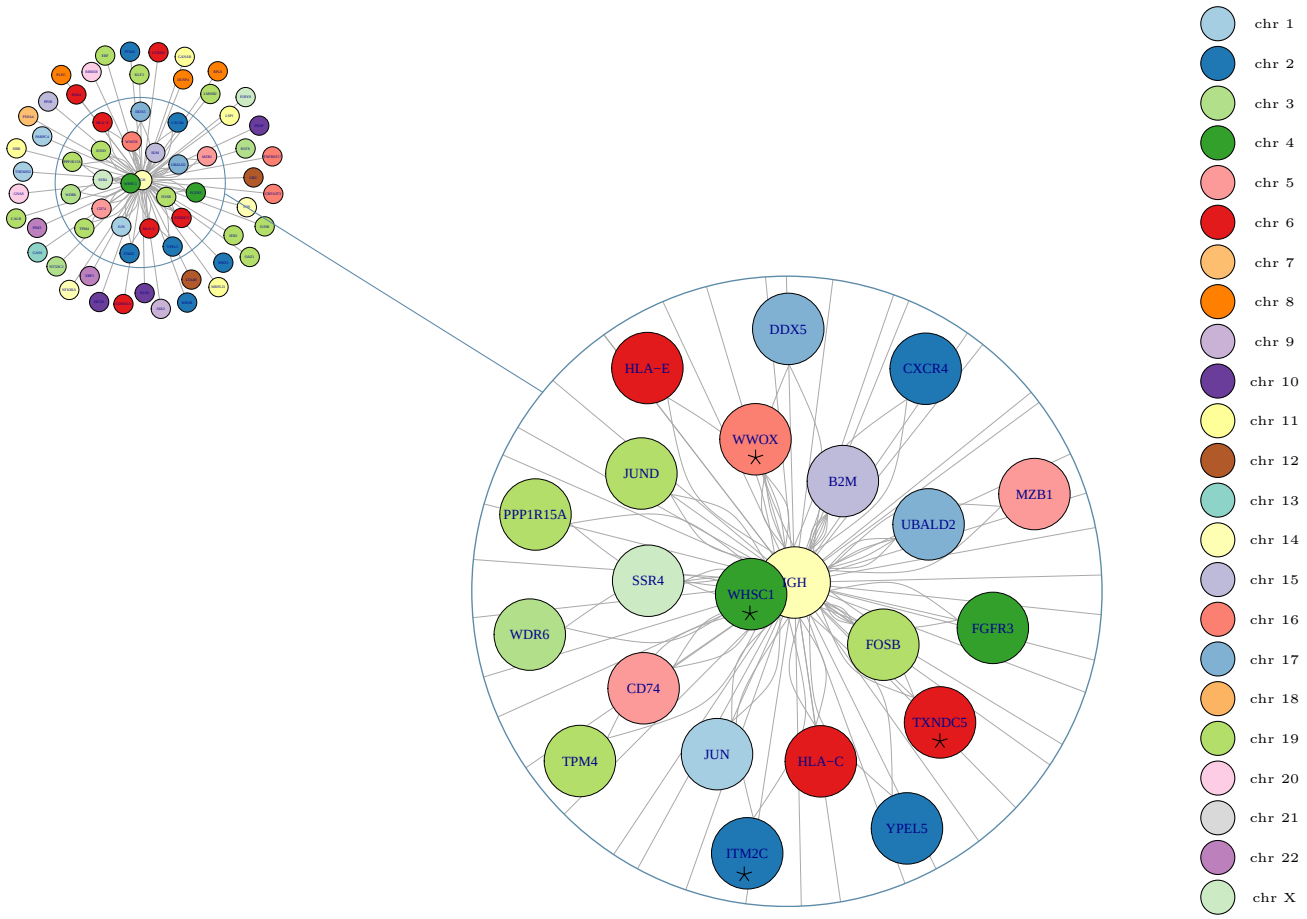
Supplementary Figure 2 – a : Boxplots of the number of fusions in each cytogenetic subgroup : known Ig-translocated (FISH experiments), high-hyperdiploid patients (over 53 chromosomes), patients with deletion 13, hypodiploid patients (less than 45 chromosomes) without deletion 13, and other patients. b : Number of fusions according to age.



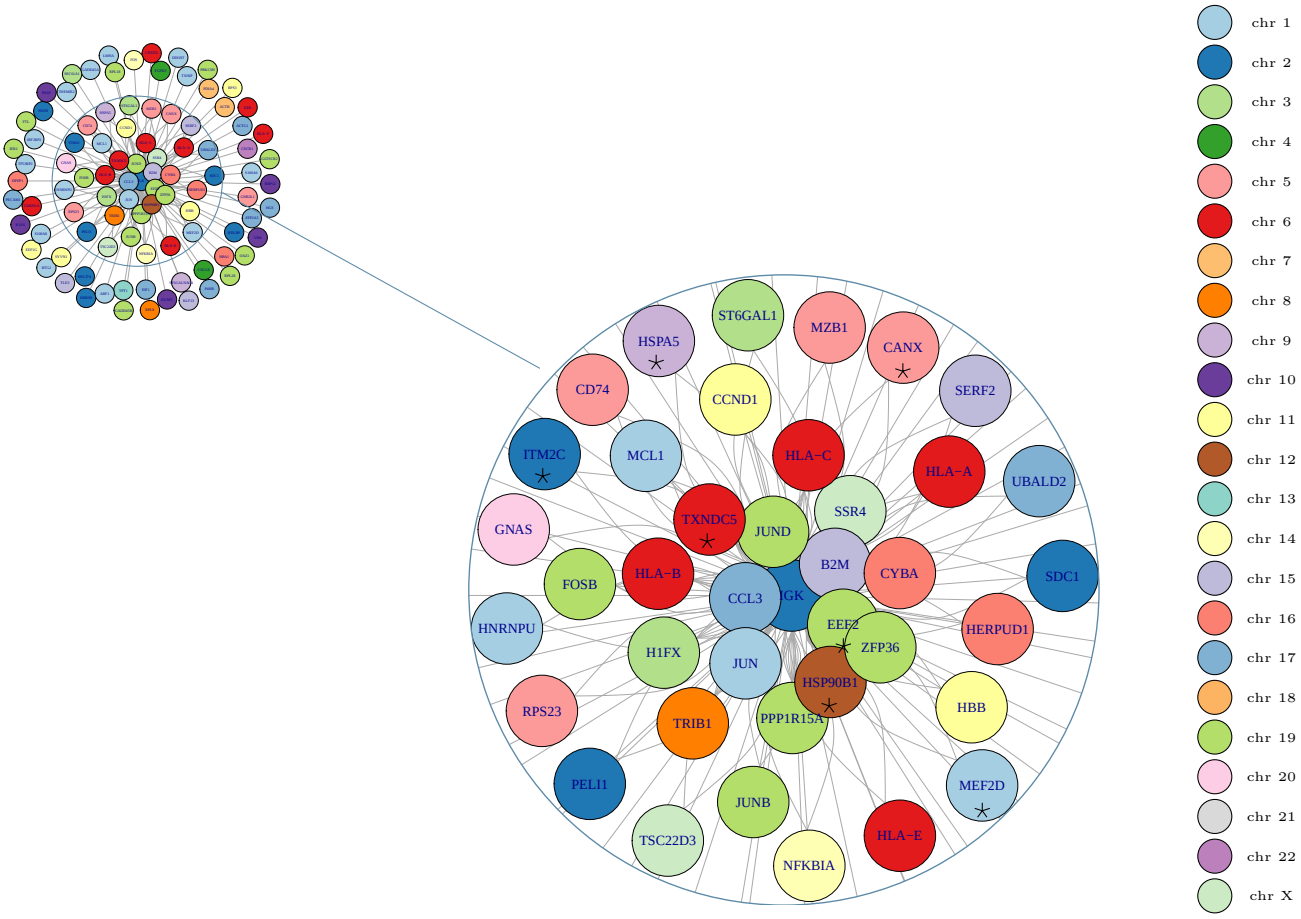
Supplementary Figure 3 – PCR validation of fusion genes. a : RT-PCR validation of IGH-MMSET fusions, with separation based on the breakpoint location : MB4-1 (MMSET intron n°2), MB4-2 (MMSET intron n°3) and MB4-3 (MMSET intron >4). b : subset of RT-PCR validation of IGH-B2M fusions.



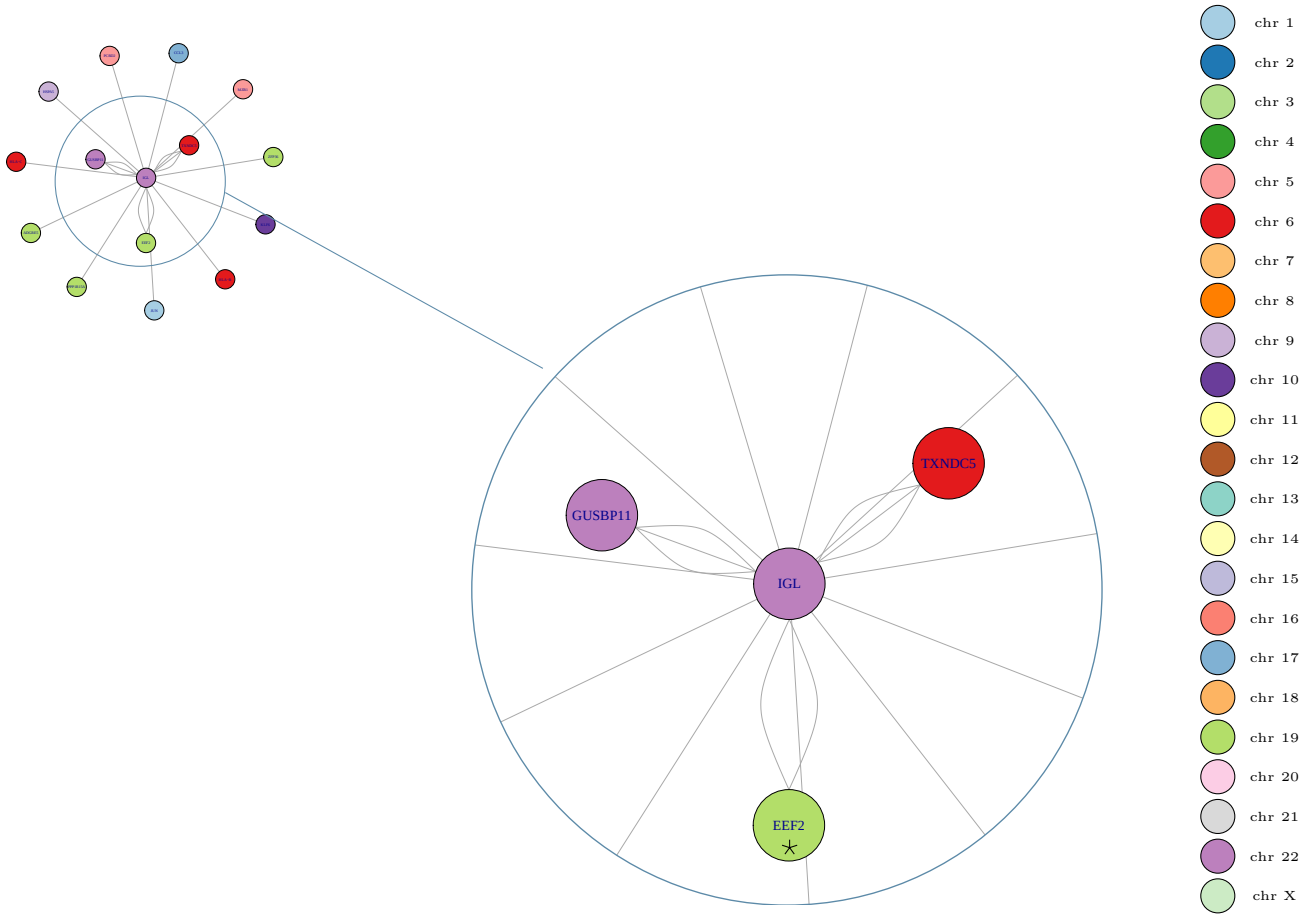
Supplementary Figure 4 – Number of IgH-MMSET fusions found by algorithms in the cell-lines known to exhibit a t(4;14) fusion. One sample was identified by TopHat only with evidence of the fusion occurring within an MMSET intron.



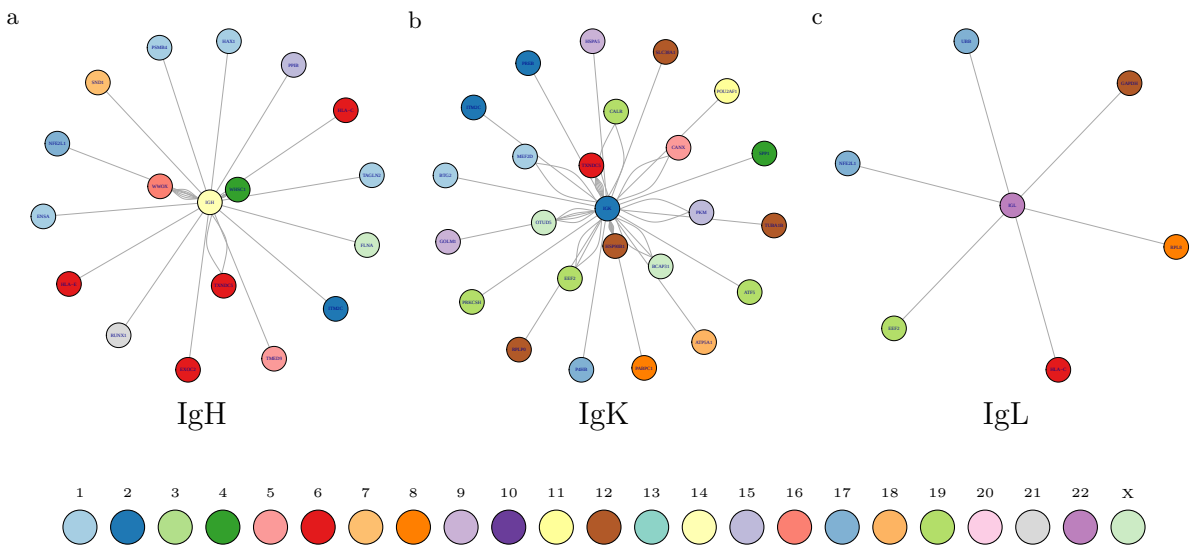
Supplementary Figure 5 – Most recurrent partner genes in IgH fusions. This figure is a zoom into main figure 3a. Stars denote fusions that were also found in cell-lines.



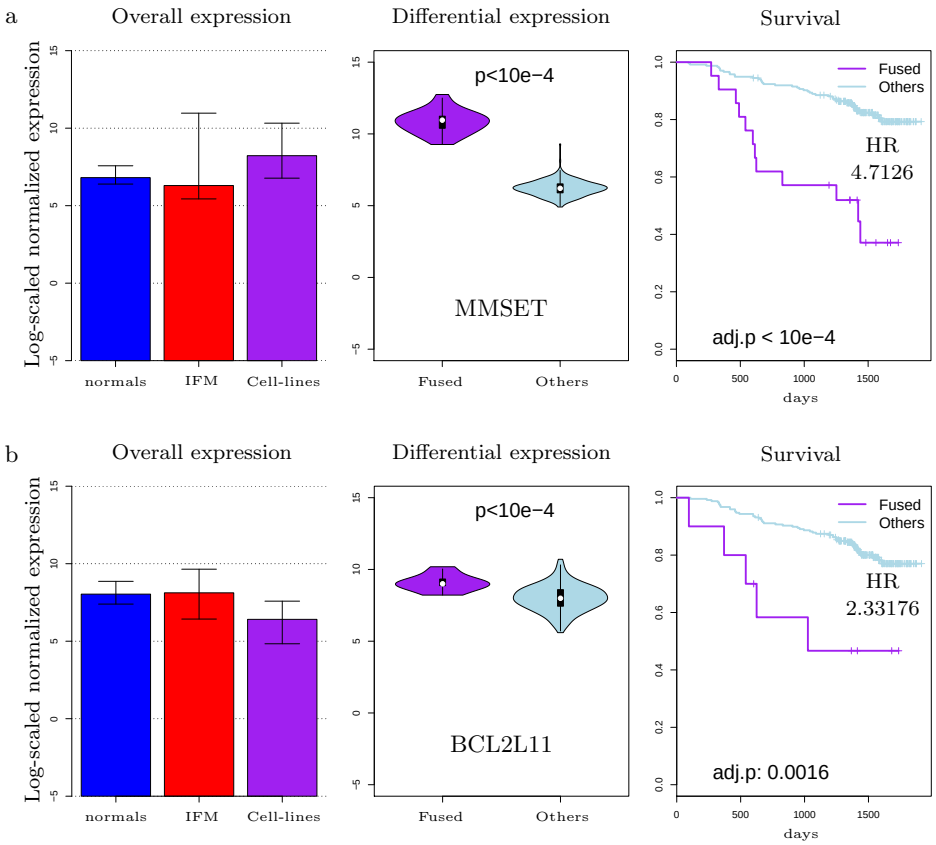
Supplementary Figure 6 – Most recurrent partner genes in IgK fusions. This figure is a zoom into main figure 3b. Stars denote fusions that were also found in cell-lines.



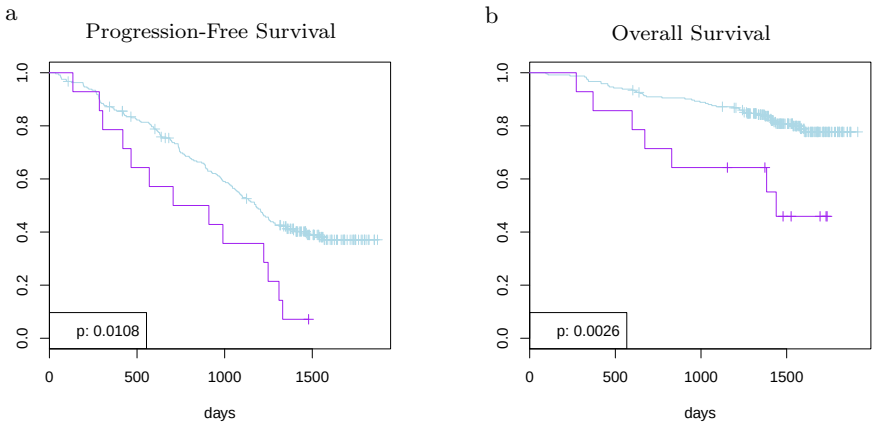
Supplementary Figure 7 – Most recurrent partner genes in IgL fusions. This figure is a zoom into main figure 3c. Stars denote fusions that were also found in cell-lines.



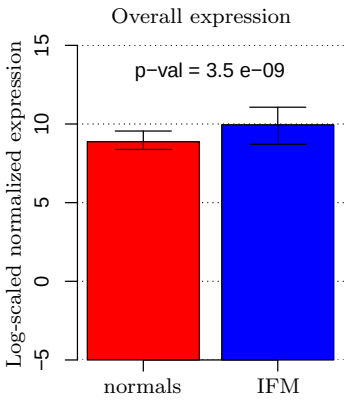
Supplementary Figure 8 – a : IgH fusions in cell-lines. The center edge is IgH, each other edge represents a partner gene, there is one node per fusion. Edges closest to the center are most recurrent. Edges are colored by chromosomes as indicated in d. b : IgK fusions in cell-lines. (Same as in a, with center edge IgK). c : IgL fusions in cell-lines. (Same as in a, with center edge IgL).



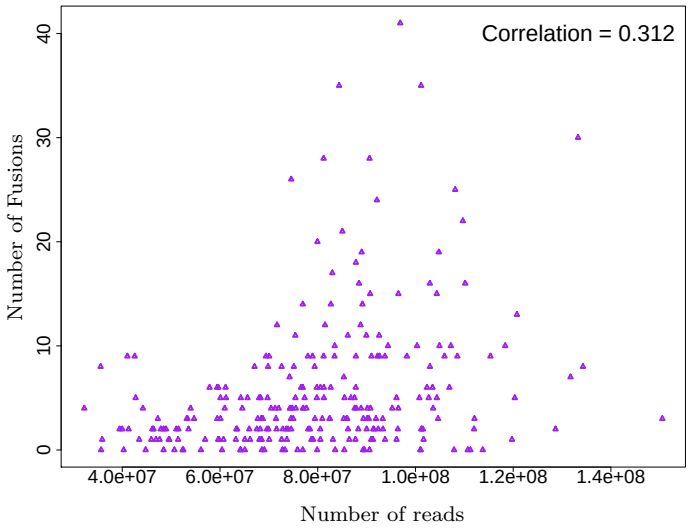
Supplementary Figure 9 – Two genes with clinical impact : MMSET (a) and BCL2L11 (b). The first sub-figure gives the expression of the gene in the normal samples, in the IFM cohort and in the cell-lines, error bars indicate standard deviation values. The second subfigure shows the distribution of gene expression within the IFM cohort, comparing patients with fusion (purple a) n=21, b) n=10), and patients without fusion (blue). The last subfigure gives the Kaplan-Meier estimate of the overall survival in the two previous subgroups, as well as the log-rank p-value adjusted for multiple testing on the 36 most frequently fused genes, and the hazard-ratio estimates from the Cox-proportional hazard model fitted with three high-risk known variables : ISS, presence of deletion 17p, and presence of t(4 ;14) translocation.



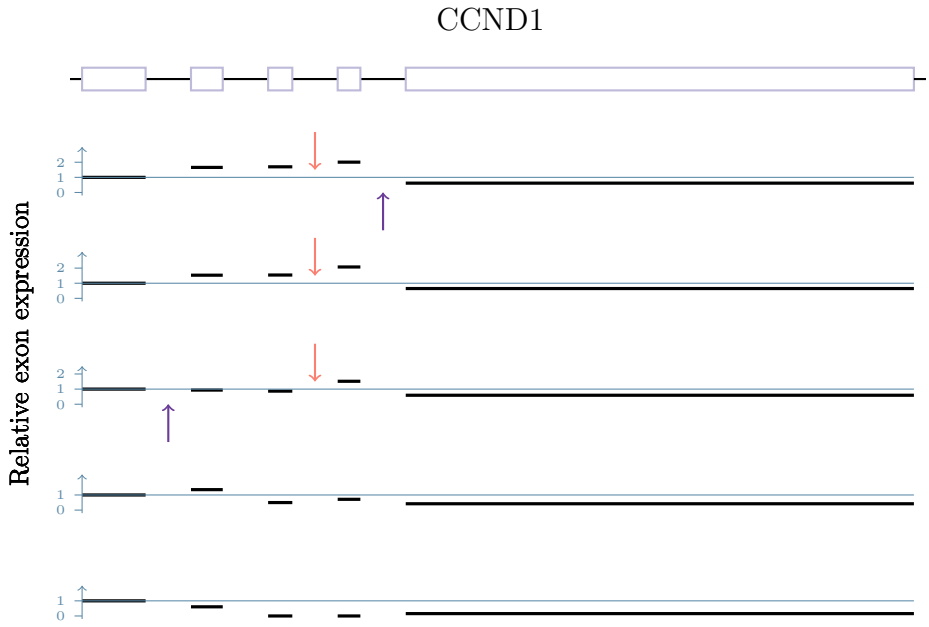
Supplementary Figure 10 – Clinical impact of the number of fusions : 16 patients with more than 16 fusions (a) Progression-free survival, (b) overall survival. P-values computed through log-rank tests.



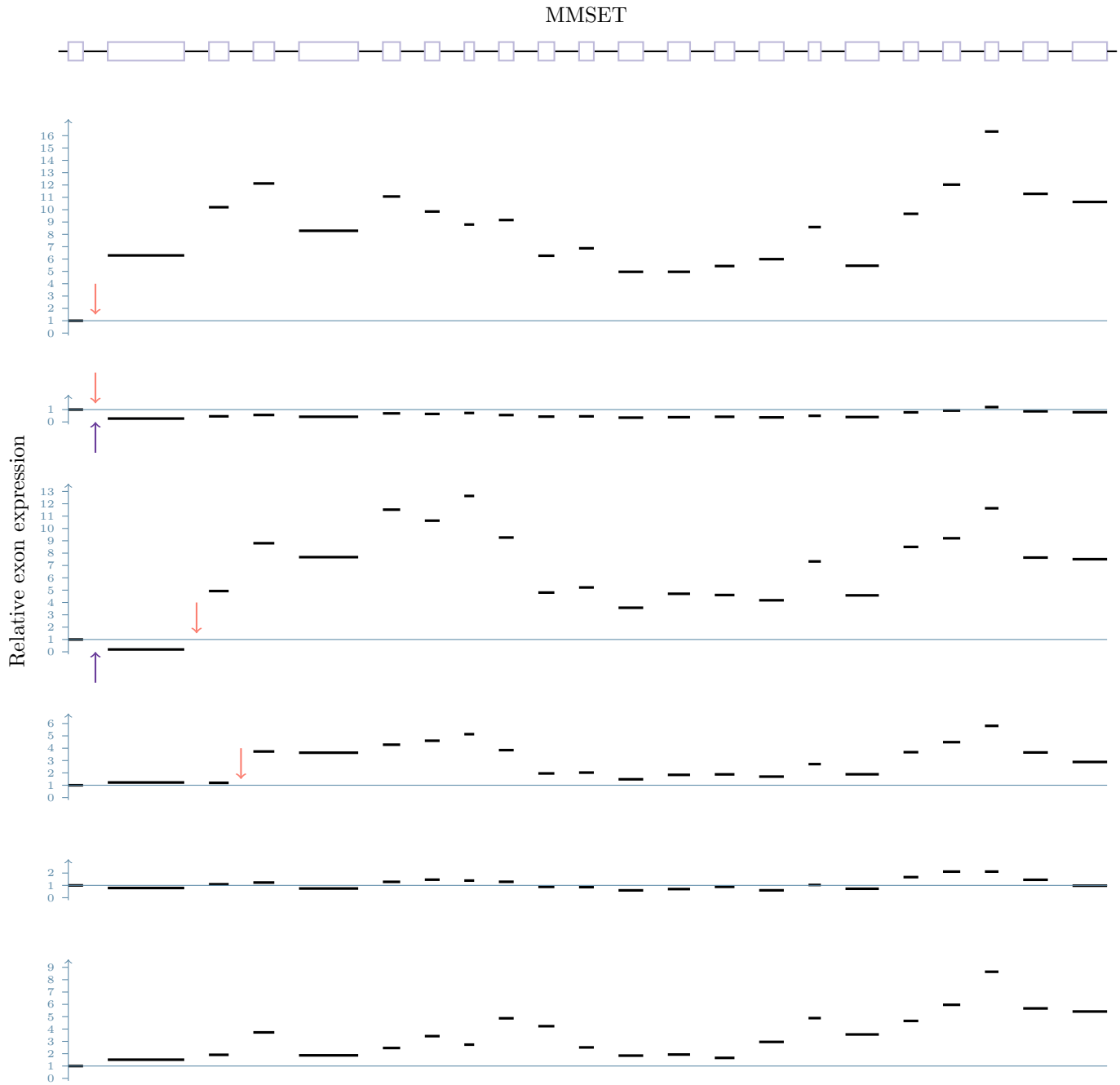
Supplementary Figure 11 – Expression of gene TXNDC5 in normal samples and in the IFM cohort, error bars indicate the 90% distribution interval. P-value computed using two-sided Student's t-test.



Supplementary Figure 12 – Correlation between sequencing depth (evaluated in terms of total amount of reads) and number of identified fusions, each triangle representing a patient sample.



Supplementary Figure 13 – Coverage of CCND1 exons in 5 patients. Levels are computed based on read counts per exon, normalized by exon length and by first exon expression. Red arrows indicate "3prime" fusions, *i.e.* exons after the arrow are involved in a fusion. Purple arrows indicate "5prime" fusions, *i.e.* exons before the arrow are involved in a fusion. Patient 1 has both a 3prime and a 5 prime fusion, Patient 2 only has a 3prime fusion, and Patient 3 has a 5prime fusion occurring before ahead of the 5 prime fusion. Patient 4 and 5 do not harbor any fusion. Expression levels do not contradict the presence of fusions, but do not support those either, especially when compared to expressions from non-fused patients.



Supplementary Figure 14 – Coverage of MMSET exons in 6 patients. Levels are computed based on read counts per exon, normalized by exon length and by first exon expression. Red arrows indicate "3prime" fusions, *i.e.* exons after the arrow are involved in a fusion. Purple arrows indicate "5prime" fusions, *i.e.* exons before the arrow are involved in a fusion. Patient 1 is MB4-1, Patient 2 is MB4-1 and both strands are fused (a reverse fusion MMSET-IgH is also predicted). Patient 3 is MB4-2 and has a reverse MMSET-IgH fusion predicted, and Patient 4 is MB4-3. Patients 5 and 6 have no predicted fusion. Expression levels support the presence of fusions, but are not sufficient to predict them.

	coef	exp(coef)	se(coef)	z	p
CSNK1G2_fusion	1.08	2.95	0.31	3.47	0.00
ISS	0.21	1.24	0.13	1.67	0.10
Del.17p	0.50	1.65	0.27	1.86	0.06
t.4.14	0.83	2.30	0.32	2.64	0.01

	loglik	Chisq	Df	P(>|Chi|)
1	-541.62			
2	-546.26	9.27	1	0.0023

Supplementary Table 1 – Output of fitted Cox-proportional hazard model and likelihood-ratio test for gene CSNK1G2 on progression-free survival

	coef	exp(coef)	se(coef)	z	p
CCND1_fusion	1.49	4.43	0.40	3.69	0.00
ISS	0.24	1.28	0.13	1.88	0.06
Del.17p	0.53	1.69	0.27	1.96	0.05
t.4.14	0.80	2.21	0.31	2.53	0.01

	loglik	Chisq	Df	P(>|Chi|)
1	-541.53			
2	-546.26	9.46	1	0.0021

Supplementary Table 2 – Output of fitted Cox-proportional hazard model and likelihood-ratio test for gene CCND1 on progression-free survival

	coef	exp(coef)	se(coef)	z	p
MMSET_fusion	1.55	4.71	0.94	1.65	0.10
ISS	0.17	1.18	0.23	0.73	0.47
Del.17p	0.82	2.27	0.41	2.02	0.04
t.4.14	-0.48	0.62	0.98	-0.49	0.63

	loglik	Chisq	Df	P(>|Chi|)
1	-181.13			
2	-182.17	2.09	1	0.1480

Supplementary Table 3 – Output of fitted Cox-proportional hazard model and likelihood-ratio test for gene MMSET on overall survival

	coef	exp(coef)	se(coef)	z	p
BCL2L11_fusion	0.83	2.29	0.58	1.44	0.15
ISS	0.18	1.20	0.23	0.79	0.43
Del.17p	0.79	2.20	0.42	1.90	0.06
t.4.14	0.85	2.33	0.45	1.86	0.06

	loglik	Chisq	Df	P(>|Chi|)
1	-181.30			
2	-182.17	1.74	1	0.1869

Supplementary Table 4 – Output of fitted Cox-proportional hazard model and likelihood-ratio test for gene BCL2L11 on overall survival