Autonomous B-cell receptor signaling and genetic aberrations in chronic lymphocytic leukemia-phenotype monoclonal B lymphocytosis in siblings of patients with chronic lymphocytic leukemia

Edwin Quinten,[1*] Julieta H. Sepúlveda-Yáñez,[1,2*] Marvyn T. Koning,[1] Janneke A. Eken,[1] Dietmar Pfeifer,[3] Valeri Nteleah,[1] Ruben A.L. de Groen,[1] Diego Alvarez Saravia,[2] Jeroen Knijnenburg,[4] Hedwig E. Stuivenberg-Bleijswijk,[1] Milena Pantic,[3] Andreas Agathangelidis,[5,6] Andrea Keppler-Hafkemeyer,[3] Cornelis A. M. van Bergen,[1] Roberto Uribe-Paredes,[7,8] Kostas Stamatopoulos,[6,9] Joost S.P. Vermaat,[1] Katja Zirlik,[3,10] Marcelo A. Navarrete,[2] Hassan Jumaa[11] and Hendrik Veelken[1]

[1]Department of Hematology, Leiden University Medical Center, Leiden, The Netherlands; [2]School of Medicine, Universidad de Magallanes, Punta Arenas, Chile; [3]Department of Medicine I, University Medical Center Freiburg, Freiburg, Germany; [4]Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands; [5]Department of Biology, School of Science, National and Kapodistrian University of Athens, Athens, Greece; [6]Institute of Applied Biosciences, Center for Research and Technology Hellas, Thessaloniki, Greece; [7]Department of Computer Engineering, Universidad de Magallanes, Punta Arenas, Chile; [8]Center for Biotechnology and Bioengineering, Santiago, Chile; [9]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; [10]Tumor- und Brustzentrum Ostschweiz, Chur, Switzerland and [11]Institute of Immunology, University of Ulm, Ulm, Germany

EQ and JHS-Y contributed equally as first authors.

Correspondence: H. Veelken
j.h.veelken@lumc.nl

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Supplemental Material to:

Autonomous BCR signaling and subclonal genetic variants in clonal CLL-phenotype B cells in siblings of CLL patients

Edwin Quinten, Julieta H. Sepúlveda-Yáñez, Marvyn T. Koning, Janneke A. Eken, Dietmar Pfeifer, Valeri Nteleah, Ruben A.L. de Groen, Diego Alvarez Saravia, Jeroen Knijnenburg, Hedwig E. Stuivenberg-Bleijswijk, Milena Pantic, Andreas Agathangelidis, Andrea Keppler-Hafkemeyer, Cornelis A. M. van Bergen, Roberto Uribe-Paredes, Kostas Stamatopoulos, Joost S.P. Vermaat, Katja Zirlik, Marcelo A. Navarrete, Hassan Jumaa, Hendrik Veelken

Supplemental Methods:

Patients, probands, and samples.

CLL patients under management of the outpatient clinics at the participating centers were asked to inform their respective living siblings about this study and to provide their contact information. Approvals by the ethical committees explicitly excluded longitudinal analyses and mandated to provide siblings with a categorical screening result.

Detection, isolation, and processing of CLL-phenotype cells

Differential blood counts were obtained for each blood sample. DNA and RNA were directly isolated from sorted CLL-phenotype cells by spun-driven silica matrix columns (Allprep DNA/RNA mini kit; Qiagen, Hilden, Germany).

Identification of clonal BCR transcripts

VDJ and VJ sequences were determined by direct Sanger sequencing from gel-purified ARTISAN PCR products (Wizard SV gel and PCR clean-up kit; Promega, Madison, WI) or after molecular cloning (Topo TA cloning vector; ThermoFisher, Waltham, MA).

Analysis of BCR signaling activity

pMIZCC and pMIZYN expression vectors[1] with inserted paired VDJ and VJ sequences from individual cases were synthesized (BaseClear BV, Leiden, The Netherlands) and packaged by liposomal cotransfection (FuGENE HD transfection reagent; Promega) of Phoenix-E cells with the pCL-eco helper vector. Murine TKO cells were transduced with virus-containing supernatant on fibronectin-coated plates at 48 h after transfection (RetroNectin; TaKaRa, Shiga, Japan).[2] TKO cells are arrested at the pro-B-cell stage by genetic deficiency of Rag2, Lambda5, and Slp65. Slp65 function is reconstituted by a Slp65-ERT2 fusion gene that enables BCR signaling in the presence of 4-hydroxytamoxifen.[1, 3]

Calcium mobilization was measured in Indo-1 AM-loaded (ThermoFisher), live-gated TKO cells by flow cytometry as the ratio of signal intensities (SIR) at 405 and 485 nm for 90 sec. After addition of 2 µM 4-hydroxytamoxifen (Sigma Aldrich), calcium mobilization was measured for additional 7.5 min. Finally, maximum BCR signaling was induced by adding an unlabeled crosslinking anti-IgM or anti-IgG gamma antibody (clones 2022-01 and 2042-01; Southern Biotech, Birmingham, AL), and measurement was resumed for additional 3 min. Every BCR-transduced TKO population was measured at least twice at

approximately 3 and 4 weeks after transduction. The 2nd measurement was used for statistical analyses with two-tailed Mann-Whitney or Wilcoxon's rank sum tests for unpaired and paired comparisons, respectively, and Spearman's correlation coefficient.

Quantitative assessment of autonomous BCR signaling

The fraction of cells with a 405/485 SIR above the 95th percentile prior to addition of tamoxifen (Q^{aut}) was determined with correction for totally unresponsive cells during BCR crosslinking. Subsequently, the calibrated median SIR observed in this Q^{aut} fraction was determined ($calSIR^{aut}$). Autonomous BCR signaling was quantitated as the arithmetic product of Q^{aut} x $calSIR^{aut}$.

Details of recording (see Figure):

Measurements of BCR signaling activity is performed in 3 phases:

1. Baseline Phase (BP): Time interval from the start of measurements until the addition of 4-hydroxytamoxifen
2. Experimental Phase (EP): Time interval from addition of tamoxifen until the addition of cross-linking agent
3. Maximum Phase (MP): Time interval from addition of cross-linking agent to the end of measurement

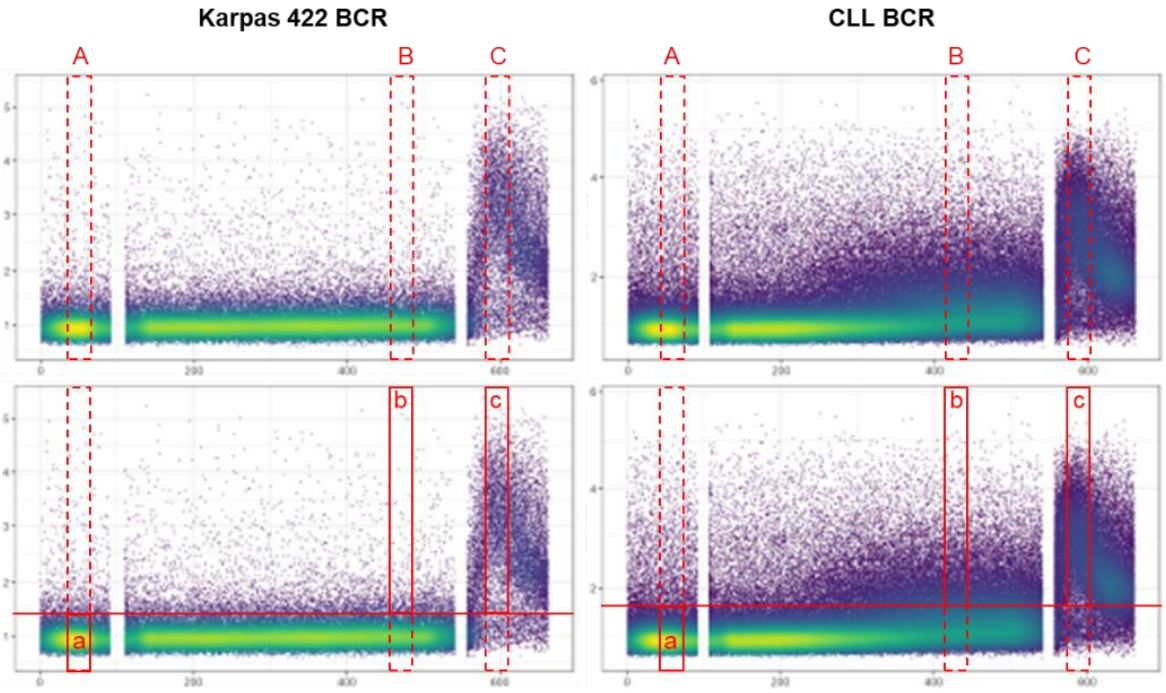
Three frames are defined and the number of events within each frame recorded:

A. Frame A: Stable interval in BP with number of events = $\mathbf{N_A}$
B. Frame B: Stable interval towards the end of EP with number of events = $\mathbf{N_B}$
C. Frame C: Interval starting at the time point of maximum increase signaling intensity ratio (SIR) and covering the interval of peak SIR in MP with number of events = $\mathbf{N_C}$.

Within each frame, a gate is defined and the number of events within each gate recorded:

a) Gate a: Part of frame A with <u>upper</u> limit (=SIR95) set to contain 95% of all events within frame A = $\mathbf{n_a}$
b) Gate b: Part of frame B with <u>lower</u> limit set at SIR95 with number of events = $\mathbf{n_b}$
c) Gate c: Part of frame C with <u>lower</u> limit set at SIR95 with number of events = $\mathbf{n_c}$

Mean SIR are recorded for gates b ($\mathbf{SIR^b}$) and c ($\mathbf{SIR^c}$).



Interpretation:

- The fraction of false-positive events is set to 0.05.
- The fraction of non-responsive cells is calculated as $(N_C\text{-}n_c) / N_C$.
- The fraction of cells with autonomous BCR signaling activity Q^{aut} with correction for 5% false-positive cells and fraction of unresponsive cells is calculated as: $Q^{aut} = (n_b N_C - 0.05 N_B N_C) / n_c N_C$
- The calibrated autonomous BCR signal $calSIR^{aut}$ is: $calSIR^{aut} = SIR^b / SIR^c$
- BCR signaling strength is calculated as the product of the corrected fraction of cells with autonomous signalling and the calibrated autonomous BCR signal: $Q^{aut} calSIR^{aut}$

Whole Exome Sequencing

FASTQ files from whole exome sequencing (WES) were processed using the Sarek workflow v2.7 and aligned to the human reference genome GRCh38 using Burrows Wheeler Algorithm (BWA) v0.7.17.[4, 5] Duplicated mapped reads were marked, local realignment of regions flanking indels and recalibration of base quality scores were performed to obtain more accurate bases according to the Genome Analysis ToolKit (GATK) best practices version v4.1.7.0.[6] Single nucleotide variants (SNV) and short insertions and deletions (INDELS) were called using Strelka2 v2.9.10.[7] Only high

confidence variants defined by quality scores (GQX) of at least 15 for SNV and 30 for INDELS were kept. The resulting variant call files were annotated by Ensembl-VEP (v103) with four filtering steps.[8] Variants were first filtered for the 120 most frequent mutated genes in CLL according the COSMIC database and an in-house cohort (Supplemental Table 3).[9, 10] Thereafter, variants were filtered based on their effect, i.e. frameshift, in-frame deletion, missense, missense variant & splice region variant, splice region variant & synonymous variant, synonymous, in-frame insertion, stop gained, stop lost, frameshift variant & stop lost, missense variant & splice region variant, and coding sequence variant. Subsequently, variants were filtered for predicted deleterious effects using a CADD phred score of >20, and benign variants annotated in Clinvar 202008 were discarded.

Workflow quality control metrics were calculated and aggregated by MultiQC v1.8.[5] One sample (MBL24.3) with a high percentage (24.4%) of unmapped reads was discarded at this stage.

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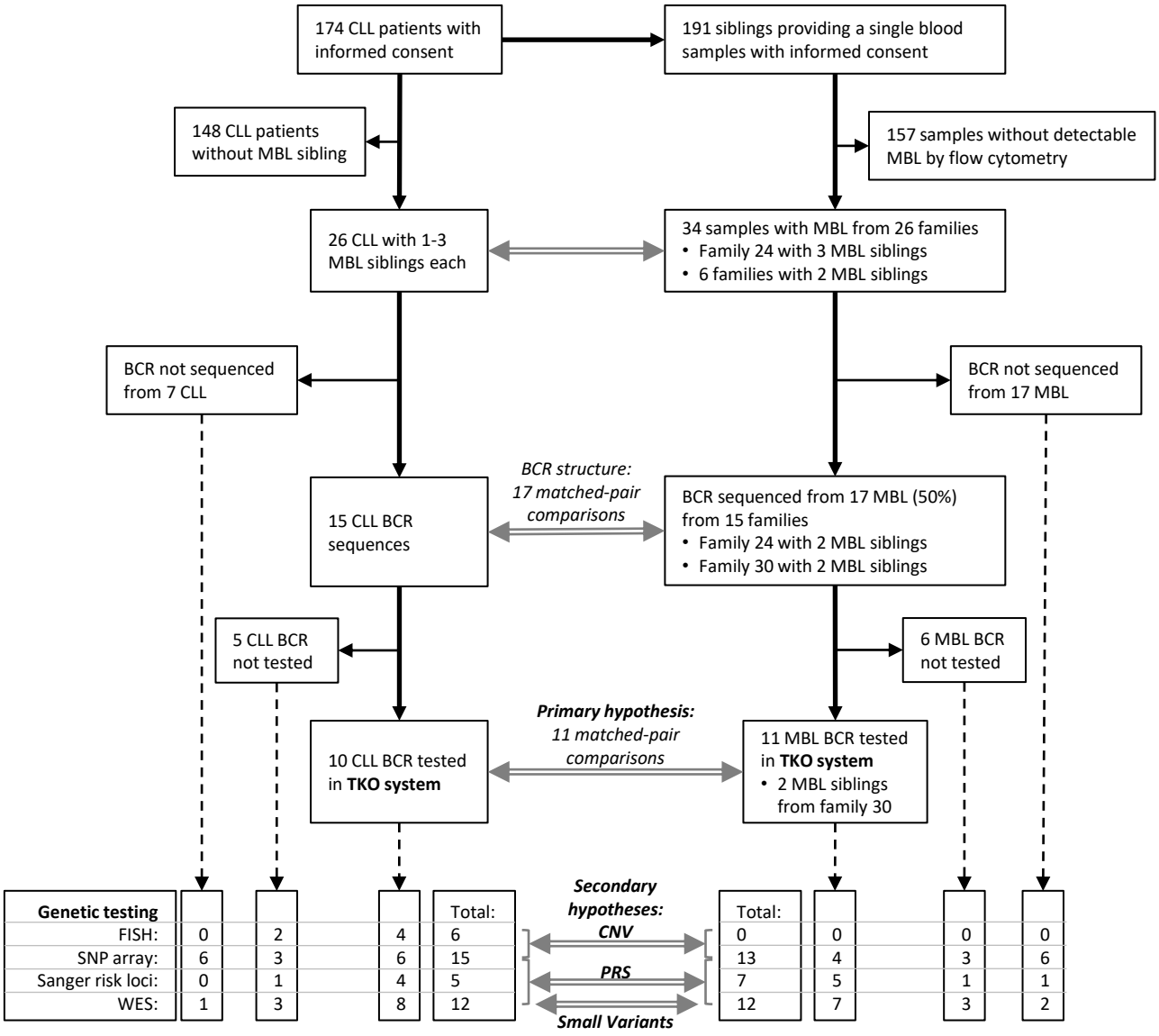
Supplemental Figure 1:
Consort-like diagram of numbers of samples and experimental analyses.
CNV: Copy number variations. PRS: Polygenic risk score.



Supplemental Table 1: Characteristics and analyses of MBL and CLL in sibling pairs

MBL

Family	Study Id	Age (years)	CLL-phenotype B- cells/ul	Kappa/lambda	IGHV (BCR Analysis)	IGHV identity to GL (%)	Junction HV	HCDR3 length	IGHJ	Isotype	VRQ motif FR2	YYC motif FR3	IGKV / IGLV	Subset	BCR signaling	SNP Array (Genetic analysis)	WES sorted MBL	WES non-MBL cells	Targeted CLL risk locus (n=25) Sanger sequencing	Targeted B-cell lymphoma gene (n-52) panel sequencing
1	MBL 01.1	57	844.22	κ	IGHV3-30-3*01 IGHV4-34*01	100.00 94.04	CARGSGSYW CARGAFVRGSYYKNDRGWFDPW	7 20	IGHJ4*02 IGHJ5*02	IgM IgM	VRQ IRQ	YYC YYC	IGKV3-15*01			x	x	x	x	
2	MBL 02.1	72	39.62	inconclusive	IGHV1-46*01	100.00	CARDLRNGDFWSGYPSRYW	17	IGHJ4*02	IgM	VRQ	YYC	IGLK1-33*01		0.243	x		x	x	
3	MBL 03.1	68	42.07	κ												x		x		
4	MBL 04.1	80	19.66	κ	IGHV3-7*01 IGHV4-34*01	96.18 90.53	CVRDDGSNYEAFDIW CARWEVTRSHWFGPW	13 13	IGHJ3*02 IGHJ5*02	IgM IgM	VRQ IRQ	YHC YYC	IGKV1-13*02 IGKV2-24*01		0.224		x	x		
5	MBL 05.1	50	480.54	λ	IGHV4-34*01	94.74	CARGRSIDVAAQRAYFDHW	17	IGHJ4*02	IgM	IRQ	YYC	IGLV3-1*01	new "mixed" subset no.60	0.563		x	x	x	
6	MBL 06.1	78	44.5	κ	IGHV1-69*01	98.61	CARVFRTGGNSSSWYEMDYYYYGMDVW	25	IGHJ6*02	IgM	VRQ	YYC	IGKV1-5*03		0.179	x			x	
6	MBL 06.2	76	8.85	κ												x			x	
7	MBL 07.1	61	11.41	λ	IGHV3-23*01	91.67	CVKDDWDYW	7	IGHJ4*02	IgM	VRQ	YYC	IGLV3-21*01 G110R	2L	0.123	x			x	
7	MBL 07.2	56	34.31	κ												x		x		
8	MBL 08.1	68	25.06	κ												x				
9	MBL 09.1	73	38.24	λ	IGHV3-23*01	96.18	CAKLSGTAASGYNYFDSW	16	IGHJ4*02	IgM	VRQ	YYC				x				
10	MBL 10.1	43	35.05	not done	IGHV1-18*01	96.88	CARGHCGGDCYSDYW	13	IGHJ4*02	IgM	VRQ	YYC	IGKV2-28*01		0.141	x			x	
11	MBL 11.1	79	67.64	λ	IGHV3-23*01	97.92	CAKDETSSGNSGGAFDYW	16	IGHJ4*02	IgM	VRQ	YYC				x				
12	MBL 12.1	47	13.87	κ												x				
13	MBL 13.1	76	11.55	inconclusive																
14	MBL 14.1	69	25.24	κ																
15	MBL 15.1	78	6.12	κ																
16	MBL 16.1	76	3.88	inconclusive												x				
16	MBL 16.2	70	18.4	λ																
21	MBL 21.1	66	1.56	inconclusive	IGHV3-15*01/02	95.58	CATDGKPGVPATSHW	13	IGHJ4*02	IgM	VRQ	YYC								
21	MBL 21.2	61	73.38	κ																
22	MBL 22.1	57	0.79	inconclusive													x			
23	MBL 23.1	77	33.14	κ	IGHV3-30-3*03	92.01	CAKELEHDVHAFDYW	13	IGHJ4*02	IgM	VRQ	FYC	IGKV3D-15		0.186		x	x		
24	MBL 24.1	68	24.54	κ	IGHV1-2*02	95.49	CARGIEVAGSGVDFDSW	15	IGHJ4*02	IgM	VRQ	FYC	IGKV1-5				x	x		
24	MBL 24.2	79	1863.49	κ	IGHV1-8*01	95.49	CARINPLRYRQCSDGVCRGGYSWFAPW	25	IGHJ5*02	IgM	VRQ	YYC	IGKV1-5				x	x		
24	MBL 24.3	73	18.48	inconclusive														x		
25	MBL 25.1	72	10.74	κ																
26	MBL 26.1	67	1.30	κ																
27	MBL 27.1	63	1.30	λ													x	x		x
27	MBL 27.2	59	50.00	λ	IGHV3-21*01	98.61	CARDANAMDVW	9	IGHJ6*02	IgM	VRQ	YYC	IGLV3-21*01 G110R	2	0.256		x	x		x
28	MBL 28.1	60	73.00	inconclusive	IGHV4-34*01	94.04	CVRGYGEDESIRRYYYYGMDVW	20	IGHJ6*02	IgG2	IRQ	YYC	IGKV2-30	4	0.485		x	x		x
29	MBL 29.1	62	0.20	λ																
30	MBL 30.1	53	22.00	κ	IGHV3-7*03	96.88	CATESYNSGWVDYW	12	IGHJ4*02	IgM	VRQ	YYC	IGKV3-20		0.480		x	x		x
30	MBL 30.2	59	235.00	λ	IGHV2-5*02	96.22	CAHRGGGFNWNDGWFDPW	16	IGHJ5*02	IgM	IRQ	YYC	IGLV2-14	148A (minor - satellite of major 148B)	0.396		x	x		x

CLL sibling

Family	Study Id	IGHV (BCR)	IGHV identity to GL (%)	Junction HV	HCDR3 length	IGHJ	Isotype	IGKV / IGLV	Subset	TKO	SNP Array (FISH) (Genetic analysis)	WES CLL	WES non-CLL	Targeted CLL risk locus (n=25) Sanger sequencing	Targeted B-cell lymphoma gene (n-52) panel sequencing
1	CLL 01.1	IGHV3-7*01	92.71	CAKDLNTYGKGGYW	12	IGHJ4*02	IgM	IGKV1-33*01			x	x	x	x	
2	CLL 02.1	IGHV3-66*02	94.39	CASGNSGTYSW	9	IGHJ5*01	IgM	IGKV6-21*01	new "mixed" subset no.107	0.628	x	x	x	x	
3	CLL 03.1	IGHV2-5	88.80	CVHRLGGYGNWNGGFFDSW	17	IGHJ4*02	IgM				x	x			
4	CLL 04.1	IGHV4-34*02	91.58	CARDYPEMATIRRYYYYGLDLW	20	IGHJ6*02	IgM	IGLV2-8*01	4	0.326	x		x		
5	CLL 05.1	IGHV3-30*03	93.06	CAKVGREGAFEPYRYFGMDAW	19	IGHJ6*02	IgM	IGLV4-60*03	252	0.572	x	x	x		
6	CLL 06.1	IGHV3-7*01	91.67	CAAHPSDNYAIFDFW	14	IGHJ4*02	IgM	IGKV1-5*03		0.868	x	x	x	x	
7	CLL 07.1	IGHV3-7*01	97.92	CARDLTELVGAQLHW	13	IGHJ1*01	IgM	IGLV3-21*01 G110R	2L	0.114	x	x	x	x	
8											x				
9	CLL 09.1	IGHV4-39*01	100.00	CAGGGDNYDSSGYYFWTGCW	18	IGHJ5*01	IgM				x				
10	CLL 10.1	IGHV4-4*02	91.67	CARDVAFQLWDVW	13	IGHJ6*02	IgM	IGLV2-14*01	V4.6|J4.5.6|11|3 (minor)	0.192	x			x	
11	CLL 11.1	IGHV3-23*01	89.93	CAKTISRSRDGVDVW	13	IGHJ6*02	IgM	IGLV1-44*01			x				
12	CLL 12.1	IGHV5-51	88.70	CARATSRGCQSPNCWFNYFDPW	20	IGHJ5*02	IgM				x				
13	CLL 13.1	IGHV1-69	100.00	CARGESGDFWSGYYPNYYYYGMDVW	23	IGHJ6*02	IgM		7C2 (major)		x				
15	CLL 15.1	IGHV3-74	93.20	CTREGGTYCGGINCWSWFDPW							x				
16											x				
21	CLL 21.1	IGHV3-23*01	88.89	CAKDSAVEAVAMEPLFLDAW	18	IGHJ3*01	IgM	IGLV4-60			(x)	x			
23	CLL 23.1	IgHV1-46*01	96.53	CARVGPTVVKVPAAHDPFDFW	19	IGHJ3*02	IgM	IGKV1-5	V1-46|J3|19|1 (minor)	0.256	(x)	x			
24	CLL 24.1	IGHV3-30	96.40	(not reported from external diagnostic laboratory)			IgM				(x)	x			
27	CLL 27.1	IGHV4-39*01	100.00	CARRPRAYYDFWSGLSWGWFDPW	21	IGHJ5*02	IgM	IGKV3-11	new "mixed" subset no.55	0.351	(x)	x			
28	CLL 28.1	IGHV4-38*02	98.26	CARVRYSGSWYNYFDYW	15	IGHJ4*02	IgM	IGLV1-44	37	0.396	(x)	x			x
30	CLL 30.1	IGHV4-59*01	93.68	CARAPRYCSDSGCYSDAFDIW	19	IGHJ3*02	IgM	IGKV3D-15	V4|J3|19|9 (minor)	0.588	(x)	x			

Supplemental Table 2: Analysis of CLL susceptibility loci in CLL-MBL sibling pairs

SNP	Chromosome	Nearest gene(s)	SNP	Position Hg19	Allele Risk	Allele Reference	OR Original	OR Law*	gnomAD reference population gnomAD version	gnomAD reference population Allele Risk	gnomAD reference population Allele Non-risk	gnomAD reference population RAF
1	2p22.2	QPCT, PRKD3	rs3770745	2:3596089	T	C	1,24	1,16	v3.1.2	15706	52198	0,2313
2	2q13	ACOXL, BCL2L11	rs17483466	2:111797458	G	A	1,39	1,37	v3.1.2	13697	54317	0,2014
3	2q33.1	CASP10/CASP8	rs3769825	2:202111380	A	G	1,19	1,16	v3.1.2	30538	37420	0,4494
4	2q37.1	SP140, SP110	rs13397985	2:231091223	G	T	1,41	1,43	v3.1.2	12718	55262	0,1871
5	2q37.3	FARP2	rs757978	2:242371101	T	C	1,39	1,29	v2.1.1	5224	44172	0,1058
6	3q26.2	MYNN, TERC	rs10936599	3:169492101	C	T	1,26	1,19	v2.1.1	38388	12372	0,7563
7	4q25	LEF1	rs898518	4:109016824	A	C	1,20	1,16	v3.1.2	40174	27776	0,5912
8	5p15.33	CLPTM1L	rs31490	5:1344458	A	G	1,18	1,09	v2.1.1	55920	72090	0,4368
9	6p21.3	HLA-DRB5	rs674313	6:32578082	T	C	1,69	1,18	v3.1.2	17549	50433	0,2581
10	6p21.33	BAK1	rs210142	6:33546837	G	A	1,40	1,23	v3.1.2	48832	19150	0,7183
11	6q25.2	IPCEF1	rs2236256	6:154478440	C	A	1,23	1,14	v3.1.2	30802	37164	0,4532
12	7q31.33	POT1	rs17246404	7:124462661	C	T	1,22	1,15	v3.1.2	48663	19185	0,7172
13	8q24.21	POU5F1B	rs2456449	8:128192981	G	A	1,26	1,23	v3.1.2	23292	44606	0,3430
14	9p21.3	CDKN2B-AS1	rs1679013	9:22206987	C	T	1,19	1,16	v3.1.2	35656	32316	0,5246
15	10q23.31	ACTA2/FAS	rs4406737	10:9059724	G	A	1,27	1,22	v3.1.2	38238	29756	0,5624
16	11p15.5	C11orf21, TSPAN32	rs7944004	11:2311152	T	G	1,20	1,09	v3.1.2	33174	34772	0,4882
17	11q24.1	GRAMD1B	rs735665	11:123361397	A	G	1,45	1,63	v3.1.2	13171	54821	0,1937
18	15q15.1	BMF	rs8024033	15:40403657	C	G	1,22	1,26	v3.1.2	34079	33817	0,5019
19	15q21.3	RFX7, NEDD4	rs7169431	15:56340896	A	G	1,36	1,32	v3.1.2	5720	62276	0,0841
20	15q23	RPLP1	rs7176508	15:70018990	A	G	1,37	1,35	v3.1.2	26735	41233	0,3933
21	16q24.1	IRF8	rs391525	16:85944439	G	A	1,52	1,33	v3.1.2	44704	23288	0,6575
22	18q21.32	PMAIP1	rs4368253	18:57622287	C	T	1,19	1,17	v3.1.2	46543	21463	0,6844
23	18q21.33	BCL2	rs4987855	18:60793549	C	T	1,47	1,36	v3.1.2	61689	6313	0,9072
24	19q13.32	PRKD2, STRN4	rs11083846	19:47207654	A	G	1,29	1,24	v2.1.1	11814	38826	0,2333
21a	16q24.1	IRF8	rs2292982	16:85944823	T	G	1,54			44710	23290	0,6575
9a	6p21.3	HLA-DQA1	rs9272535	6:32606756	A	G	1,61			2009	29983	0,0628

Method:	San	San	San	San	San	San	SNP	San	San	WES	San	San	SNP	SNP	SNP	SNP	SNP	SNP	W&S	WES	WES	San	San	SNP	WES	WES	WES	WES	WES	WES	WES	WES	WES	WES	WES	WES	WES	WES
Family:	1	1	2	2	6	6	6	7	7	7	10	10	8	8	12	12	16	16	4	4	5	5	3	3	9	9	23	23	24	24	24	24	27	27	27	28	28	30	30	30
Sample:	CLL 01.1	MBL 01.1	CLL 02.1	MBL 02.1	CLL 06.1	MBL 06.1	MBL 06.2	CLL 07.1	MBL 07.1	MBL 07.2	CLL 10.1	MBL 10.1	CLL 08.1	MBL 08.1	CLL 12.01	MBL 12.01	CLL 16.01	MBL 16.01	CLL 04.1	MBL 04.1	CLL 05.1	MBL 05.1	CLL 03.1	MBL 03.1	CLL 09.1	MBL 09.1	CLL 09.1	MBL 09.1	CLL 24.1	MBL 24.1	MBL 24.2	MBL 24.3	CLL 27.1	MBL 27.1	MBL 27.2	CLL 28.1	MBL 28.1	CLL 30.1	MBL 30.1	MBL 30.2
1	CC	CC	TC	CC	TC	TC		TT	CC	TT	TC	TC							TT	CC	TT	TT		TT															
2	GG	AA	GA	GA	GG	GA	GA	GG	GG		AA	GA	AA	AA	AA	GA	GA	GA	GA			AA		GA	AA														
3	TC	TT	TT	TT	TC	TT	TC	TT	CC		TT	TT	TT	TT	TC	CC	TC	TC	CC			TT		TT	TC														
4	TT	TT	TT	GG	GT	GG		TT	GT		TT	TT										TT		TT															
5	CC	CC	CC	CC	TC	CC		TC	TC	TC	TT	CC							CC	CC	CC	CC		CC			CC	CC	TC	CC	CC	CC	CC	CC	CC	CC	TC	TC
6	CC	CC	CC	CC	CC	CC		CC	CC	CC	CC	CC							CC	CC	CC	CC		CC			CC	CC	CC	CC	CC		CC	CC	CC	CC	CC	CT	CT	CT
7	AC	AC	AA	AA	CC	CC		AA	CC		AC	AA										CC		AA															
8	GG	GG	AG	GG	GG	GG		AG	AG	AG	AG	AG							GG	GG	AG	AG		AA			AG	GG	GG	GG	GG	GG	AG	AG	AG	GG	GG	GG	GG	AG
9	CC	CC	TC	CC	TC	TC		TC	TC		TC	CC										TC		CC									TT							
10	CC	CT	CC	CC	CC	CT		CC	CT		CC	CT										CT		CC															
11	CC	CC	CC	CC	CA	CC		CC	CA		CA	CC										CC		CC									.							
12	CC	CC	CC	CC	CC	CC		CC	CC	CC	CC	CC							CT	CT	CT	CC		CC			CC	CC	CT	CT	CT	CC	CC	CC	CC	CC	CC	CC	CC
13	AA	AA	GG	AA	AA	GG		AA	AA		AA	AA										AA		AA															
14	CC	CC	CT	CT	TT	TT		CT	CT		CT	CC										CC		CT															
15	GG	GA	GA	AA	GG	GA		GG	GG		GA	GA										GA		GA															
16	TT	GG	GG	TT	TT	GG		TT	GG		TT	TT										TT		TT															
17	AA	AG	AG	AG	GG	AG		GG	AA		GG	AG										AG		AG															
18	CC	GG	CC	CC	CC	CG		CC	CG		CC	CG										CC		CG															
19	AA	GG	GG	GG	GG	GG	-	GG	GG		AA	GG	GG	GG	GG	GG	GG	GG	GG			AG		GG	GG														
20	AA	AA	AG	AG	GG	AG		GG	AG		AG	GG										AG		GG															
21	AA	AA	GA	GA	GG	GG		GA	GG		GG	AA										GG		GG															
22	CC	CC	CC	TT	CT	CT	TT	CC	CC		CC	CC	CC	CC	CC	CC	CC	CC	CC			CC		GC	CC														
23	GG	GG	GG	GG	GG	GG		GA	GA		GG	GG										GG		GG															
24	GG	AA	GG	AA	GG	AG		AG	AG	AG	GG	GG							AG	AG	AG	AG		AG			GG	AG	GG	GG	GG	GG	GG	GG	GG	GG	AG	AG	AG	AG
21a	TT	TT	TG	TG	GG	TG	TG	TG	TG	TG	GG	GG	GG	TG	TG	TT	TG	TG	TT	TG	TG	TG		TT	TG														
9a	GG	GG	GG	GG	GG	GG	AG	GG	GG	na	GG	GG	GG	AG	GG	GG	AA	AG	GG	GG	GG	GG		GG	GG		AG	GG	GG	GG	GG		GG		GG		GG	GG	GG

MBL+CLL Risk	MBL+CLL Non-risk	MBL+CLL RAF	Fisher's exact p
17	15	0,531	**0,0002**
18	24	0,429	**0,0008**
29	13	0,690	**0,0018**
6	18	0,250	0,4318
6	26	0,188	0,1439
32	0	1,000	**0,0002**
13	11	0,542	0,6800
10	22	0,313	0,2115
7	17	0,292	0,6481
19	5	0,792	0,5034
21	3	0,875	**<0,0001**
29	3	0,906	**0,0171**
20	4	0,833	**<0,0001**
14	10	0,583	0,6839
15	9	0,625	0,6816
16	8	0,667	0,1017
11	13	0,458	**0,0029**
18	6	0,750	**0,0227**
5	35	0,125	0,3829
10	14	0,417	0,8365
15	9	0,625	0,8301
34	6	0,850	**0,0259**
22	2	0,917	1,0000
13	19	0,406	**0,0336**
25	23	0,521	**0,0491**
5	41	0,109	0,2111

*Law PJ, Berndt SI, Speedy HE, et al. Genome-wide association analysis implicates dysregulation of immunity genes in chronic lymphocytic leukaemia. Nat Commun. 2017;8:14175.

Supplemental Table 3: CLL-related genes analyzed for small variants

ADAM19	DLG2	LINGO2	PCLO
ADGRL2	DLGAP2	LRMDA	PDE4D
ADGRL3	DMD	LRP1B	PDIA4
AGBL1	DPP10	LRRTM4	PDZD3
AGBL4	DPP6	LUZP2	PRKCH
AKAP13	DSCAM	MACROD2	PRKG1
ANKS1B	EPHA5	MAGI2	PRKN
ASTN2	EPHA6	MCL1	PTPRD
ATM	ERBB4	MDGA2	PTPRN2
ATRNL1	EYS	MYD88	PTPRT
BIRC3	FAM155A	MYH15	RBFOX1
BRINP3	FAT3	NAALADL2	RIN3
CACNA2D1	FHIT	NAGPA	ROBO1
CACNA2D3	FSTL5	NCAM2	ROBO2
CCSER1	GABRG3	NCKAP5	ROS1
CDH12	GALNTL6	NEGR1	RYR2
CDH13	GPC5	NELL1	SEMA6D
CDH18	GPC6	NKAIN2	SF3B1
CELSR1	GREB1L	NLGN1	SGCZ
CNTN4	GRID2	NOTCH1	SH3TC1
CNTN5	GRIK2	NPAS3	SNTG1
CNTNAP2	GRM7	NRG3	SPAG16
CNTNAP5	H1-2	NRXN1	SPOCK3
CSMD1	H1-3	NRXN3	THSD7B
CSMD3	H1-5	OPCML	TP53
CTNNA2	IGLL5	PARD3B	UNC5D
CTNNA3	IL1RAPL1	PARP4	USH2A
CTNND2	IL1RAPL2	PAX5	XPO1
DCC	KCNIP4	PCDH11X	ZFHX3
DGKB	KLHL1	PCDH15	ZFPM2

Supplemental Table 4: Non-shared variants in 120 CLL-related genes

Family	sample	CHROM	POS	SYMBOL	Gene	REF	ALT	QUAL	Allele	Consequence	IMPACT	cDNA_position	CDS_position	Protein_position	Amino_acids	Codons	Existing_variation
1	CLL01.1	chr1	49245770	AGBL4	ENSG00000186094	C	A	18	A	missense_variant&splice_region_variant	MODERATE	535	377	126	W/L	tGg/tTg	rs1370279151
1	CLL01.1	chr1	71407471	NEGR1	ENSG00000172260	T	G	46	G	missense_variant	MODERATE	1085	1040	347	Y/S	tAc/tCc	rs41289154&COSV60833851&COSV60866382
1	CLL01.1	chr2	137160352	THSD7B	ENSG00000144229	T	A	118	A	missense_variant	MODERATE	1687	1509	503	D/E	gaT/gaA	rs4954474&COSV55680598
1	CLL01.1	chr3	108470146	MYH15	ENSG00000144821	G	A	259	A	missense_variant	MODERATE	1567	1510	504	H/Y	Cac/Tac	rs9868484&COSV56308865
1	CLL01.1	chr4	61979743	ADGRL3	ENSG00000150471	C	G	73	G	missense_variant	MODERATE	1154	1156	386	L/V	Ctg/Gtg	rs12509110&COSV72232449&COSV99072504
1	CLL01.1	chr6	64307032	EYS	ENSG00000188107	T	C	47	C	missense_variant	MODERATE	6668	6129	2043	I/M	atA/atG	
1	CLL01.1	chr9	136510700	NOTCH1	ENSG00000148400	C	T	21	T	missense_variant	MODERATE	2955	2693	898	G/D	gGc/gAc	rs1166646402
1	CLL01.1	chr20	14085630	MACROD2	ENSG00000172264	C	T	122	T	missense_variant	MODERATE	568	173	58	T/I	aCt/aTt	rs2990505&COSV53960729
1	MBL01.1	chr1	216207290	USH2A	ENSG00000042781	T	A	18	A	missense_variant	MODERATE	3738	3299	1100	E/V	gAg/gTg	
1	MBL01.1	chr2	140274548	LRP1B	ENSG00000168702	C	G	15	G	missense_variant	MODERATE	13305	13018	4340	D/H	Gat/Cat	COSV101251919
1	MBL01.1	chr3	108441130	MYH15	ENSG00000144821	G	A	316	A	missense_variant	MODERATE	2903	2846	949	T/I	aCt/aTt	rs12638212&COSV56309895
1	MBL01.1	chr8	1565843	DLGAP2	ENSG00000198010	C	A	67	A	missense_variant	MODERATE	1571	1391	464	P/Q	cCa/cAa	rs2301963&COSV70102130
1	MBL01.1	chr14	92651884	RIN3	ENSG00000100599	C	T	337	T	missense_variant	MODERATE	987	835	279	R/C	Cgc/Tgc	rs117068593&COSV53649944
1	MBL01.1	chrX	31507453	DMD	ENSG00000198947	C	A	18	A	missense_variant&splice_region_variant	MODERATE	8455	8218	2740	D/Y	Gac/Tac	
2	CLL02.1	chr2	115753241	DPP10	ENSG00000175497	G	C	299	C	missense_variant	MODERATE	1156	1018	340	A/P	Gct/Cct	rs2053724&COSV59673831
2	CLL02.1	chr2	132783534	NCKAP5	ENSG00000176771	T	A	258	A	missense_variant	MODERATE	3654	3277	1093	N/Y	Aat/Tat	rs16841277&COSV58444336
2	CLL02.1	chr2	137160352	THSD7B	ENSG00000144229	T	A	99	A	missense_variant	MODERATE	1687	1509	503	D/E	gaT/gaA	rs4954474&COSV55680598
2	CLL02.1	chr2	140371210	LRP1B	ENSG00000168702	C	G	163	G	missense_variant	MODERATE	11131	10844	3615	G/A	gGa/gCa	rs76554185&COSV67206902&COSV67273739
2	CLL02.1	chr3	78667911	ROBO1	ENSG00000169855	G	T	154	T	missense_variant	MODERATE	2235	1938	646	S/R	agC/agA	
2	CLL02.1	chr3	108470146	MYH15	ENSG00000144821	G	A	1030	A	missense_variant	MODERATE	1567	1510	504	H/Y	Cac/Tac	rs9868484&COSV56308865
2	CLL02.1	chr3	108470780	MYH15	ENSG00000144821	C	T	139	T	missense_variant	MODERATE	1418	1361	454	R/Q	cGg/cAg	rs4299484&COSV56310353
2	CLL02.1	chr3	175627355	NAALADL2	ENSG00000177694	C	G	132	G	missense_variant	MODERATE	1939	1865	622	P/R	cCc/cGc	rs9866564
2	CLL02.1	chr4	161386160	FSTL5	ENSG00000168843	C	A	164	A	missense_variant	MODERATE	2533	2131	711	D/Y	Gat/Tat	rs3749598
2	CLL02.1	chr5	22078475	CDH12	ENSG00000154162	C	T	241	T	missense_variant	MODERATE	1011	202	68	V/M	Gtg/Atg	rs4371716&CM067358&COSV66394300
2	CLL02.1	chr5	157502808	ADAM19	ENSG00000135074	C	T	893	T	missense_variant	MODERATE	1382	1303	435	E/K	Gaa/Aaa	rs56384823
2	CLL02.1	chr5	157509356	ADAM19	ENSG00000135074	T	C	138	C	missense_variant	MODERATE	929	850	284	S/G	Agt/Ggt	rs1422795&CM093420&COSV57425399
2	CLL02.1	chr6	117301070	ROS1	ENSG00000047936	C	T	115	T	missense_variant	MODERATE	6905	6619	2207	D/N	Gac/Aac	rs529038&CM053396&COSV63850799
2	CLL02.1	chr8	50553159	SNTG1	ENSG00000147481	T	C	19	C	missense_variant	MODERATE	1717	790	264	S/P	Tca/Cca	
2	CLL02.1	chr8	112228859	CSMD3	ENSG00000164796	T	G	129	G	missense_variant	MODERATE	10946	10861	3621	N/H	Aat/Cat	rs1592624&COSV52174720
2	CLL02.1	chr8	112241725	CSMD3	ENSG00000164796	A	G	201	G	missense_variant	MODERATE	10548	10463	3488	L/P	cTa/cCa	rs61753736&COSV104398217
2	CLL02.1	chr10	82979088	NRG3	ENSG00000185737	G	T	81	T	missense_variant	MODERATE	1698	1551	517	R/S	agG/agT	rs761374063&COSV64583486
2	CLL02.1	chr11	92353347	FAT3	ENSG00000165323	C	T	404	T	missense_variant	MODERATE	1609	1235	412	S/F	tCt/tTt	rs10830902
2	CLL02.1	chr13	24455080	PARP4	ENSG00000102699	C	T	426	T	missense_variant	MODERATE	2769	2695	899	A/T	Gcc/Acc	rs2275660&COSV67960444
2	CLL02.1	chr15	85580133	AKAP13	ENSG00000170776	G	A	322	A	missense_variant	MODERATE	2272	2065	689	E/K	Gag/Aag	rs7177107&COSV63448301
2	CLL02.1	chr20	14085630	MACROD2	ENSG00000172264	C	T	82	T	missense_variant	MODERATE	568	173	58	T/I	aCt/aTt	rs2990505&COSV53960729
2	CLL02.1	chr21	21373867	NCAM2	ENSG00000154654	T	C	185	C	missense_variant	MODERATE	1204	1049	350	L/P	cTg/cCg	rs232518
2	CLL02.1	chr22	46535180	CELSR1	ENSG00000075275	G	C	398	C	missense_variant	MODERATE	2441	1991	664	S/W	tCg/tGg	rs4823850&COSV53084542
2	CLL02.1	chrX	32362843	DMD	ENSG00000198947	A	G	37	G	missense_variant	MODERATE	5507	5270	1757	I/T	aTc/aCc	rs201516290&COSV63773732
2	CLL02.1	chrX	105767516	IL1RAPL2	ENSG00000189108	A	G	186	G	missense_variant	MODERATE	2788	1916	639	H/R	cAt/cGt	rs368014818
4	MBL04.1	chr1	216070175	USH2A	ENSG00000042781	T	C	248	C	missense_variant	MODERATE	6414	5975	1992	Y/C	tAt/tGt	rs41303287&CM104140&COSV56354439
4	MBL04.1	chr2	115753241	DPP10	ENSG00000175497	G	C	204	C	missense_variant	MODERATE	1156	1018	340	A/P	Gct/Cct	rs2053724&COSV59673831
4	MBL04.1	chr2	132783032	NCKAP5	ENSG00000176771	G	T	281	T	missense_variant	MODERATE	4156	3779	1260	P/Q	cCa/cAa	rs13016342&COSV58445700
4	MBL04.1	chr2	132785012	NCKAP5	ENSG00000176771	C	G	291	G	missense_variant	MODERATE	2176	1799	600	S/T	aGt/aCt	rs17325719&COSV58430764&COSV58445709
4	MBL04.1	chr2	137160352	THSD7B	ENSG00000144229	T	A	351	A	missense_variant	MODERATE	1687	1509	503	D/E	gaT/gaA	rs4954474&COSV55680598
4	MBL04.1	chr3	108470146	MYH15	ENSG00000144821	G	A	155	A	missense_variant	MODERATE	1567	1510	504	H/Y	Cac/Tac	rs9868484&COSV56308865
4	MBL04.1	chr3	108470780	MYH15	ENSG00000144821	C	T	65	T	missense_variant	MODERATE	1418	1361	454	R/Q	cGg/cAg	rs4299484&COSV56310353
4	MBL04.1	chr4	61934862	ADGRL3	ENSG00000150471	A	T	15	T	missense_variant	MODERATE	303	305	102	N/I	aAc/aTc	
4	MBL04.1	chr5	22078475	CDH12	ENSG00000154162	C	T	182	T	missense_variant	MODERATE	1011	202	68	V/M	Gtg/Atg	rs4371716&CM067358&COSV66394300
4	MBL04.1	chr5	157490332	ADAM19	ENSG00000135074	A	C	523	C	missense_variant	MODERATE	2297	2218	740	S/A	Tcc/Gcc	rs10067096&COSV57429259
4	MBL04.1	chr5	157491842	ADAM19	ENSG00000135074	C	T	378	T	missense_variant	MODERATE	2058	1979	660	G/D	gGc/gAc	rs2287749
4	MBL04.1	chr7	83155814	PCLO	ENSG00000186472	C	T	142	T	missense_variant	MODERATE	1119	827	276	R/Q	cGa/cAa	rs747593233&COSV61667530
4	MBL04.1	chr7	158138452	PTPRN2	ENSG00000155093	C	T	439	T	missense_variant	MODERATE	1128	974	325	S/N	aGt/aAt	rs1130499&COSV67024020
4	MBL04.1	chr8	1565843	DLGAP2	ENSG00000198010	C	A	69	A	missense_variant	MODERATE	1571	1391	464	P/Q	cCa/cAa	rs2301963&COSV70102130
4	MBL04.1	chr8	112228859	CSMD3	ENSG00000164796	T	G	117	G	missense_variant	MODERATE	10946	10861	3621	N/H	Aat/Cat	rs1592624&COSV52174720
4	MBL04.1	chr10	66766407	CTNNA3	ENSG00000183230	C	T	21	T	missense_variant	MODERATE	1339	1138	380	A/T	Gct/Act	rs772731501

Family	sample	CHROM	POS	SYMBOL	Gene	REF	ALT	QUAL	Allele	Consequence	IMPACT	cDNA_position	CDS_position	Protein_position	Amino_acids	Codons	Existing_variation
4	MBL04.1	chr11	20783740	NELL1	ENSG00000165973	G	A	202	A	missense_variant	MODERATE	383	245	82	R/Q	cGg/cAg	rs8176785&CM074381
4	MBL04.1	chr11	92831816	FAT3	ENSG00000165323	G	A	242	A	missense_variant	MODERATE	10050	9676	3226	V/I	Gtt/Att	rs766505847
4	MBL04.1	chr13	24455080	PARP4	ENSG00000102699	C	T	381	T	missense_variant	MODERATE	2769	2695	899	A/T	Gcc/Acc	rs2275660&COSV67960444
4	MBL04.1	chr22	46535180	CELSR1	ENSG00000075275	G	C	330	C	missense_variant	MODERATE	2441	1991	664	S/W	tCg/tGg	rs4823850&COSV53084542
5	CLL05.1	chr4	65365968	EPHA5	ENSG00000145242	C	T	234	T	missense_variant	MODERATE	2698	1951	651	A/T	Gca/Aca	rs36050417&COSV56636694
5	CLL05.1	chr4	65490601	EPHA5	ENSG00000145242	A	G	326	G	missense_variant	MODERATE	1925	1178	393	I/T	aTt/aCt	rs780551761
5	CLL05.1	chr7	14685305	DGKB	ENSG00000136267	A	C	16	C	missense_variant	MODERATE	1116	769	257	Y/D	Tat/Gat	COSV104385499
5	CLL05.1	chr11	20928414	NELL1	ENSG00000165973	C	T	120	T	missense_variant	MODERATE	1070	932	311	P/L	cCt/cTt	rs55926004
5	CLL05.1	chr20	14085630	MACROD2	ENSG00000172264	C	T	62	T	missense_variant	MODERATE	568	173	58	T/I	aCt/aTt	rs2990505&COSV53960729
5	CLL05.1	chr22	22893818	IGLL5	ENSG00000254709	G	A	44	A	missense_variant&splice_region_variant	MODERATE	563	325	109	G/S	Ggt/Agt	rs201857114&COSV101138586&COSV66537362
5	MBL05.1	chr1	71407471	NEGR1	ENSG00000172260	T	G	129	G	missense_variant	MODERATE	1085	1040	347	Y/S	tAc/tCc	rs41289154&COSV60833851&COSV60866382
5	MBL05.1	chr6	117301070	ROS1	ENSG00000047936	C	T	155	T	missense_variant	MODERATE	6905	6619	2207	D/N	Gac/Aac	rs529038&CM053396&COSV63850799
5	MBL05.1	chr7	158167251	PTPRN2	ENSG00000155093	G	C	166	C	missense_variant	MODERATE	744	590	197	A/G	gCc/gGc	rs140999965
6	CLL06.1	chr1	71407471	NEGR1	ENSG00000172260	T	G	138	G	missense_variant	MODERATE	1085	1040	347	Y/S	tAc/tCc	rs41289154&COSV60833851&COSV60866382
6	CLL06.1	chr2	115746095	DPP10	ENSG00000175497	G	A	47	A	missense_variant	MODERATE	1000	862	288	V/M	Gtg/Atg	rs36044503
6	CLL06.1	chr2	115753241	DPP10	ENSG00000175497	G	C	173	C	missense_variant	MODERATE	1156	1018	340	A/P	Gct/Cct	rs2053724&COSV59673831
6	CLL06.1	chr2	132783032	NCKAP5	ENSG00000176771	G	T	452	T	missense_variant	MODERATE	4156	3779	1260	P/Q	cCa/cAa	rs13016342&COSV58445700
6	CLL06.1	chr2	132785012	NCKAP5	ENSG00000176771	C	G	631	G	missense_variant	MODERATE	2176	1799	600	S/T	aGt/aCt	rs17325719&COSV58430764&COSV58445709
6	CLL06.1	chr2	141810341	LRP1B	ENSG00000168702	T	C	134	C	missense_variant	MODERATE	430	143	48	Q/R	cAg/cGg	rs12990449&COSV67182532
6	CLL06.1	chr3	78635874	ROBO1	ENSG00000169855	C	T	107	T	missense_variant	MODERATE	3569	3272	1091	S/N	aGc/aAc	rs35456279&COSV71397020
6	CLL06.1	chr3	108470146	MYH15	ENSG00000144821	G	A	1153	A	missense_variant	MODERATE	1567	1510	504	H/Y	Cac/Tac	rs9868484&COSV56308865
6	CLL06.1	chr3	175627355	NAALADL2	ENSG00000177694	C	G	273	G	missense_variant	MODERATE	1939	1865	622	P/R	cCc/cGc	rs9866564
6	CLL06.1	chr4	61979743	ADGRL3	ENSG00000150471	C	G	138	G	missense_variant	MODERATE	1154	1156	386	L/V	Ctg/Gtg	rs12509110&COSV72232449&COSV99072504
6	CLL06.1	chr5	22078475	CDH12	ENSG00000154162	C	T	416	T	missense_variant	MODERATE	1011	202	68	V/M	Gtg/Atg	rs4371716&CM067358&COSV66394300
6	CLL06.1	chr6	117301070	ROS1	ENSG00000047936	C	T	74	T	missense_variant	MODERATE	6905	6619	2207	D/N	Gac/Aac	rs529038&CM053396&COSV63850799
6	CLL06.1	chr7	149015000	PDIA4	ENSG00000155660	G	A	605	A	missense_variant	MODERATE	615	518	173	T/M	aCg/aTg	rs2290971&CM1511790
6	CLL06.1	chr7	158167203	PTPRN2	ENSG00000155093	C	T	30	T	missense_variant	MODERATE	792	638	213	R/H	cGc/cAc	rs1130496&COSV67046421
6	CLL06.1	chr8	1565843	DLGAP2	ENSG00000198010	C	A	16	A	missense_variant	MODERATE	1571	1391	464	P/Q	cCa/cAa	rs2301963&COSV70102130
6	CLL06.1	chr8	112228859	CSMD3	ENSG00000164796	T	G	258	G	missense_variant	MODERATE	10946	10861	3621	N/H	Aat/Cat	rs1592624&COSV52174720
6	CLL06.1	chr11	20783740	NELL1	ENSG00000165973	G	A	70	A	missense_variant	MODERATE	383	245	82	R/Q	cGg/cAg	rs8176785&CM074381
6	CLL06.1	chr13	24455080	PARP4	ENSG00000102699	C	T	639	T	missense_variant	MODERATE	2769	2695	899	A/T	Gcc/Acc	rs2275660&COSV67960444
6	CLL06.1	chr14	92651884	RIN3	ENSG00000100599	C	T	34	T	missense_variant	MODERATE	987	835	279	R/C	Cgc/Tgc	rs117068593&COSV53649944
6	CLL06.1	chr15	85580133	AKAP13	ENSG00000170776	G	A	546	A	missense_variant	MODERATE	2272	2065	689	E/K	Gag/Aag	rs7177107&COSV63448301
6	CLL06.1	chr15	85735078	AKAP13	ENSG00000170776	G	A	206	A	missense_variant	MODERATE	7576	7369	2457	G/S	Ggt/Agt	rs2241268&COSV63448267
6	CLL06.1	chr17	7670613	TP53	ENSG00000141510	A	C	178	C	missense_variant	MODERATE	1238	1096	366	S/A	Tcc/Gcc	rs17881470&CM078492&COSV52875421
6	CLL06.1	chr20	14085630	MACROD2	ENSG00000172264	C	T	80	T	missense_variant	MODERATE	568	173	58	T/I	aCt/aTt	rs2990505&COSV53960729
6	CLL06.1	chr21	21373867	NCAM2	ENSG00000154654	T	C	315	C	missense_variant	MODERATE	1204	1049	350	L/P	cTg/cCg	rs232518
6	CLL06.1	chr21	40353698	DSCAM	ENSG00000171587	C	T	41	T	missense_variant	MODERATE	1198	701	234	R/H	cGc/cAc	rs41395652
6	CLL06.1	chr22	46535180	CELSR1	ENSG00000075275	G	C	520	C	missense_variant	MODERATE	2441	1991	664	S/W	tCg/tGg	rs4823850&COSV53084542
21	CLL21.1	chr2	115753241	DPP10	ENSG00000175497	G	C	162	C	missense_variant	MODERATE	1156	1018	340	A/P	Gct/Cct	rs2053724&COSV59673831
21	CLL21.1	chr2	132783032	NCKAP5	ENSG00000176771	G	T	905	T	missense_variant	MODERATE	4156	3779	1260	P/Q	cCa/cAa	rs13016342&COSV58445700
21	CLL21.1	chr2	132785012	NCKAP5	ENSG00000176771	C	G	1173	G	missense_variant	MODERATE	2176	1799	600	S/T	aGt/aCt	rs17325719&COSV58430764&COSV58445709
21	CLL21.1	chr2	137160352	THSD7B	ENSG00000144229	T	A	843	A	missense_variant	MODERATE	1687	1509	503	D/E	gaT/gaA	rs4954474&COSV55680598
21	CLL21.1	chr2	141810341	LRP1B	ENSG00000168702	T	C	560	C	missense_variant	MODERATE	430	143	48	Q/R	cAg/cGg	rs12990449&COSV67182532
21	CLL21.1	chr2	213930019	SPAG16	ENSG00000144451	A	C	593	C	missense_variant	MODERATE	1294	1274	425	K/T	aAa/aCa	rs12623569&COSV59078990
21	CLL21.1	chr3	108470146	MYH15	ENSG00000144821	G	A	759	A	missense_variant	MODERATE	1567	1510	504	H/Y	Cac/Tac	rs9868484&COSV56308865
21	CLL21.1	chr3	108470780	MYH15	ENSG00000144821	C	T	557	T	missense_variant	MODERATE	1418	1361	454	R/Q	cGg/cAg	rs4299484&COSV56310353
21	CLL21.1	chr3	175627355	NAALADL2	ENSG00000177694	C	G	657	G	missense_variant	MODERATE	1939	1865	622	P/R	cCc/cGc	rs9866564
21	CLL21.1	chr5	157509356	ADAM19	ENSG00000135074	T	C	1981	C	missense_variant	MODERATE	929	850	284	S/G	Agt/Ggt	rs1422795&CM093420&COSV57425399
21	CLL21.1	chr6	26234599	H1-3	ENSG00000124575	G	C	49	C	missense_variant	MODERATE	389	335	112	A/G	gCg/gGg	rs140433263
21	CLL21.1	chr6	27866899	H1-5	ENSG00000184357	C	T	259	T	missense_variant	MODERATE	690	631	211	A/T	Gca/Aca	rs34144478
21	CLL21.1	chr6	117301070	ROS1	ENSG00000047936	C	T	240	T	missense_variant	MODERATE	6905	6619	2207	D/N	Gac/Aac	rs529038&CM053396&COSV63850799
21	CLL21.1	chr7	158138452	PTPRN2	ENSG00000155093	C	T	551	T	missense_variant	MODERATE	1128	974	325	S/N	aGt/aAt	rs1130499&COSV67024020
21	CLL21.1	chr8	1565843	DLGAP2	ENSG00000198010	C	A	547	A	missense_variant	MODERATE	1571	1391	464	P/Q	cCa/cAa	rs2301963&COSV70102130
21	CLL21.1	chr11	20783740	NELL1	ENSG00000165973	G	A	2263	A	missense_variant	MODERATE	383	245	82	R/Q	cGg/cAg	rs8176785&CM074381
21	CLL21.1	chr11	108310218	ATM	ENSG00000149311	G	C	283	C	missense_variant	MODERATE	5971	5821	1941	V/L	Gtt/Ctt	rs147187700&CM094667&COSV53739000&COSV53750671
21	CLL21.1	chr13	24455080	PARP4	ENSG00000102699	C	T	616	T	missense_variant	MODERATE	2769	2695	899	A/T	Gcc/Acc	rs2275660&COSV67960444

Family	sample	CHROM	POS	SYMBOL	Gene	REF	ALT	QUAL	Allele	Consequence	IMPACT	cDNA_position	CDS_position	Protein_position	Amino_acids	Codons	Existing_variation
21	CLL21.1	chr15	85735078	AKAP13	ENSG00000170776	G	A	417	A	missense_variant	MODERATE	7576	7369	2457	G/S	Ggt/Agt	rs2241268&COSV63448267
21	CLL21.1	chr15	86264612	AGBL1	ENSG00000273540	T	C	696	C	missense_variant	MODERATE	1543	1441	481	S/P	Tcc/Ccc	rs11857527&COSV66866512
21	CLL21.1	chr21	21373867	NCAM2	ENSG00000154654	T	C	1106	C	missense_variant	MODERATE	1204	1049	350	L/P	cTg/cCg	rs232518
21	CLL21.1	chr22	46535180	CELSR1	ENSG00000075275	G	C	1999	C	missense_variant	MODERATE	2441	1991	664	S/W	tCg/tGg	rs4823850&COSV53084542
22	MBL22.1	chr1	81907079	ADGRL2	ENSG00000117114	T	A	18	A	missense_variant	MODERATE	352	136	46	S/T	Tct/Act	
22	MBL22.1	chr2	213930019	SPAG16	ENSG00000144451	A	C	181	C	missense_variant	MODERATE	1294	1274	425	K/T	aAa/aCa	rs12623569&COSV59078990
22	MBL22.1	chr8	1565843	DLGAP2	ENSG00000198010	C	A	343	A	missense_variant	MODERATE	1571	1391	464	P/Q	cCa/cAa	rs2301963&COSV70102130
22	MBL22.1	chr8	112228859	CSMD3	ENSG00000164796	T	G	420	G	missense_variant	MODERATE	10946	10861	3621	N/H	Aat/Cat	rs1592624&COSV52174720
22	MBL22.1	chr13	94382448	GPC6	ENSG00000183098	A	G	26	G	missense_variant	MODERATE	1837	1187	396	K/R	aAa/aGa	
22	MBL22.1	chr21	40338287	DSCAM	ENSG00000171587	A	G	15	G	missense_variant	MODERATE	2094	1597	533	Y/H	Tac/Cac	
23	CLL23.1	chr5	157509356	ADAM19	ENSG00000135074	T	C	375	C	missense_variant	MODERATE	929	850	284	S/G	Agt/Ggt	rs1422795&CM093420&COSV57425399
23	CLL23.1	chr14	92651884	RIN3	ENSG00000100599	C	T	773	T	missense_variant	MODERATE	987	835	279	R/C	Cgc/Tgc	rs117068593&COSV53649944
23	CLL23.1	chr20	42104665	PTPRT	ENSG00000196090	G	T	825	T	missense_variant	MODERATE	3471	3471	1157	N/K	aaC/aaA	rs201162919&COSV61980909
23	CLL23.1	chr21	40353698	DSCAM	ENSG00000171587	C	T	210	T	missense_variant	MODERATE	1198	701	234	R/H	cGc/cAc	rs41395652
23	MBL23.1	chr1	237566732	RYR2	ENSG00000198626	A	G	624	G	missense_variant	MODERATE	3718	3380	1127	E/G	gAg/gGg	rs200525962
23	MBL23.1	chr4	8218302	SH3TC1	ENSG00000125089	G	A	238	A	missense_variant	MODERATE	1015	871	291	D/N	Gac/Aac	rs1281138
23	MBL23.1	chr4	8240900	SH3TC1	ENSG00000125089	C	A	239	A	missense_variant	MODERATE	4100	3956	1319	P/H	cCt/cAt	rs150702535
23	MBL23.1	chr6	27866899	H1-5	ENSG00000184357	C	T	278	T	missense_variant	MODERATE	690	631	211	A/T	Gca/Aca	rs34144478
23	MBL23.1	chr7	154052980	DPP6	ENSG00000130226	C	T	21	T	missense_variant	MODERATE	583	160	54	R/W	Cgg/Tgg	COSV66748904
24	MBL24.1	chr1	215728169	USH2A	ENSG00000042781	G	A	254	A	missense_variant	MODERATE	12366	11927	3976	T/M	aCg/aTg	rs142381713&CM073404&COSV56393885
24	MBL24.1	chr5	157509356	ADAM19	ENSG00000135074	T	C	353	C	missense_variant	MODERATE	929	850	284	S/G	Agt/Ggt	rs1422795&CM093420&COSV57425399
24	MBL24.1	chr6	117362658	ROS1	ENSG00000047936	G	A	555	A	missense_variant	MODERATE	3597	3311	1104	S/L	tCa/tTa	rs2229079&COSV63860865
24	MBL24.1	chr6	117404285	ROS1	ENSG00000047936	T	G	450	G	missense_variant	MODERATE	746	460	154	T/P	Act/Cct	rs1998206&COSV63854406
24	MBL24.1	chr11	92837690	FAT3	ENSG00000165323	G	T	422	T	missense_variant	MODERATE	10626	10252	3418	A/S	Gcc/Tcc	rs201449521&COSV53125665&COSV99973667
24	MBL24.1	chr13	24442624	PARP4	ENSG00000102699	G	A	74	A	missense_variant	MODERATE	3583	3509	1170	T/I	aCa/aTa	rs113301501&CM160622&COSV67960155
24	MBL24.1	chr13	24447185	PARP4	ENSG00000102699	A	G	87	G	missense_variant&splice_region_variant	MODERATE	3190	3116	1039	I/T	aTa/aCa	rs73172125&COSV67960144
24	MBL24.1	chr14	46957592	MDGA2	ENSG00000139915	C	T	632	T	missense_variant	MODERATE	1612	977	326	R/Q	cGa/cAa	rs553082374&COSV62105261
24	MBL24.1	chr17	7674917	TP53	ENSG00000141510	T	C	993	C	missense_variant	MODERATE	756	614	205	Y/C	tAt/tGt	rs1057520007&COSV52665440&COSV52677268&COSV52688506
24	MBL24.1	chr22	22888193	IGLL5	ENSG00000254709	G	A	243	A	missense_variant	MODERATE	378	140	47	S/N	aGc/aAc	rs540568540&COSV73249672
24	MBL24.2	chr2	197402110	SF3B1	ENSG00000115524	T	C	842	C	missense_variant	MODERATE	2127	2098	700	K/E	Aaa/Gaa	rs559063155&COSV59205318&COSV59216586
24	MBL24.2	chr3	108470780	MYH15	ENSG00000144821	C	T	665	T	missense_variant	MODERATE	1418	1361	454	R/Q	cGg/cAg	rs4299484&COSV56310353
24	MBL24.3	chr1	215647626	USH2A	ENSG00000042781	A	T	27	T	missense_variant	MODERATE	15126	14687	4896	L/H	cTt/cAt	
24	MBL24.3	chr1	215790251	USH2A	ENSG00000042781	A	C	15	C	missense_variant	MODERATE	10429	9990	3330	N/K	aaT/aaG	
24	MBL24.3	chr1	237569176	RYR2	ENSG00000198626	A	G	23	G	missense_variant	MODERATE	3793	3455	1152	Y/C	tAt/tGt	
24	MBL24.3	chr1	237674166	RYR2	ENSG00000198626	A	T	61	T	missense_variant	MODERATE	8999	8661	2887	E/D	gaA/gaT	
24	MBL24.3	chr2	132783534	NCKAP5	ENSG00000176771	T	A	1027	A	missense_variant	MODERATE	3654	3277	1093	N/Y	Aat/Tat	rs16841277&COSV58444336
24	MBL24.3	chr2	141062161	LRP1B	ENSG00000168702	C	A	18	A	missense_variant	MODERATE	1413	1126	376	A/S	Gca/Tca	
24	MBL24.3	chr2	197396311	SF3B1	ENSG00000115524	G	T	34	T	missense_variant	MODERATE	3313	3284	1095	A/D	gCt/gAt	
24	MBL24.3	chr3	108410799	MYH15	ENSG00000144821	C	A	16	A	missense_variant	MODERATE	4396	4339	1447	V/F	Gtc/Ttc	COSV56321473
24	MBL24.3	chr5	21783409	CDH12	ENSG00000154162	C	T	33	T	missense_variant	MODERATE	2151	1342	448	D/N	Gac/Aac	
24	MBL24.3	chr5	59893589	PDE4D	ENSG00000113448	C	G	250	G	missense_variant	MODERATE	138	34	12	A/P	Gcg/Ccg	
24	MBL24.3	chr7	81991211	CACNA2D1	ENSG00000153956	C	T	36	T	stop_gained	HIGH	2088	1770	590	W/*	tgG/tgA	rs1554341873
24	MBL24.3	chr7	147132332	CNTNAP2	ENSG00000174469	A	T	31	T	missense_variant	MODERATE	1247	1171	391	N/Y	Aac/Tac	COSV62189039
24	MBL24.3	chr7	148147676	CNTNAP2	ENSG00000174469	A	G	25	G	missense_variant	MODERATE	2816	2740	914	T/A	Acc/Gcc	
24	MBL24.3	chr8	2978629	CSMD1	ENSG00000183117	G	A	36	A	missense_variant	MODERATE	9047	8549	2850	S/F	tCc/tTc	
24	MBL24.3	chr8	14324194	SGCZ	ENSG00000185053	C	A	26	A	missense_variant	MODERATE	1053	245	82	G/V	gGa/gTa	COSV65998392&COSV66047381
24	MBL24.3	chr9	117214604	ASTN2	ENSG00000148219	A	T	3070	T	missense_variant	MODERATE	888	769	257	S/T	Tct/Act	rs139148246
24	MBL24.3	chr11	92837708	FAT3	ENSG00000165323	C	G	175	G	missense_variant	MODERATE	10644	10270	3424	P/A	Cct/Gct	
24	MBL24.3	chr13	93830302	GPC6	ENSG00000183098	T	G	63	G	missense_variant	MODERATE	1118	468	156	N/K	aaT/aaG	
24	MBL24.3	chr14	61485534	PRKCH	ENSG00000027075	T	G	30	G	missense_variant	MODERATE	1693	1311	437	N/K	aaT/aaG	
24	MBL24.3	chr15	85645868	AKAP13	ENSG00000170776	C	A	29	A	missense_variant	MODERATE	4495	4288	1430	Q/K	Caa/Aaa	
24	MBL24.3	chr18	21384368	GREB1L	ENSG00000141449	A	C	149	C	missense_variant	MODERATE	475	320	107	Q/P	cAa/cCa	rs1425668691
24	MBL24.3	chr21	40187251	DSCAM	ENSG00000171587	C	A	30	A	missense_variant	MODERATE	3156	2659	887	D/Y	Gac/Tac	
24	MBL24.3	chr22	46386404	CELSR1	ENSG00000075275	A	G	505	G	missense_variant&splice_region_variant	MODERATE	7187	6737	2246	M/T	aTg/aCg	rs749104236
24	MBL24.3	chr22	46537122	CELSR1	ENSG00000075275	C	G	27	G	missense_variant	MODERATE	499	49	17	A/P	Gcc/Ccc	
27	CLL27.1	chr1	81990901	ADGRL2	ENSG00000117114	G	A	551	A	missense_variant	MODERATE	4184	3968	1323	R/K	aGa/aAa	rs41292984&COSV54685119
27	CLL27.1	chr2	115746095	DPP10	ENSG00000175497	G	A	542	A	missense_variant	MODERATE	1000	862	288	V/M	Gtg/Atg	rs36044503

Family	sample	CHROM	POS	SYMBOL	Gene	REF	ALT	QUAL	Allele	Consequence	IMPACT	cDNA_position	CDS_position	Protein_position	Amino_acids	Codons	Existing_variation
27	CLL27.1	chr2	197402635	SF3B1	ENSG00000115524	C	A	139	A	missense_variant	MODERATE	2027	1998	666	K/N	aaG/aaT	rs377023736&COSV59205777&COSV59205799
27	CLL27.1	chr8	1565843	DLGAP2	ENSG00000198010	C	A	572	A	missense_variant	MODERATE	1571	1391	464	P/Q	cCa/cAa	rs2301963&COSV70102130
27	CLL27.1	chr10	115334318	ATRNL1	ENSG00000107518	A	C	923	C	missense_variant	MODERATE	3460	3074	1025	N/T	aAt/aCt	rs1050159510
27	CLL27.1	chr11	99819645	CNTN5	ENSG00000149972	C	T	371	T	stop_gained	HIGH	688	157	53	R/*	Cga/Tga	rs12292659&COSV54311010
27	MBL27.1	chr4	161386160	FSTL5	ENSG00000168843	C	A	810	A	missense_variant	MODERATE	2533	2131	711	D/Y	Gat/Tat	rs3749598
27	MBL27.1	chr9	136515524	NOTCH1	ENSG00000148400	C	T	117	T	missense_variant	MODERATE	2124	1862	621	R/H	cGc/cAc	rs138504021&COSV99487877
27	MBL27.1	chr11	83962888	DLG2	ENSG00000150672	G	A	769	A	missense_variant	MODERATE	1723	1337	446	T/I	aCc/aTc	rs140599607
27	MBL27.2	chr1	215799051	USH2A	ENSG00000042781	G	T	1925	T	missense_variant	MODERATE	10253	9814	3272	P/T	Ccg/Acg	COSV100239515
27	MBL27.2	chr3	175737328	NAALADL2	ENSG00000177694	A	G	571	G	missense_variant	MODERATE	1993	1919	640	Q/R	cAa/cGa	rs62286105
27	MBL27.2	chr9	136523093	NOTCH1	ENSG00000148400	G	A	15	A	missense_variant	MODERATE	761	499	167	P/S	Cca/Tca	rs1439038323&COSV53077398
27	MBL27.2	chr13	24447125	PARP4	ENSG00000102699	T	C	54	C	missense_variant	MODERATE	3250	3176	1059	Q/R	cAg/cGg	rs77269056&COSV67960139
27	MBL27.2	chr13	24447185	PARP4	ENSG00000102699	A	G	194	G	missense_variant&splice_region_variant	MODERATE	3190	3116	1039	I/T	aTa/aCa	rs73172125&COSV67960144
28	CLL28.1	chr2	61492051	XPO1	ENSG00000082898	T	C	209	C	missense_variant	MODERATE	2672	1871	624	D/G	gAt/gGt	COSV68944745
28	CLL28.1	chr3	54569985	CACNA2D3	ENSG00000157445	G	A	672	A	missense_variant	MODERATE	931	769	257	V/M	Gtg/Atg	rs372465588&COSV55530096&COSV55536891
28	CLL28.1	chr5	157490332	ADAM19	ENSG00000135074	A	C	836	C	missense_variant	MODERATE	2297	2218	740	S/A	Tcc/Gcc	rs10067096&COSV57429259
28	CLL28.1	chr5	157509356	ADAM19	ENSG00000135074	T	C	462	C	missense_variant	MODERATE	929	850	284	S/G	Agt/Ggt	rs1422795&CM093420&COSV57425399
28	CLL28.1	chr5	157575687	ADAM19	ENSG00000135074	C	T	116	T	missense_variant	MODERATE	89	10	4	G/S	Ggc/Agc	rs11465228
28	CLL28.1	chr8	112636939	CSMD3	ENSG00000164796	A	G	695	G	missense_variant	MODERATE	3678	3593	1198	F/S	tTt/tCt	rs765163979
28	CLL28.1	chr15	85735078	AKAP13	ENSG00000170776	G	A	413	A	missense_variant	MODERATE	7576	7369	2457	G/S	Ggt/Agt	rs2241268&COSV63448267
28	MBL28.1	chr2	211630569	ERBB4	ENSG00000178568	T	A	238	A	missense_variant	MODERATE	2244	1972	658	I/F	Att/Ttt	rs190654033
28	MBL28.1	chr7	158138452	PTPRN2	ENSG00000155093	C	T	1271	T	missense_variant	MODERATE	1128	974	325	S/N	aGt/aAt	rs1130499&COSV67024020
28	MBL28.1	chr11	92797959	FAT3	ENSG00000165323	C	T	638	T	missense_variant	MODERATE	5320	4946	1649	P/L	cCg/cTg	rs375193261&COSV104590304&COSV53099591
28	MBL28.1	chr13	24447185	PARP4	ENSG00000102699	A	G	21	G	missense_variant&splice_region_variant	MODERATE	3190	3116	1039	I/T	aTa/aCa	rs73172125&COSV67960144
28	MBL28.1	chr13	91693325	GPC5	ENSG00000179399	C	T	367	T	missense_variant	MODERATE	890	464	155	A/V	gCg/gTg	rs553717&COSV65586039
28	MBL28.1	chr15	85580133	AKAP13	ENSG00000170776	G	A	764	A	missense_variant	MODERATE	2272	2065	689	E/K	Gag/Aag	rs7177107&COSV63448301
30	CLL30.1	chr2	124869717	CNTNAP5	ENSG00000155052	G	A	535	A	missense_variant	MODERATE	3752	3388	1130	V/I	Gta/Ata	rs1240405090
30	CLL30.1	chr11	100061213	CNTN5	ENSG00000149972	C	G	145	G	missense_variant&splice_region_variant	MODERATE	1513	982	328	P/A	Ccc/Gcc	rs201910584&COSV54330963
30	CLL30.1	chr13	24447185	PARP4	ENSG00000102699	A	G	63	G	missense_variant&splice_region_variant	MODERATE	3190	3116	1039	I/T	aTa/aCa	rs73172125&COSV67960144
30	CLL30.1	chr20	14085630	MACROD2	ENSG00000172264	C	T	133	T	missense_variant	MODERATE	568	173	58	T/I	aCt/aTt	rs2990505&COSV53960729
30	CLL30.1	chr22	22888259	IGLL5	ENSG00000254709	G	A	162	A	missense_variant&splice_region_variant	MODERATE	444	206	69	R/K	aGg/aAg	rs745485743&COSV73251123
30	MBL30.2	chr2	211722434	ERBB4	ENSG00000178568	G	T	367	T	missense_variant	MODERATE	1114	842	281	A/E	gCa/gAa	
30	MBL30.2	chr7	158138452	PTPRN2	ENSG00000155093	C	T	142	T	missense_variant	MODERATE	1128	974	325	S/N	aGt/aAt	rs1130499&COSV67024020
30	MBL30.2	chr15	85735078	AKAP13	ENSG00000170776	G	A	1813	A	missense_variant	MODERATE	7576	7369	2457	G/S	Ggt/Agt	rs2241268&COSV63448267
30	MBL30.1	chr1	81990901	ADGRL2	ENSG00000117114	G	A	326	A	missense_variant	MODERATE	4184	3968	1323	R/K	aGa/aAa	rs41292984&COSV54685119
30	MBL30.1	chr2	124524333	CNTNAP5	ENSG00000155052	C	T	416	T	missense_variant	MODERATE	1719	1355	452	S/L	tCg/tTg	rs17727261&COSV70497527
30	MBL30.1	chr2	137160352	THSD7B	ENSG00000144229	T	A	1207	A	missense_variant	MODERATE	1687	1509	503	D/E	gaT/gaA	rs4954474&COSV55680598
30	MBL30.1	chr13	24442624	PARP4	ENSG00000102699	G	A	230	A	missense_variant	MODERATE	3583	3509	1170	T/I	aCa/aTa	rs113301501&CM160622&COSV67960155
30	MBL30.1	chr18	21473100	GREB1L	ENSG00000141449	G	A	420	A	missense_variant	MODERATE	2080	1925	642	R/H	cGt/cAt	rs1343579561
30	MBL30.1	chr22	46364248	CELSR1	ENSG00000075275	A	C	22	C	missense_variant	MODERATE	9233	8783	2928	I/S	aTc/aGc	