Supplemental Materials and Methods

Whole-exome capture and massively parallel sequencing

Purified tumor and germline genomic DNA from the discovery panel FR-CLL patients was enriched in protein coding sequences using the in-solution exome capture SureSelect Human All Exon 50Mb kit (Agilent Technologies). The latter encompasses all coding exons annotated by the GENCODE project, including all exons in the Consensus CDS (CCDS, March 2009) database, 10 bp of flanking sequence for each targeted region, and small noncoding RNAs from miRBase (v.13) and Rfam.

As quality controls for the pre-capture and post-capture steps, randomly selected PCR-amplified clones of the PCR products were subjected to Sanger sequencing to verify their preferential alignment to human genomic regions and to human coding transcripts (n = 50/library).

The performance of the sequencing was as follows: on average, ~104.1 million reads per case were mapped, at a mean depth of 81.5 (range, 38-112); 84% of the target sequence was covered by at least 30 reads (range, 68.6-88.6%). The comparison with data obtained by high-density SNP array analysis of the same tumor/normal pairs established the sensitivity of the method at 94% for heterozygous SNP calls.

Validation of candidate somatic mutations by Sanger sequencing

The sequences surrounding the genomic locations of the candidate tumor-specific non-silent mutations were obtained from the UCSC Human Genome database, and PCR primers were derived from previously published studies[18] or were custom-designed using the Primer 3 online software (http://frodo.wi.mit.edu/primer3/) and the *in silico* PCR tool of the UCSC Human Genome database (http://genome.ucsc.edu/) to verify the uniqueness of the match. Primers sequences are available upon request.

To assess whether the mutations identified preferentially targeted specific dinucleotides, the expected frequencies were based on the dinucleotide sequence composition of the Consensus CDS, and statistical significance of differences in overrepresented changes was assessed by a Poisson distribution after correction for multiple hypotheses.

In silico analysis of the mutated genes

The genes identified by WES in the discovery panel, were assigned to functional categories or annotated pathways by means of the “Functional Annotation cluster” of

DAVID software (http://david.abcc.ncifcrf.gov/).[1] This tool groups terms with similar annotations in clusters, and subsequently ranks them by Enrichment Score; clusters were then selected by retaining only the ones including at least one significant (p<0.05) term. The DAVID software was also used to run a "Functional Annotation chart" analysis based on KEGG, BIOCARTA, PANTHER, REACTOME and BBID pathways.

To the same purpose, the tools provided by the Molecular Signatures Database (Broad Institute, http://www.broadinstitute.org/gsea/msigdb/index.jsp), namely the "Compute overlap" and "Investigate Gene Sets" were applied.[2]

The consequences of somatic non-silent mutations were evaluated *in silico* by using the PolyPhen-2 (Polymorphism Phenotyping) algorithm (http://genetics.bwh.harvard.edu/pph2/), which predicts the possible effect of an aminoacid substitution on the structure and function of a human protein using physical and comparative considerations.

Screening of recurrently mutated genes

The sequences of the coding regions and splice sites of the recurrently mutated genes (*FAT1*, *UTRN*, *FPGT*, *TSC1*), required to have a Phred score ≥ 20, were compared with the Reference sequence by the Mutation Surveyor Version 3.97 software (SoftGenetics) to identify candidate somatic mutations automatically and/or by manual curation. Synonymous mutations and variants reported as SNP (in NCBI dbSNP 137 and 1000 Genomes Project, http://www.1000genomes.org/) were filtered out. The remaining candidate somatic mutations were validated on high-molecular-weight genomic DNA from both tumor and normal (when available) samples by performing PCR amplification and bidirectional direct sequencing.

Copy number analysis by high-density SNP array

Data processing and identification of regions of abnormal copy number were performed according to a previously described workflow that implies the use of the dChipSNP software (https://sites.google.com/site/dchipsoft/) and a karyotype-guided normalization procedure).[4] For normalization purposes, matched normal DNA was simultaneously analyzed for the discovery panel patients; for samples belonging to the screening panel, the segmentation was computed against a diploid reference set of three normal DNA samples included in the same experiment as the tumor samples.

Visual inspection of the segments was performed by dChipSNP to exclude false calls due to experimental artifacts. Furthermore, to exclude calls of genomic gains or losses arising from inherited genomic CNVs in the unpaired samples, 130 normal DNAs from an independent study[5] were visualized simultaneously with the tumor samples. Alterations present in the pool of reference samples were presumed to be inherited and therefore eliminated. In addition, CNVs were excluded if the same regions were present in the Database of Genomic Variants (http://dgvbeta.tcag.ca/dgv/app/home).

Chromotripsis was suggested when at least 10 switches within the same chromosome were observed, in agreement with previously published papers.[6,7]

In order to identify CNAs that might have pathogenetic relevance, two approaches were used: i) identification of focal Minimal Common Regions (MCR) of aberration, ii) Genomic Identification of Significant Targets in Cancer (GISTIC) analysis.

The recognition of MCR was performed as follows: we first scanned through the curated segmented data across the affected samples to determine all consensus regions that are targeted by overlapping events of similar nature (gains and losses, separately) in ≥ 2 samples; we then refined the list of consensus regions by visual inspection using the Integrative Genomics Viewer (IGV) software (http://www.broadinstitute.org/igv) to retain only the core consensus regions. In particular, we focused on focal MCRs of gain or loss, which were defined according to the following criteria: i) the consensus interval across all affected tumors is smaller than 1Mb and/or encompasses 1-10 genes; and ii) in at least one of the affected sample, the aberrant segment encompasses 1-10 genes. MCRs encompassing ≤ 10 genes, but deriving from the overlap between large segments, and regions devoid of coding genes were not considered.

The second approach was represented by the GISTIC method, which was applied to the curated segmentation results as described by Beroukhim *et al*.[8]

GISTIC identifies significantly amplified or deleted regions of the genome across a set of samples taking into account its amplitude and the probability of detecting it by chance. Each significant region is represented by a peak and a q-value is assigned.

References

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Table S1. Characteristics of the screening panel cases at refractoriness.

Sample ID	Timing of refractoriness	Gender	Age	Binet stage	Lymphocytes ($x10^9$/L)	CD5+/CD19+ (%)	IGHV	IGHD	IGHJ	IGHV homology	IGHV status	Cytogenetics	*TP53* mutational status	*NOTCH1* mutational status	*BIRC3* mutational status	*BIRC3* deletion by SNP or FISH	ZAP-70^ expression	CD38^^ expression	SNP experiment
3878	Primary	F	73	A	11.5	80	4-34*01	2-2*01	6*02	100.00	UM	+12, del13q14	WT	M	M	No	P	P	Yes
3981	Acquired	M	75	C	70.0	85	3-21*01	nd	6*02	95.83	M	del11q22-q23, del13q14	WT	WT	WT	Yes	N	P	Yes
4047	Acquired	M	79	A	17.4	85	1-2*04	2-2*01	6*03	100.00	UM	NA	WT	WT	WT	No	NA	P	Yes
4232	Primary	M	52	C	33.3	80	1-69*01	3-3*01	6*03	100.00	UM	del17p13, del13q14	M	WT	WT	No	N	N	Yes
4262	Acquired	M	65	C	100.0	93	4-59*07	3-9*01	3*02	92.37	M	+12, del17p13, del13q14	WT	WT	WT	No	N	P	Yes
4380	Acquired	F	76	C	21.0	98	4-59*01	nd	6*03	98.09	UM	+12, del17p13	WT	WT	WT	No	P	N	Yes
4845	Primary	M	77	A	19.5	80	1-46*01	6-19*01	4*02	99.58	UM	del17p13, del13q14	M	WT	WT	No	P	N	Yes
4885	Acquired	M	93	C	66.7	89	1-2*04	3-3*01	6*02	100.00	UM	del11q22-q23, del13q14	WT	WT	WT	Yes	P	N	Yes
5610	Acquired	F	78	C	19.5	80	3-30*03	6-19*01	2*01	89.86	M	+12	WT	WT	M	No	N	P	Yes
5675	Acquired	M	64	C	16.0	70	4-39*01	6-13*01	5*02	100.00	UM	+12, del17p13, del11q22-q23	WT	M	WT	No	N	P	Yes
5977	Acquired	F	78	C	7.5	90	1-69*01	3-3*01	6*02	100.00	UM	del11q22-q23	WT	WT	M	Yes	P	N	Yes
6012	Primary	M	82	B	13.7	95	4-34*02	6-13*01	4*02	95.43	M	del17p13, del13q14	M	WT	WT	No	N	N	Yes
6342	Acquired	F	82	C	20.2	90	4-34*01	3-3*01	4*02	88.26	M	del13q14	M	WT	WT	No	P	N	Yes
6496	Acquired	M	80	B	30.8	90	4-39*01	6-13*01	5*02	100.00	UM	+12	WT	M	M	No	NA	P	Yes
6550	Acquired	M	59	C	23.0	70	5-51*01	3-22*01	4*02	100.00	UM	del11q22-q23, del13q14	WT	WT	M	Yes	N	P	Yes
6944	Primary	M	59	A	80	94	4-61*01	2-2*02	6*02	88.6	M	del17p13, del11q22-q23	M	WT	WT	No	N	N	Yes
7228	Primary	F	83	C	435.0	90	4-4*02	2-2*01	5*02	100.00	UM	Normal	WT	WT	WT	No	N	P	Yes
7425	Primary	M	70	B	21.9	90	4-34*01	3-10*01	3*01	89.47	M	del11q22-q23, del13q14	WT	WT	WT	Yes	NA	N	No
7916	Primary	M	79	C	51.0	94	4-30-4*01	3-22*01	5*02	100.00	UM	del17p13	M	WT	WT	No	P	N	Yes
8081	Acquired	M	82	C	15.0	80	4-59*01	6-13*01	4*02	97.18	M	del13q14	WT	WT	WT	Yes	NA	P	Yes
8253	Primary	M	71	C	36	NA	2-05*01	2-2*02	6*02	100	UM	+12, del13q14	WT	WT	WT	No	P	NA	Yes
9244	Acquired	M	69	B	112.0	90	3-23*01	6-13*01	4*02	87.28	M	+12, del11q22-q23, del13q14	WT	WT	WT	Yes	N	N	Yes
9303	Acquired	F	69	B	31.7	82	1-69*01	6-19*01	4*02	99.21	UM	+12	WT	M	WT	No	P	N	Yes
9311	Acquired	F	84	C	168.0	90	1-69*01	2-15*01	6*02	99.65	UM	del17p13	M	WT	WT	No	P	P	Yes
9930	Primary	F	60	C	26.0	92	4-39*01	4-4*01	6*02	100.00	UM	+12, del17p13	M	M	WT	No	P	N	Yes
10320	Primary	F	78	C	40.7	88	2-5*10	3-3*01	6*03	99.51	UM	del13q14	WT	M	WT	No	P	P	Yes
10649	Primary	M	55	C	50.0	70	1-69*13	2-15*01	6*02	100.00	UM	del11q22-q23, del13q14	WT	WT	WT	Yes	N	N	Yes
11203	Primary	M	73	A	43.6	91	3-64*05	3-3*01	4*02	100.00	UM	+12	WT	WT	WT	No	NA	N	Yes
12477	Acquired	F	75	C	48.5	96	3-74*01	3-3*01	6*02	100.00	UM	+12	WT	M	WT	No	P	N	Yes
12521	Primary	F	53	C	NA	88	1-3*01	6-19*01	4*02	99.65	UM	+12, del17p13	M	WT	WT	NA	P	N	No
12525	Primary	M	58	B	NA	76	1-2*02	3-3*01	4*02	100.00	UM	del17p13, del13q14	M	M	WT	NA	P	N	No
12530	Primary	M	65	A	NA	93	1-46*01, or	6-6*01	6*02	100.00	UM	Normal	WT	M	WT	No	P	P	No
12534	Primary	F	64	B	NA	75	1-2*04	5-5*01	6*02	100.00	UM	del13q14	WT	M	M	No	N	P	No
12535	Primary	M	49	B	NA	90	3-21*01	3-9*01	4*02	99.65	UM	del17p13	WT	WT	WT	No	P	P	No
12539	Acquired	M	72	B	NA	90	1-2*02	1-26*01	6*02	99.65	UM	del11q22-q23, del13q14	WT	WT	WT	Yes	N	P	No
12542	Primary	M	85	B	NA	77	1-69*01	2-2*01	6*02	100.00	UM	del11q22-q23, del13q14	WT	WT	M	NA	P	N	No
12547	Primary	M	68	B	NA	83	1-69*02	3-3*01	4*02	100.00	UM	+12, del13q14	WT	WT	WT	No	N	P	No
12557	Primary	M	63	B	NA	85	5-a*03	6-19*01	4*02	100.00	UM	del13q14	WT	WT	WT	NA	P	P	No
12562	Acquired	F	64	C	NA	80	3-74*01	2-2*01	4*02	98.61	UM	del11q22-q23	WT	WT	WT	Yes	P	P	No
12568	Primary	F	81	C	NA	80	3-23*01	3-10*01	4*02	98.96	UM	del13q14	M	M	M	No	P	P	No
12570	Primary	M	66	C	NA	90	NA	NA	NA	NA	NA	del13q14	WT	WT	WT	NA	P	N	No
12571	Acquired	M	83	A	NA	75	4-34*01	3-3*01	6*04	100.00	UM	+12	WT	WT	WT	No	P	P	No
12627	Acquired	M	73	A	NA	NA	4-04	3-03	6c	100.00	UM	NA	WT	WT	WT	NA	NA	N	No
12628	Acquired	F	68	C	211.7	97	1-69	3-22	4b	100.00	UM	del17p13, del13q14	WT	WT	WT	NA	P	N	No
12631	Acquired	M	61	C	15.1	NA	1-69	3-10	6b	100.00	UM	Normal	WT	WT	WT	NA	P	P	No
12632	Acquired	M	73	NA	30.0	76	3-20	7-27	4b	98.60	UM	del13q14	WT	WT	M	NA	P	P	No
13931	Acquired	M	78	C	21.6	90	3-30*01	3-22*01	4*02	100.00	UM	del17p13, del11q22-q23, del13q14	M	M	WT	No	P	P	Yes
FR-CLL_11	Acquired	M	45	B	42.0	93	4-31*03	3-10*01	4*02	100.0	UM	del11q22-q23, del13q14	WT	WT	WT	NA	N	P	No

^Considered positive if the percentage of positive leukemic cells was >20% by FACS analysis

^^Considered positive if he percentage of positive leukemic cells was >30%

Abbreviations. NA, not available.

Table S2. Characteristics of the unselected CLL at diagnosis series.

Characteristics [a]	All (n=174)	
	n	%
Age >70 years	91	52.3
Male	99	56.9
Binet A	130	74.7
Binet B	23	13.2
Binet C	21	12.1
IGHV identity ≥98% [b]	64	37.0
13q14 deletion	95	54.6
Trisomy 12	41	23.6
11q22-q23 deletion	15	8.6
17p13 deletion	20	11.5
TP53 mutations	18	10.3
TP53 lesions [c]	24	13.8
NOTCH1 mutation	22	12.6
SF3B1 mutation	12	6.9
BIRC3 deletion	6	3.4
BIRC3 mutation	4	2.3
BIRC3 disruption	8	4.6
MYD88 mutation	7	4.0

[a] *IGHV*, immunoglobulin heavy variable gene
[b] *IGHV* mutation status was assessable in 173 patients; 1 patient lacked productive *IGHV-IGHD-IGHJ* rearrangements
[c] Clonal *TP53* mutations and/or 17p13 deletion

Table S3. Illumina sequencing summary.

Sample ID	Target Region Coverage (%)		Mean Depth^	N of mapped reads (%)	% of SNP detection
	≥10X	≥30X			
FR-CLL_1T	93.1	84.2	71.5	90318158 (98.3)	95.8
FR-CLL_1N	93.1	83.6	67.5	84859696 (98.4)	94.5
FR-CLL_2T	93.5	84.8	75.5	97120344 (98.2)	94.8
FR-CLL_2N	92.6	81.3	60.2	78584417 (98.2)	94.8
FR-CLL_3T	93.7	86.0	88.6	114597200 (97.8)	94.6
FR-CLL_3N	93.6	85.5	86.5	107516681 (97.6)	95.3
FR-CLL_4T	89.3	68.6	38.6	49349074 (97.1)	93.9
FR-CLL_4N	94.3	87.1	92.5	119892880 (96.7)	95.2
FR-CLL_5T	93.8	86.2	89.8	115021059 (98)	95.7
FR-CLL_5N	93.3	84.7	79.4	101185263 (98)	95.3
FR-CLL_6T	91.5	79.4	58.7	74517848 (98.1)	94.0
FR-CLL_6N	95.0	88.6	112.4	142049821 (97.8)	94.8
FR-CLL_7T	93.3	84.5	76.9	99151994 (97.9)	93.3
FR-CLL_7N	94.2	86.2	82.7	107175995 (97.6)	94.6
FR-CLL_8T	91.8	83.0	88.4	109547573 (96.8)	92.8
FR-CLL_8N	94.4	87.5	102.7	128926720 (96.4)	94.8
FR-CLL_9T	93.8	86.7	104.2	134109285 (96.9)	93.9
FR-CLL_9N	93.5	85.6	85.2	106582658 (96.5)	93.7
FR-CLL_10T	93.8	86.4	95.9	126789600 (97.1)	89.2
FR-CLL_10N	93.1	83.9	72.9	94721988 (96.6)	94.1

^Mean number of sequence reads covering the target exome

Table S4. Validated somatic mutations identified by whole exome sequencing in the FR-CLL discovery panel.

Sample ID	Gene	Exon^	Chr	Start^^	End^^	Ref nt	Var nt	T frequency	T total depth	N total depth	Mutation Type	AA change	PolyPhen-2 prediction (probability)	COSMIC total alterations	CGC database*	CCDS ID
FR-CLL_1	ABCC9#	4	12	22069925	22069925	C	T	16	394	373	Missense	M173I	neutral (0.045)	6	No	CCDS8693.1,CCDS8694.1
FR-CLL_1	ATM	31	11	108165701	108165701	G	-	25	112	100	Frameshift del	L1608fs	nd	240	No	CCDS31669.1
FR-CLL_1	BACE2	8,9,8	21	42647351	42647351	G	A	46	84	90	Missense	M396I,V453I,V403I	neutral (0)	2	No	CCDS13670.1,CCDS13668.1,CCDS13669.1
FR-CLL_1	CNTF	2	11	58391620	58391620	C	A	19	100	99	Missense	N76K	deleterious (0.914)	1	No	CCDS31554.1
FR-CLL_1	ELF4	2	X	129208703	129208703	C	A	21	98	94	Missense	A34S	deleterious (0.993)	1	Yes	CCDS14617.1
FR-CLL_1	FAT1	5	4	187557371	187557371	C	T	11	199	184	Missense	G1331S	deleterious (1)	12	No	CCDS47177.1
FR-CLL_1	FPGT-TNNI3K,TNNI3K	4,2	1	74701801	74701801	A	T	18	94	85	Missense	K120I,K19I	deleterious (0.651)	10	No	CCDS44161.1,CCDS664.1
FR-CLL_1	LARS	25	5	145509655	145509655	T	C	18	107	99	Missense	I852V	neutral (0.09)	0	No	CCDS34265.1
FR-CLL_1	MUC5B	32	11	1273599	1273599	C	T	16	128	123	Nonsense	R4967*	nd	0	No	CCDS44515.1
FR-CLL_1	MYO1B	19	2	192257876	192257876	G	A	40	77	83	Nonsense	W718*	nd	8	No	CCDS46477.1,CCDS2311.1
FR-CLL_1	PDE7B	12	6	136508176	136508176	G	A	47	117	99	Missense	E350K	neutral (0.025)	1	No	CCDS5175.1
FR-CLL_1	PPEF1#	14,13	X	18842130	18842130	A	G	17	193	171	Missense	N531D,N469D	neutral (0.129)	0	No	CCDS14188.1,CCDS43920.1
FR-CLL_1	PTCHD1	3	X	23412261	23412261	A	T	14	167	155	Missense	I876F	neutral (0)	6	No	CCDS35215.2
FR-CLL_1	RGS4	4,6,4,5	1	163044131	163044131	C	A	19	296	304	Missense	Q78K,T230T,T115T,T133T	unknown	3	No	CCDS44271.1,CCDS44270.1,CCDS44272.1,CCDS1243.1
FR-CLL_1	SF3B1	14	2	198267361	198267361	T	C	25	114	123	Missense	K666E	deleterious (0.995)	6	No	CCDS33356.1
FR-CLL_1	SLC9A4		2	103120167	103120167	G	A	21	118	106	Splice site		nd	3	No	CCDS33264.1
FR-CLL_1	SPATA19	3	11	133714475	133714475	C	T	25	103	139	Missense	G66S	neutral (0.006)	0	No	CCDS8493.1
FR-CLL_2	ABCA4	31	1	94490595	94490595	G	A	52	71	50	Missense	R1517C	deleterious (0.957)	12	No	CCDS747.1
FR-CLL_2	AMOTL1	8	11	94587204	94587204	G	A	49	162	109	Missense	R634Q	deleterious (0.999)	2	No	CCDS44712.1
FR-CLL_2	ARID5B	6	10	63816919	63816919	A	C	46	111	82	Missense	N297T	deleterious (0.854)	4	No	CCDS31208.1
FR-CLL_2	CEACAM5#	2	19	42213644	42213644	C	T	6	313	295	Missense	T37I	deleterious (0.998)	2	No	CCDS12584.1
FR-CLL_2	CXorf40B	2	X	149100913	149100913	T	G	78	103	100	Missense	N109T	neutral (0.001)	0	No	CCDS35426.1
FR-CLL_2	ENTPD4	3	8	23305216	23305216	G	A	41	283	275	Missense	P130L	deleterious (0.994)	2	No	CCDS47827.1,CCDS6041.1
FR-CLL_2	GRAMD1C	17	3	113659113	113659113	C	T	24	95	91	Missense	A610V	neutral (0)	3	No	CCDS33826.1
FR-CLL_2	IQCF1	4	3	51929109	51929109	G	A	44	116	113	Missense	R139C	deleterious (1)	1	No	CCDS2836.1
FR-CLL_2	KLHL6	1	3	183273248	183273248	A	G	43	151	121	Missense	L65P	deleterious (0.919)	3	No	CCDS3245.2
FR-CLL_2	MAGEA8	1	X	149013882	149013882	G	C	14	167	135	Missense	R279T	deleterious (0.992)	0	No	CCDS14692.1
FR-CLL_2	MED26	3	19	16687433	16687433	G	A	48	54	38	Missense	T403M	deleterious (0.982)	2	No	CCDS12347.1
FR-CLL_2	OMG	1	17	29623256	29623256	A	G	22	127	96	Missense	C32R	deleterious (1)	2	No	CCDS11265.1
FR-CLL_2	S100A2	1	1	153536274	153536274	T	G	39	84	67	Missense	K26T	deleterious (0.982)	1	No	CCDS1044.1
FR-CLL_2	SCGB1D4	2	11	62065064	62065064	G	A	24	240	173	Missense	A41V	neutral (0.001)	0	No	CCDS31583.1
FR-CLL_2	SLC25A37	4	8	23429040	23429040	G	A	32	94	90	Missense	R230Q	deleterious (1)	0	No	CCDS47828.1
FR-CLL_2	SPAG16	14	2	214972935	214972935	T	C	41	73	57	Missense	S515P	deleterious (0.774)	2	No	CCDS2396.1
FR-CLL_2	TSC1	13	9	135780970	135780970	G	-	39	137	134	Frameshift del	N665fs	nd	14	Yes	CCDS6956.1
FR-CLL_2	ZNF536	2	19	31025826	31025826	C	T	21	158	132	Missense	S748L	neutral (0.302)	11	No	CCDS32984.1
FR-CLL_3	ABCA12	43,35	2	215820048	215820048	G	A	34	94	82	Missense	L2091F,L1773F	neutral (0)	11	No	CCDS33372.1,CCDS33373.1
FR-CLL_3	AHNAK2	7	14	105414251	105414251	C	T	53	395	409	Missense	V2513M	neutral (0.417)	1	No	CCDS45177.1
FR-CLL_3	ANK1	41,42,41,3	8	41519440	41519440	C	A	35	49	79	Missense	R1833L,R1874L,R1833L,R108L	deleterious (0.971)	9	No	CCDS6119.1,CCDS47849.1,CCDS6121.1,CCDS6122.1
FR-CLL_3	ATP12A	13	13	25274955	25274955	C	A	37	124	124	Missense	N592K	deleterious (0.999)	6	No	CCDS31948.1
FR-CLL_3	C10orf53		10	50916667	50916667	C	T	49	162	150	Splice site		nd	0	No	CCDS31202.1
FR-CLL_3	CCR7	3	17	38711057	38711057	A	T	39	70	74	Nonsense	C358*	nd	1	No	CCDS11369.1
FR-CLL_3	COL6A1	3	21	47404310	47404310	G	A	48	44	37	Missense	A119T	neutral (0.074)	1	No	CCDS13727.1
FR-CLL_3	DSP	23	6	7580154	7580154	G	C	44	196	189	Missense	R1244T	deleterious (0.824)	9	No	CCDS4501.1
FR-CLL_3	FPGT-TNNI3K,TNNI3K	11,9	1	74808793	74808793	G	A	42	88	73	Missense	E389K,E288K	neutral (0.228)	10	No	CCDS44161.1,CCDS664.1
FR-CLL_3	IKZF3	5	17	37947776	37947776	A	C	42	187	249	Missense	L162R	deleterious (0.995)	6	No	CCDS11346.1,CCDS11348.1,CCDS11349.1,CCDS11351.1
FR-CLL_3	MPDZ	1	9	13250312	13250312	C	A	33	99	96	Missense	M1I	neutral (0.395)	6	No	CCDS47951.1
FR-CLL_3	ODZ3	15	4	183652049	183652049	T	A	35	246	215	Missense	N908K	deleterious (0.818)	0	No	CCDS47165.1
FR-CLL_3	PDGFRA	9	4	55139874	55139874	G	A	50	92	91	Missense	R512Q	deleterious (0.999)	674	Yes	CCDS3495.1
FR-CLL_3	PEX1	16	7	92129115	92129115	C	A	49	91	109	Missense	R874I	deleterious (0.987)	2	No	CCDS5627.1
FR-CLL_3	PKHD1L1	69	8	110520004	110520004	G	A	40	415	441	Missense	A3703T	neutral (0.137)	14	No	CCDS47911.1
FR-CLL_3	PTPRU		1	29642023	29642023	C	T	45	99	109	Splice site		nd	7	No	CCDS334.1,CCDS335.1,CCDS44098.1
FR-CLL_3	SF3B1	15	2	198266832	198266837	TTTCTG	-	37	126	162	In frame deletion	DK700-Q699	nd	6	No	CCDS33356.1
FR-CLL_3	TG	37	8	134025965	134025965	G	A	56	72	84	Missense	R2173Q	neutral (0.001)	15	No	CCDS34944.1
FR-CLL_3	TP53	6	17	7577069	7577069	G	A	82	24	50	Missense	R290H	deleterious (1)	22245	Yes	CCDS45605.1,CCDS45606.1,CCDS11118.1
FR-CLL_3	XPO1	14	2	61719472	61719472	C	T	50	88	76	Missense	E571K	deleterious (0.996)	4	No	CCDS33205.1
FR-CLL_3	ZBTB38	1	3	141164202	141164202	A	C	37	75	65	Missense	K991T	neutral (0.127)	3	No	CCDS43157.1

FR-CLL_3	ZFHX4	9	8	77768210	77768210	C	T	47	301	287	Missense	A2973V	deleterious (0.651)	15	No	CCDS47878.1
FR-CLL_4	ATF7	1	12	53994750	53994750	G	A	59	41	126	Missense	P12L	neutral (0.002)	2	No	CCDS44905.1,CCDS44906.1,CCDS44907.1
FR-CLL_4	C12orf50	10	12	88379789	88379789	G	A	59	61	149	Missense	R322C	neutral (0.001)	3	No	CCDS9031.1
FR-CLL_4	CYP8B1	1	3	42916567	42916569	TCT	-	44	16	64	In frame deletion	DK248	nd	2	No	CCDS2707.1
FR-CLL_4	ELAVL4	7	1	50666509	50666509	G	T	51	136	285	Missense	A268S	neutral (0.001)	2	No	CCDS553.1
FR-CLL_4	FAM60A	3	12	31446745	31446745	G	T	62	26	69	Missense	R117S	deleterious (0.806)	0	No	CCDS8723.1
FR-CLL_4	HEXA	6	15	72643485	72643485	G	A	60	48	94	Missense	L221F	deleterious (0.973)	4	No	CCDS10243.1
FR-CLL_4	KRTAP8-1	1	21	32185527	32185527	G	T	69	54	125	Missense	D4E	neutral (0)	0	No	CCDS13607.1
FR-CLL_4	LAMA2	37	6	129714359	129714359	C	T	48	44	124	Missense	R1802C	deleterious (0.942)	10	No	CCDS5138.1
FR-CLL_4	MKNK2	5	19	2043553	2043553	C	T	46	28	75	Missense	R123Q	deleterious (0.998)	2	No	CCDS12079.1,CCDS12080.1
FR-CLL_4	PNN	9	14	39650571	39650571	A	C	47	114	237	Missense	K553T	deleterious (0.948)	1	No	CCDS9671.1
FR-CLL_4	SLCO1A2	7	12	21453377	21453377	T	G	64	42	109	Missense	K272T	deleterious (0.984)	4	No	CCDS8686.1
FR-CLL_4	SORL1	26	11	121454269	121454269	C	A	54	28	85	Missense	S1228Y	deleterious (0.998)	15	No	CCDS8436.1
FR-CLL_4	TP53	6	17	7577580	7577580	T	C	84	19	53	Missense	Y234C	deleterious (1)	22245	Yes	CCDS45605.1,CCDS45606.1,CCDS11118.1
FR-CLL_5	ADAMTS12	14	5	33624414	33624414	C	T	22	121	98	Missense	D689N	deleterious (0.999)	9	No	CCDS34140.1
FR-CLL_5	ADARB2	2	10	1421289	1421289	G	A	31	140	125	Missense	T56M	neutral (0.001)	3	No	CCDS7058.1
FR-CLL_5	ANO2	18	12	5724438	5724438	A	-	21	173	134	Frameshift del	F614fs	nd	7	No	CCDS44807.1
FR-CLL_5	CSMD3	42,41,42	8	113353899	113353899	A	T	26	65	78	Missense	F2153L,F2049L,F2113L	deleterious (0.999)	63	No	CCDS6315.1,CCDS6316.2,CCDS6317.1
FR-CLL_5	ELFN2	1	22	37770311	37770311	G	A	17	150	130	Missense	R422W	deleterious (0.996)	2	No	CCDS33642.1
FR-CLL_5	FBLN5	7	14	92353549	92353549	C	T	17	320	265	Missense	V243I	neutral (0.025)	6	No	CCDS9898.1
FR-CLL_5	GFRAL	5	6	55216180	55216180	G	A	28	285	266	Missense	C167Y	deleterious (1)	2	No	CCDS4957.1
FR-CLL_5	GP5#	1	3	194118638	194118638	T	C	22	129	121	Missense	E125G	deleterious (0.992)	3	No	CCDS3307.1
FR-CLL_5	IQCA1	18	2	237240051	237240051	G	A	16	299	275	Missense	A775V	neutral (0)	1	No	CCDS46549.1
FR-CLL_5	NPHP1	8	2	110922206	110922206	C	T	27	354	275	Missense	R277Q	neutral (0)	2	No	CCDS46385.1,CCDS2086.1
FR-CLL_5	NRP1	13	10	33481263	33481263	G	A	28	577	503	Nonsense	Q670*	nd	4	No	CCDS7177.1
FR-CLL_5	PABPC3	1	13	25671861	25671861	G	T	21	126	114	Missense	A509S	neutral (0)	4	No	CCDS9311.1
FR-CLL_5	ROBO2	12	3	77614244	77614244	C	T	33	177	256	Missense	P608S	deleterious (0.994)	11	No	CCDS43109.1
FR-CLL_5	SLC5A8#	5	12	101587434	101587434	C	T	16	233	204	Missense	A221T	neutral (0.009)	0	No	CCDS9080.1
FR-CLL_5	TP53	3	17	7579358	7579358	C	A	20	75	87	Missense	R110L	deleterious (0.898)	22245	Yes	CCDS45605.1,CCDS45606.1,CCDS11118.1
FR-CLL_6	BRAF	15	7	140453145	140453145	A	T	28	60	151	Missense	L597Q	deleterious (0.998)	18290	Yes	CCDS5863.1
FR-CLL_6	CHAT		10	50870832	50870832	C	T	24	133	264	Splice site		nd	3	No	CCDS44389.1,CCDS7232.1,CCDS7233.1
FR-CLL_6	MCM2	2	3	127318291	127318291	T	-	28	136	179	Frameshift del	L46fs	nd	4	No	CCDS3043.1
FR-CLL_6	OSBPL8	10,8	12	76784414	76784414	C	T	28	116	204	Missense	R318Q,R276Q	deleterious (0.54)	1	No	CCDS31862.1,CCDS41814.1
FR-CLL_6	REV3L	13	6	111695585	111695585	T	C	26	131	190	Missense	N1325D	neutral (0)	6	No	CCDS5091.2
FR-CLL_6	SLIT1	13	10	98816156	98816156	G	A	21	80	128	Missense	S408L	neutral (0.303)	4	No	CCDS7453.1
FR-CLL_6	TSC1	16	9	135778080	135778080	C	T	24	165	327	Missense	R768H	neutral (0.012)	14	Yes	CCDS6956.1
FR-CLL_6	VWF	50	12	6059041	6059041	G	T	38	82	167	Missense	P2722T	neutral (0.063)	12	No	CCDS8539.1
FR-CLL_6	ZMYM3	1	X	70472487	70472487	G	A	71	14	24	Nonsense	Q207*	nd	1	No	CCDS14409.1
FR-CLL_7	ARMC2#	13	6	109282844	109282844	A	T	10	189	202	Missense	Y662F	neutral (0.001)	0	No	CCDS5069.2
FR-CLL_7	CCDC80	7	3	112324501	112324501	G	T	25	120	107	Missense	D872E	deleterious (0.99)	2	No	CCDS2968.1
FR-CLL_7	COL12A1	23,38	6	75836148	75836148	C	T	29	126	134	Missense	E963K,E2127K	deleterious (0.993)	9	No	CCDS43481.1,CCDS43482.1
FR-CLL_7	CRB1	6	1	197390996	197390996	C	A	32	184	165	Missense	P680T	deleterious (0.999)	9	No	CCDS1390.1
FR-CLL_7	EGR2	2,2	10	64573164	64573164	C	G	21	125	160	Missense	E362Q,E412Q	deleterious (0.637)	2	No	CCDS44409.1,CCDS7267.1
FR-CLL_7	HMGCLL1	5,6	6	55378896	55378896	T	G	33	67	73	Missense	K164N,K194N	neutral (0.004)	4	No	CCDS43474.1,CCDS43475.1
FR-CLL_7	SAMHD1	6	20	35555625	35555625	C	-	54	109	134	Frameshift del	G219fs	nd	0	No	CCDS13288.1
FR-CLL_7	SF3B1	15	2	198266834	198266834	T	C	28	115	127	Missense	K700E	deleterious (0.986)	6	No	CCDS33356.1
FR-CLL_7	SLC23A2	8	20	4855316	4855316	G	C	24	148	145	Missense	S284C	neutral (0.033)	2	No	CCDS13085.1
FR-CLL_7	TBC1D19	4	4	26622273	26622273	A	T	18	120	103	Missense	H86L	deleterious (0.988)	1	No	CCDS3439.1
FR-CLL_7	TECPR1	2	7	97874313	97874313	C	T	33	48	58	Missense	V98M	deleterious (0.88)	1	No	CCDS47648.1
FR-CLL_8	ACSS3	5	12	81537018	81537018	T	G	61	116	127	Missense	L305V	neutral (0.06)	4	No	CCDS9022.1
FR-CLL_8	ANKRD50	3	4	125593540	125593540	T	G	55	85	68	Missense	K298Q	deleterious (0.788)	1	No	CCDS34060.1
FR-CLL_8	C4orf7	3	4	71099899	71099899	A	C	50	218	196	Missense	K85Q	neutral (0.36)	1	No	CCDS3537.1
FR-CLL_8	COL19A1	16	6	70831830	70831830	A	C	46	142	68	Missense	N446T	deleterious (0.872)	4	No	CCDS4970.1
FR-CLL_8	FAT1	13	4	187532909	187532909	A	G	38	110	90	Missense	Y3162H	deleterious (0.997)	12	No	CCDS47177.1
FR-CLL_8	GLYAT	4	11	58478159	58478159	C	T	49	138	200	Missense	R131H	neutral (0.051)	0	No	CCDS7971.1,CCDS7970.1
FR-CLL_8	HAS2	3	8	122626359	122626360	AG	CT	38	150	233	Missense	L550T	deleterious (0.877)	15	No	CCDS6335.1
FR-CLL_8	HSP90AB1	2	6	44217294	44217294	A	G	44	354	583	Missense	T110A	neutral (0.146)	4	No	CCDS4909.1
FR-CLL_8	JPH2	4	20	42744324	42744324	G	A	71	34	52	Missense	A664V	neutral (0)	0	No	CCDS13325.1
FR-CLL_8	KCNE1L	1	X	108868117	108868117	G	A	25	28	25	Missense	P45S	deleterious (0.979)	0	No	CCDS14547.1
FR-CLL_8	KIAA1210	6	X	118242320	118242320	C	A	22	279	296	Missense	A298S	neutral (0.001)	5	No	CCDS48156.1

FR-CLL_8	OR51S1	1	11	4869505	4869505	T	C	21	201	301	Missense	N312D	neutral (0.063)	4	No	CCDS31362.1
FR-CLL_8	POTEE[#]	15	2	132021826	132021826	G	A	23	345	681	Missense	S933N	neutral (0.475)	0	No	CCDS46414.1
FR-CLL_8	RNLS	1	10	90342937	90342937	A	T	56	25	52	Missense	V4E	deleterious (0.992)	1	No	CCDS7388.1,CCDS31239.1
FR-CLL_8	SAMD9L	1	7	92761912	92761912	G	C	49	277	246	Missense	Q1125E	deleterious (0.956)	4	No	CCDS34681.1
FR-CLL_8	SPTY2D1	6	11	18631423	18631423	C	G	41	159	164	Missense	K681N	deleterious (0.907)	1	No	CCDS31441.1
FR-CLL_8	SRPX2	7	X	99921802	99921802	C	G	44	72	76	Missense	T278S	neutral (0)	2	No	CCDS14471.1
FR-CLL_8	TRO	2	X	54949591	54949591	A	C	40	81	89	Missense	K209T	deleterious (0.964)	1	No	CCDS43958.1,CCDS43959.1
FR-CLL_8	UTRN	9	6	144757083	144757083	G	A	23	70	79	Missense	E290K	neutral (0.063)	5	No	CCDS34547.1
FR-CLL_9	ACAT1	6	11	108009632	108009632	T	C	43	166	128	Missense	M148T	deleterious (0.998)	3	No	CCDS8339.1
FR-CLL_9	ARSI	2	5	149677702	149677702	T	C	47	57	51	Missense	K262R	neutral (0.068)	2	No	CCDS34275.1
FR-CLL_9	ATM	11	11	108123639	108123639	G	-	40	48	45	Frameshift del	C633fs	nd	240	Yes	CCDS31669.1
FR-CLL_9	DSC2	13	18	28651777	28651777	T	A	39	124	104	Missense	D640V	neutral (0.015)	3	No	CCDS11892.1,CCDS11893.1
FR-CLL_9	MED12	2	X	70339253	70339253	G	A	92	73	61	Missense	G44S	deleterious (0.98)	4	No	CCDS43970.1
FR-CLL_9	MGST2	4	4	140624672	140624672	C	T	63	150	89	Missense	S98L	neutral (0.157)	1	No	CCDS3749.1
FR-CLL_9	MMP16	8	8	89068458	89068458	G	A	49	176	127	Missense	P424L	deleterious (1)	8	No	CCDS6246.1
FR-CLL_9	OR56B4	1	11	6129824	6129824	G	T	49	171	183	Missense	K272N	neutral (0.418)	1	No	CCDS31406.1
FR-CLL_9	PDCD5	2	19	33073122	33073122	C	T	41	70	52	Nonsense	Q30*	nd	2	No	CCDS12423.1
FR-CLL_9	PRM2	1	16	11370049	11370049	C	T	52	96	90	Missense	R60Q	neutral (0.003)	0	No	CCDS42118.1
FR-CLL_9	ROS1	33	6	117647498	117647498	T	A	38	117	78	Missense	T1816S	deleterious (0.799)	25	Yes	CCDS5116.1
FR-CLL_9	SVEP1	25	9	113209237	113209237	A	C	45	110	90	Missense	L1402V	deleterious (0.899)	7	No	CCDS48004.1
FR-CLL_9	TMEM132B	9	12	126138750	126138750	G	T	61	253	168	Missense	A911S	deleterious (0.813)	19	No	CCDS41859.1
FR-CLL_9	TRPC5	2	X	111155820	111155820	T	C	85	115	130	Missense	Y200C	deleterious (1)	1	No	CCDS14561.1
FR-CLL_9	TRPC5	2	X	111155830	111155830	G	C	85	108	125	Missense	L197V	deleterious (0.967)	1	No	CCDS14561.1
FR-CLL_9	UBR5	45	8	103289248	103289248	G	A	49	185	160	Missense	A2154V	neutral (0.002)	28	No	CCDS34933.1
FR-CLL_9	UTRN	14	6	144768390	144768390	A	G	40	75	50	Missense	N553S	neutral (0)	5	No	CCDS34547.1
FR-CLL_10	ALK	29	2	29416604	29416604	C	G	28	126	123	Missense	G1450A	neutral (0)	1218	Yes	CCDS33172.1
FR-CLL_10	CPXCR1	1	X	88008943	88008943	A	T	48	58	49	Missense	K176N	neutral (0.001)	3	No	CCDS14458.1
FR-CLL_10	FAM47A	1	X	34149725	34149725	C	G	40	57	43	Missense	R224P	deleterious (0.995)	5	No	CCDS43926.1
FR-CLL_10	GALNT10	4	5	153709223	153709223	G	A	47	159	172	Missense	V165I	neutral (0.032)	2	No	CCDS4325.1
FR-CLL_10	HMCN1	81	1	186092259	186092259	G	T	39	74	64	Missense	A4136S	deleterious (0.625)	23	No	CCDS30956.1
FR-CLL_10	INVS	7	9	103009037	103009037	A	G	23	236	167	Missense	D349G	deleterious (0.992)	2	No	CCDS6746.1,CCDS6747.1
FR-CLL_10	KIAA1967	11	8	22473091	22473091	A	-	41	92	71	Frameshift del	P453fs	nd	3	No	CCDS34863.1
FR-CLL_10	LRRC49	5	15	71197094	71197094	G	C	39	192	138	Missense	R167T	deleterious (0.995)	1	No	CCDS32282.1
FR-CLL_10	MCART2	1	18	29340297	29340297	G	A	41	446	315	Missense	R110W	neutral (0.144)	1	No	CCDS32812.1
FR-CLL_10	MGEA5	8,9	10	103559161	103559161	G	-	47	249	173	Frameshift del	P363fs,P416fs	nd	3	No	CCDS44471.1,CCDS7520.1
FR-CLL_10	NTRK3	8	15	88678619	88678619	C	T	52	54	63	Missense	R306H	deleterious (0.961)	281	Yes	CCDS10340.1,CCDS32322.1,CCDS32323.1
FR-CLL_10	NUDCD3	2	7	44524646	44524646	G	A	45	114	75	Missense	H144Y	neutral (0.157)	0	No	CCDS5490.2
FR-CLL_10	RPE65	5	1	68910251	68910251	G	A	47	200	167	Missense	T153I	deleterious (1)	1	No	CCDS643.1
FR-CLL_10	RPS15	4	19	1440414	1440414	C	T	37	43	43	Missense	P131S	deleterious (0.822)	0	No	CCDS12067.1
FR-CLL_10	SAMD4A	2	14	55168817	55168817	A	C	45	181	132	Missense	K77N	deleterious (0.873)	0	No	CCDS32084.1
FR-CLL_10	SGOL2		2	201434616	201434616	G	A	21	293	184	Splice site		nd	4	No	CCDS42796.1
FR-CLL_10	SIPA1L2	19	1	232539242	232539242	G	T	56	82	56	Missense	P1631H	deleterious (0.587)	6	No	CCDS41474.1
FR-CLL_10	SULT1C4[#]	7	2	109003830	109003830	A	T	25	150	117	Missense	D284V	deleterious (0.958)	0	No	CCDS2077.1
FR-CLL_10	TP53	6	17	7577569	7577569	A	T	87	23	39	Missense	C238S	deleterious (1)	22245	Yes	CCDS45605.1,CCDS45606.1,CCDS11118.1
FR-CLL_10	ZNF114	3	19	48790127	48790127	T	A	51	102	108	Missense	C416S	deleterious (0.814)	0	No	CCDS12713.1

[#]Gene affected by a subclonal mutation

*Cancer Gene Census database (http://www.sanger.ac.uk/genetics/CGP/Census)

^In CCDS Reference Sequence

^^Numbering according to the Human Genome hg19 assembly

Abbreviations: Ref nt, reference nucleotide; Var nt, variant nucleotide; AA, amino acid; fs, frameshift; D, deletion; nd, not determined (The PolyPhen-2 algorithm predicts only the impact of amino acid substitutions)

Table S5. Enriched functional categories and pathways in FR-CLL altered genes (DAVID analysis)

	Cluster	Category	Genes	Enrichment score	PValue	Benjamini
GO categories	1	cell adhesion	NRP1, SVEP1, PTPRU, PNN, LAMA2, VWF, GP5, COL19A1, TSC1, FAT1, TRO, FBLN5, DSC2, COL12A1, COL6A1, ROBO2, OMG, MUC5B, NPHP1	3.8346	1.13E-05	0.0119
	2	plasma membrane part	KCNE1L, SORL1, UTRN, AMOTL1, ABCA4, ATP12A, PNN, GP5, ANK1, SLC23A2, FAT1, TRO, CEACAM5, ROBO2, ROS1, SAMD4A, NPHP1, MPDZ, TRPC5, MMP16, PTPRU, ALK, NTRK3, VWF, CCR7, ABCC9, PDGFRA, DSC2, DSP, HAS2	2.0379	0.0069	0.2704
	3	extracellular matrix	LAMA2, VWF, HMCN1, COL19A1, FBLN5, CCDC80, COL6A1, COL12A1, MMP16, ADAMTS12	2.0324	0.0014	0.2793
	4	cell-cell junction	MPDZ, DSP, DSC2, AMOTL1, PNN	1.5844	0.0095	0.2665
	5	extracellular structure organization/skeletal muscle organization	COL19A1, TSC1, FBLN5, UTRN, CCDC80, PDGFRA, COL12A1, CHAT	1.3683	3.45E-04	0.1145
	6	regulation of cell morphogenesis/nervous system development	NTRK3, NRP1, CNTF, ROBO2, OMG	1.3024	0.0011	0.2591
	7	regulation of membrane potential	CNTF, EGR2, TSC1, HEXA, MGEA5	1.2982	0.0230	0.6907
	8	protein tyrosine kinase activity	NTRK3, NRP1, PDGFRA, ALK, ROS1	1.2694	0.0023	0.4831
	9	wound healing	VWF, GP5, HMCN1, FBLN5, PDGFRA, DSP	1.2377	0.0191	0.7671
	10	insoluble fraction	JPH2, MPDZ, UTRN, TP53, ABCA4, ABCC9, TSC1, SLC23A2, BACE2, CYP8B1, ROS1, SAMD4A, MGST2	1.2051	0.0476	0.5733
	11	ion homeostasis	CCR7, CNTF, JPH2, EGR2, TSC1, SLC9A4, HEXA, MGEA5, TP53, ATP12A	1.1944	0.0057	0.5813
	12	plasma membrane	KCNE1L, JPH2, NRP1, SLC9A4, SORL1, UTRN, CSMD3, RPE65, AMOTL1, ABCA4, ATP12A, PNN, OR56B4, GP5, SLCO1A2, ANK1, CRB1, SLC23A2, TRO, FAT1, COL6A1, CEACAM5, ROBO2, ROS1, SAMD4A, NPHP1, BRAF, GFRAL, MPDZ, TRPC5, MMP16, PTPRU, ALK, NTRK3, LAMA2, VWF, ABCC9, CCR7, OR51S1, PDGFRA, SLC5A8, DSC2, TNNI3K, DSP, HAS2, OMG, FPGT	1.1369	0.0038	0.1950
	13	protein heterodimerization activity	IKZF3, BRAF, HEXA, PDGFRA, TP53, ROBO2	0.9078	0.0298	0.5415
	14	metal ion transport	ABCC9, JPH2, TSC1, TRPC5, SLC23A2, SLC9A4, SLC5A8, SLC25A37, ATP12A	0.8911	0.0341	0.7303
	15	chaperone binding	VWF, TSC1, TP53	0.7181	0.0155	0.5221
	16	protein N-terminus binding	VWF, TSC1, TP53, ATM	0.5839	0.0237	0.5307
KEGG pathways		Pathways in cancer	HSP90AB1, LAMA2, BRAF, PDGFRA, TP53	0.8070	0.0434	0.9815
		Focal adhesion	LAMA2, VWF, BRAF, PDGFRA, COL6A1	0.7970	0.1005	0.9077

Table S6. CNAs detected in the Discovery panel by SNP 6.0 arrays. Genes in CNAs encompassing ≤10 CCDS genes are also listed

Sample ID	Chrom	Cytoband	Start^	End^	Number of markers	CN value	Segment size (kb)	Aberration	Number of CCDS genes	CCDS genes	Number of RefSeq	RefSeq genes
FR-CLL_1	11	q22.3	107527048	107929706	183	1.48	402.658	loss focal	5	ATM,C11orf65,EXPH5,KDELC2,NPAT	5	ATM,C11orf65,EXPH5,KDELC2,NPAT
FR-CLL_1	13	q14.11	40388583	41808882	904	1.51	1420.299	loss focal	10	AKAP11,C13orf15,DGKH,ELF1,KBTBD6, KBTBD7,KIAA0564,MTRF1,NAA16,WBP4	12	AKAP11,C13orf15,DGKH,ELF1,KBTBD6, KBTBD7,KIAA0564,MTRF1, NAA16,OR7E37P,SUGT1P3,WBP4
FR-CLL_1	13	q14.12-q14.3	44783591	50681315	3882	1.50	5897.724	loss	33		46	
FR-CLL_2	13	q14.12-q14.3	45700118	50495220	3151	1.56	4795.102	loss	25		34	
FR-CLL_4	13	q14.3	49482488	49862328	218	0.87	379.84	loss focal	2	KCNRG,TRIM13	7	DLEU1,DLEU2,KCNRG,MIR15A, MIR16, ST13P4,TRIM13
FR-CLL_4	13	q32.3	98646972	98879985	149	0.89	233.013	loss focal	1	UBAC2	6	FKSG29,GPR18,GPR183, LOC100289373,MIR623, UBAC2
FR-CLL_4	17	p11.1-q11.1	514	22294526	13259	1.00	22294.012	loss	276		384	
FR-CLL_4	18	p11.21-p11.32	1543	15392396	10589	0.99	15390.853	loss	54		79	
FR-CLL_4	21	q22.11	33204749	33216192	14	0.73	11.443	loss	0		0	
FR-CLL_5	3	p12.3-p14.1	70103185	81779987	7427	1.62	11676.802	loss focal	9	CNTN3,EIF4E3,FOXP1,GPR27,PDZRN3, PPP4R2,PROK2,ROBO2,SHQ1	21	
FR-CLL_5	13	q14.2--q14.3	47841512	49515159	991	1.642621402	1673.647		17		19	
FR-CLL_5	13	q14.3	49516995	50200311	439	1.08	683.316	loss focal	0		6	DLEU1,DLEU2,DLEU7,MIR15A,MIR16,ST13P4
FR-CLL_5	13	q14.3	50201343	50422445	161	1.57123612	221.102		1	RNASEH2B	2	DLEU7,RNASEH2B
FR-CLL_5	17	p11.2-p13.3	514	22069633	13221	1.54	22069.119	loss	276		384	
FR-CLL_6	2	p23.3	24475782	26137612	808	1.33	1661.83	loss focal	9	ADCY3,CENPO,DNAJC27,DNMT3A,KIF3C, NCOA1, POMC,PTRHD1,RAB10	14	
FR-CLL_6	2	p23.2-p23.3	26545820	27905293	625	1.35	1359.473	loss	43		45	
FR-CLL_6	2	q31.1	171495172	172086291	324	1.40	591.119	loss	4	DCAF17,GORASP2,METTL8,TLK1	4	DCAF17,GORASP2,METTL8,TLK1
FR-CLL_6	2	q36.3-q37.1	230668575	231112634	273	1.36	444.059	loss focal	3	SP100,SP110,SP140	4	SP100,SP110,SP140,SP140L
FR-CLL_6	2	q37.1	232258404	234045405	1023	1.51	1787.001	loss	21		31	
FR-CLL_6	3	p24.2-p26.3	1121645	26253855	19168	1.52	25132.21	loss	99		136	
FR-CLL_6	3	p12.3-p21.31	45516933	76285834	20948	1.40	30768.901	loss	208		277	
FR-CLL_6	3	q27.2-q29	186225109	199380503	8681	1.46	13155.394	loss	85		119	
FR-CLL_6	6	p11.2-p21.1	41967125	57448332	9748	1.52	15481.207	loss	117		138	
FR-CLL_6	17	p11.1-p13.3	74399	22159777	13221	1.26	22085.378	loss	276		384	
FR-CLL_6	17	q21.33-q22	47190109	52149620	3639	2.64	4959.511	gain	11		11	
FR-CLL_8	4	q35.2	189466210	189487325	33	0.93	21.115	loss	0		0	
FR-CLL_8	12	p11.1-q24.33	20691	132288250	85902	3.70	132267.559	gain	882		1127	
FR-CLL_9	4	p14-p16.3	56707	38715653	26054	1.01	38658.946	loss (whole short arm)	128		193	
FR-CLL_9	4	p11-q35.2	38720286	191210542	92423	2.99	152490.256	gain (whole long arm)	491		637	
FR-CLL_9	6	q13	74045884	74461064	198	1.15	415.18	loss focal	7	C6orf221,DDX43,DPPA5,EEF1A1,MB21D1, MTO1, SLC17A5	9	C6orf147,C6orf221,DDX43,DPPA5, EEF1A1,MB21D1,MTO1,OOEP, SLC17A5
FR-CLL_9	12	p11.1-q24.33	20691	132288250	85907	3.02	132267.559	gain	882		1127	
FR-CLL_9	15	q11.2-q12	19123066	23766243	2405	2.97	4643.177	gain	14		117	
FR-CLL_9	15	q12-q15.1	23768183	38629477	9636	1.11	14861.294	loss	53		85	
FR-CLL_9	15	q15.1	38639047	39793744	502	3.63	1154.697	gain	23		28	
FR-CLL_9	15	q15.1	39798024	40175398	231	1.35	377.374	loss focal	4	EHD4,JMJD7-PLA2G4B,MAPKBP1,PLA2G4D	11	
FR-CLL_9	17	p11.2-p13.3	514	17820020	11375	1.07	17819.506	loss	238		324	
FR-CLL_10	6	p25.2-p25.3	94649	3844660	3135	3.20	3750.011	gain	22		191	
FR-CLL_10	7	q31.1-q31.33	112128770	125548872	8011	1.36	13420.102	loss	39		52	
FR-CLL_10	7	q32.3-q34	130873717	139995719	6083	1.48	9122.002	loss	41		52	
FR-CLL_10	7	q36.3	158358509	158810195	312	1.30	451.686	loss focal	1	VIPR2	3	LOC154822,VIPR2,WDR60
FR-CLL_10	15	q11.1-q11.2	18276329	21609880	1103	1.48	3333.551	loss focal	9	CYFIP1,MKRN3,NDN,NIPA1,NIPA2, OR4M2,OR4N4,POTEB,TUBGCP5	27	
FR-CLL_10	17	p11.2-p13.3	514	18863446	11815	1.09	18862.932	loss	256		350	

^Numbering according to the Human Genome hg18 assembly

Note: segments highlighted in grey represent subclonal lesions. These segments were not computed in the calculation of the total load of genetic lesions presented in Figure 1

Table S7. Clinico-biological characteristics of patients displaying an outlier number of CNAs.

Sample ID	Timing of refractoriness	Gender	Age at refractoriness	IGHV status	FISH	Mutations detected	Evolution to Richter syndrome	Chromosomes with mutliple CN switches
FR-CLL_7228	Primary	F	83	UM	Normal	*SF3B1*	No	6
FR-CLL_4845	Primary	M	77	UM	del17p13, del13q14	*TP53, SF3B1*	No	8, 13
FR-CLL_6012	Primary	M	82	M	del17p13, del13q14	*TP53, FAT1*	No	8, 9
FR-CLL_4380	Acquired	F	76	UM	del17p13, +12	*FAT1*	No	3, 12
FR-CLL_9311	Acquired	F	84	UM	del17p13	*TP53*	No	14
FR-CLL_9244	Acquired	M	69	M	del11q22-q23, +12, del13q14	-	No	3

Table S8. Frequency and description of MCRs generated by the chromotripsis phenomenon. CNs occurring in ≥2 samples are included. Genes in MCRs encompassing ≤10 genes are also listed.

Cytoband	Type of CNA	N° of patients (%)	MCR size	Genes in MCR
14q31.3	Loss	4 (10.2)	1.2 Mb	7 (*GALC,GPR65,KCNK10,SPATA7,PTPN21,ZC3H14,TTC8*)
14q32.11-q32.12	Loss	4 (10.2)	1.5 Mb	10 (*C14orf143,TDP1,KCNK13,PSMC1,C14orf102,CALM1,TTC7B,RPS6KA5,C14orf159,GPR68)*
14q32.13-q32.2	Loss	4 (10.2)	1.1 Mb	9 (*CLMN,C14orf49,GLRX5,TCL6,TCL1B,TCL1A,BDKRB2,BDKRB1,ATG2B*)
8p23.3-p23.1	Loss	3 (7.6)	6.1 Mb	13
8p23.1	Loss	3 (7.6)	647 kb	9 (*FAM167A,BLK,GATA4,NEIL2,FDFT1,CTSB,DEFB137,DEFB136,DEFB134*)
8p12	Loss	3 (7.6)	2 Mb	6 (NRG1,FUT10,MAK16,C8orf41,RNF122,DUSP26)
14q24.3	Loss	3 (7.6)	1.1 Mb	22
6p21.1-p12.3	Loss	2 (5.1)	1.3 Mb	11 (including *NFKBIE* and *RUNX2*)
6p12.3	Loss	2 (5.1)	3.2 Mb	14
6p12.3	Loss	2 (5.1)	619 kb	7 (*PGK2,CRISP1,DEFB114,DEFB113,DEFB110,DEFB111,DEFB112)*
8p21.1	Loss	2 (5.1)	205 Kb	2 (*FBXO16,FZD3*)
8p21.1	Loss	2 (5.1)	76 kb	2 (*EXTL3,INTS9*)
8p12	Loss	2 (5.1)	3.9 Mb	17 (including *FGFR1*)

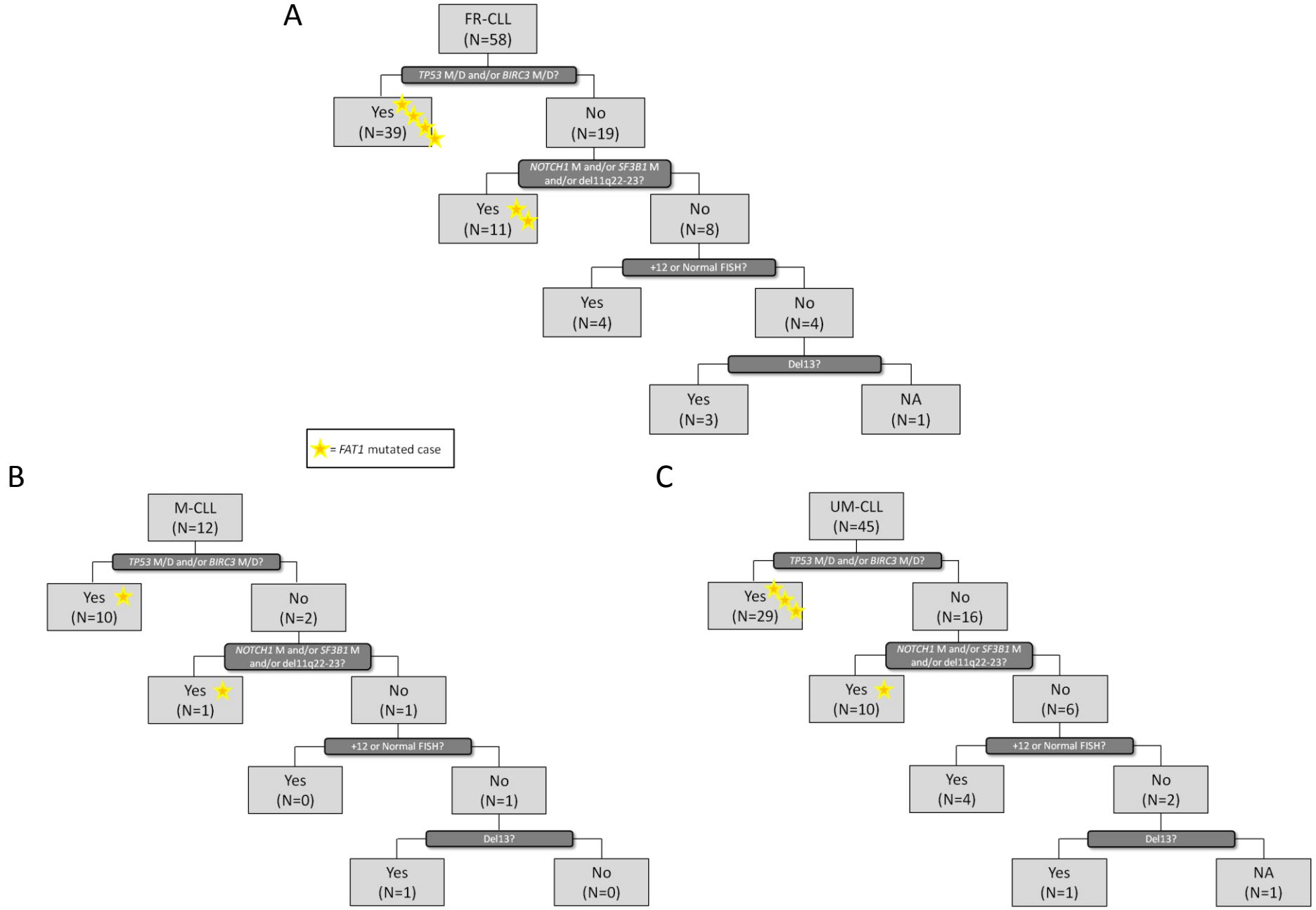

Figure S1. CONSORT diagram of all FR-CLL patients (A), of *IGHV*-M (B) and of *IGHV*-UM cases (C), according the integrated mutational and cytogenetic hierarchical approach proposed by Rossi D. (*Blood* 2013).

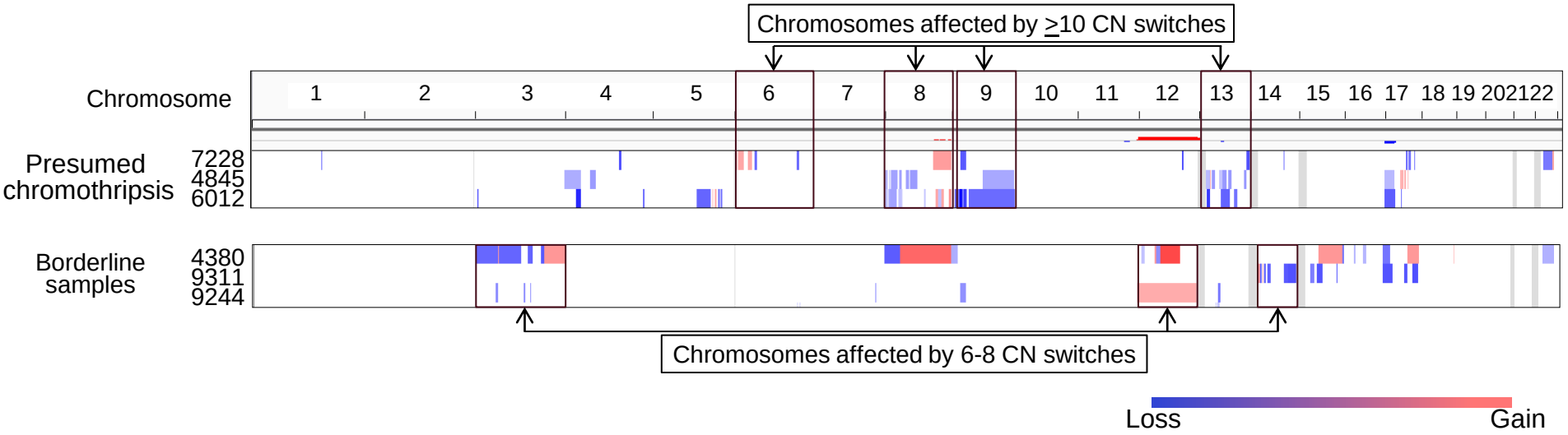

Figure S2. Curated segmented Copy number data of samples presumed to be affected by chromothripsis. The chromosomes involved are also indicated. Losses are depicted in blue and Gains in red. CN: Copy number.