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Supplementary Information for

Single-cell whole-genome sequencing reveals the functional landscape of somatic mutations in B lymphocytes across the human lifespan

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Supplementary Information Text

Alignment for whole-genome sequencing. For each single cell or bulk sample, sequencing reads were adapter- and quality-trimmed using Trim Galore (version 0.3.7). Reads before and after trimming were subjected to quality checking using FastQC (version 0.11.4). The trimmed reads were aligned to the human reference genome (build 37) using BWA MEM (version 0.7.10) (1). Sequence duplications were removed using samtools (version 0.1.19) (2). The alignment was further indel-realigned based on known indels from the 1000 Genomes Project (phase I) (3), and their base quality scores were recalibrated based on known indels from the 1000 Genomes Project (phase I) and SNVs from dbSNP (build 144), both using GATK (version 3.5.0) (4). The somewhat uneven depth of the reads across the genome for the single cells as compared to bulk DNA is due to some level of locus bias of the MDA reaction (SI Appendix, Table S1). This is well-documented (5), but does not affect variant calling with SCcaller (6).

Calling somatic SNVs. We used SCcaller (version 1.2) for identifying somatic mutations following its online instructions (https://github.com/biosinodx/SCcaller), requiring a minimum 20x sequencing depth and at least 4 reads containing the mutation (6). As illustrated in the previous paper, the SCcaller identify somatic mutations from single cells by filtering out potential amplification artifacts. The filtering is based on a kernel smoother for estimating local allelic amplification bias and a likelihood ratio test to separate three models, one for heterozygous mutation, one for homozygous mutation and the other for the potential artifacts, at every locus. Because the SCcaller requires heterozygous SNPs to correct for allelic amplification bias, we only called mutations on autosomes. The heterozygous SNPs were identified in the bulk whole genome sequences using haplotypecaller of GATK. All somatic SNVs were called only in regions of at least 20x depth. The frequency of somatic SNVs per cell was estimated after normalizing genomic coverage (≥20x) and sensitivity.

Estimating sensitivity of SNV calling. The sensitivity of *de novo* mutation calling in the single cells was estimated as the ratio of the number of heterozygous SNPs detected in single cells to the total number of heterozygous SNPs detected in bulk DNA, at a minimum sequencing depth of 20x in both single cells and bulk (SI Appendix, Table S3).

Estimating specificity of SNV calling. To validate variant calling, we performed Sanger sequencing on 20 randomly selected variants, 30 variants located at mutation clusters at immunoglobulin H chain and immunoglobulin L chain genes and 15 recurrent variants (identified in more than one cells) from the 56 single B lymphocytes.

Detection of clonal hematopoiesis (CHIP) from bulk sequencing. Besides looking at recurrent mutations from single cells, we also search from bulk sequencing for possible somatic CHIP mutations with variant allele frequencies significantly less than germline at 50%. First, candidate variants from bulk sequencing (the majority of which are germline) were called using GATK (version 3.5.0) (4), HaplotypeCaller (option: -stand_call_conf 30 -stand_emit_conf 10) without additional stringent filtering to include as many candidates as possible. Second, we annotated the candidate variants with ANNOVAR (7). Third, using the ANNOVAR's annotations, we compared our variants with the CHIP variant provided by ref (8), and kept any overlapping ones. Finally, we tested if any of the remaining variants has a variant allele frequency significantly differentiate from germline (50%) according to the method described in ref (8). None of the variants was observed in the genes associated with CHIP (8).

Detection of mutational hotspots. For detecting potential hotspot regions, we pooled the mutations identified in the 56 single B cells, in total 30,426 SNVs. We then applied the "shower" method using R package "ClusteredMutations" (9-11), requiring a minimum of 4 mutations within a distance that is less than or equal to 5kb. The average distance between two random, neighboring mutations is ~100kb. To calculate the false discovery rate (FDR) of the hotspots identified, we randomly distributed the 30,426 SNVs across the genome and applied the same criteria to discover potential hotspots to calculate the chance of false positives. This random process was repeated 2,000 times and resulted in the FDR estimations provided in SI Appendix, Table S4.

Analyzing non-immunoglobulin mutation hotspots. We annotated the 19 non-immunoglobulin hotspots through ENSEMBLE, ENCODE and by searching the literature. Eight of the 19 off-target hotspots (42%) were previously reported being off-target SHM hotspots in B cell-related cancers in humans or mice (SI Appendix, Table S4), with 6 of the 19 (32%) overlapping with specific TF binding sites, including E-Box binding regions, YY1 or C/EBP target regions associated with AID binding (SI Appendix, Table S4) (12). Using ATAC sequencing of B cells collected from two of our donors, we found the off-target hotspots significantly more likely to be in or close to (<1kb) open chromatin regions (3.8-fold more likely than random, P=0.003 with 2,000 permutations). We also found that significantly more off-target hotspots were close to transcription start sites (TSS; <1kb, 3.3-fold more likely than random, Monte Carlo P=0.013 with 2,000 permutations). A full annotation of all hotspots is provided as SI Appendix, Table S4.

The "outlier" cell. A SHM+ B cell from the 52-year old donor has a substantially higher mutation frequency than any other cell in this study (Fig. 1a). This cell has a stop codon loss of gene *HIST1H1E*, which is one of the most frequently mutated genes found in human lymphoma (13, 14). When performing the regression analysis in SI Appendix, Fig. S10a, we excluded this cell because it is the only SHM+ cell sequenced of the 52-year donor and is unlikely to be representative for mutation frequency of healthy SHM+ cells of this donor. However, this cell was included in all the other analyses in our study because in all the other analyses, this cell is not the only cell representing one donor or one group.

Identifying CSR. CSR can be identified as depletions of both IGHM and IGHD loci in the genome (15). We first calculated the sequencing depths of the IGHM and IGHD loci as the average sequencing depths of all base pairs of the loci for every single B cell. We then calculated normalized depths as the ratio of the sequencing depths to genome-wide average sequencing depths of the same cells. To reliably distinguish CSR+ and CSR- cells, we applied an unsupervised method on the normalized depths as follows. We performed a principal component analysis (PCA) on the normalized depths of the two loci. All cells clearly separated into two groups based on values of the first principle component (PC1 in SI Appendix, Fig. S9a). We then modeled the distribution of PC1 values as a mixture of two normal distributions estimated using an Expectation–Maximization algorithm from R package "mixtools" (SI Appendix, Fig. S9b) (16). Posterior probabilities of every single cell as a member of either of the two normal distributions were calculated using the same R package (SI Appendix, Fig. S9c). Based on the posterior probabilities, we distinguished CSR+ and CSR- cells as indicated in SI Appendix, Fig. S9c.

Analysis of mutation spectra of the affected bases. The mutation spectra of human B lymphocytes were found to be dominated by mutations at cytosines and guanines and to differ significantly from those of the dermal fibroblasts analyzed previously (SI Appendix, Fig. S11a) (6). More GC>AT transitions were observed in the B lymphocytes than in the fibroblasts (21%), with GC>AT transitions overall significantly more dominant in B lymphocytes from the newborns (66%) than in those from the other age groups (44% to 47%; $P=2.18\text{x}10^{-9}$, t-test, two-tailed).

Since the GC>AT transition is the major fraction of the spectra, we tested the correlation of CpG methylation and mutation frequency because cytosine in CpG dinucleotides is prone to deamination and methylated CpG is even more vulnerable without the protection of uracil glycosylase (17). CpG methylation data at single cytosine resolution as determined by whole-genome bisulfite sequencing of adult B lymphocytes (CD19+) was obtained from the ENCODE (Table S5; see the following paragraph). We found a significantly higher number of mutations at methylated CpGs than what would be expected by chance alone (SI Appendix, Fig. S11b). These results are similar to what has been found for germline mutations and somatic mutations in human tumors (18, 19).

To analyze mutations in relation to methylated cytosines, we used data from ENCODE. Raw sequencing reads of whole-genome bisulfite sequencing of B cells (CD19+) of a 37yr old male donor were downloaded from ENCODE database (https://www.encodeproject.org/experiments/ENCSR284TCU) and were adapter and quality-trimmed using Trim Galore (version 0.3.7). Reads before and after trimming were subjected to quality checking using FastQC (version 0.11.4). First and second end of trimmed reads were aligned to the human reference genome (GRCh37.73) using Bismark (version 0.14.4) with the alignment tool Bowtie2 (version 2.2.3) separately (20, 21). Sequence duplicates were removed, and single CpG methylation called using Bismark, then CpG calls from the two ends of reads were merged with inconstant CpG calls of the two ends discarded. Single CpGs with at least 5 reads were considered for the methylation analysis in SI Appendix, Fig. S11b. Bisulfite conversion rate of the ENCODE experiment was estimated to be over 99%.

Identifying mutation signatures. We pooled mutations from the following groups of cells: cord blood, SHM- B cells of the 27-30yr old, SHM- B cells of the 52-75yr old, SHM- B cells of the 97-106yr old, SHM+ B cells of the 27-30yr old, SHM+ B cells of the 52-75yr old, SHM+ B cells of the 97-106yr old, and the 6 fibroblasts analyzed previously (6). Using NMF decomposition in the R package "SomaticSignatures" (22), we identified 4 signatures from the above 8 groups. Thirty cancer mutation signatures from COSMIC were downloaded from http://cancer.sanger.ac.uk/cosmic/signatures and we calculated the Spearman's correlation coefficients ρ between COSMIC signatures and ours using R.

RNA sequencing. We performed RNA sequencing on frozen B lymphocytes from two donors (F1 and M2; SI Appendix, Table S1), in duplicate. For each donor, the two replicates were from two blood draws on separate days. Total RNA of B lymphocytes was extracted using RNeasy Micro Kit (Qiagen) according to the manufacturer's specification. The concentrations of RNA were quantified with Qubit RNA HS Assay Kit (Invitrogen Life Science) and the qualities of RNA were evaluated using bioanalyzer with Agilent RNA 6000 Pico Kit (Agilent Technologies). The RIN number of each sample submitted for sequencing was about 9.0. Libraries were prepared from 500 ng RNA using KAPA Stranded RNA-Seq Kit with RiboErase (KK8483, KAPA Biosystems) with Trueseq Index (Illumina) by the Einstein Epigenomics Core. Briefly, rRNA was depleted by hybridization with complementary DNA oligonucleotides, treated with RNase H and DNase to remove rRNA duplexed to DNA and the DNA oligonucleotides. RNA was fragmented using heat and magnesium. Subsequently, 1st strand and 2nd strand were synthesized to generate double-stranded cDNA (dscDNA). A-tailing was added to 3'-ends of the dscDNA and ligated with adapters. The ligated library was amplified by PCR. The libraries of the four RNA samples were sequenced on the Illumina HiSeq 2500, with 2×100 bp paired-end reads.

After quality check using FastQC (version 0.11.4), raw sequence reads for each sample were aligned to human reference genome (GRCh37.73) using STAR (version 2.5.2b; options: --outSAMattrIHstart 0 --outFilterIntronMotifs RemoveNoncanonical --alignIntronMin 20 --alignIntronMax 1000000 --outFilterMultimapNmax 1 --outSAMtype BAM SortedByCoordinate)(23), and sequence duplications were filtered out using Picard tools (version

1.119). FPKM values of gene expression were calculated using cufflinks (version 2.2.1) with gene annotation from ENSEMBL database (GRCh37.73)(24). Finally, genes with FPKM consistently larger than 1 in all four samples are considered as transcribed, and the other genes untranscribed.

ATAC sequencing. ATAC sequencing was performed on fresh B lymphocytes from F1 and M2 donors. Libraries were prepared as described (25). Briefly, to isolate nuclei, we spun 25,000 B cells and washed once with cold PBS. Cells were lysed using 10 mM Tris-HCl, pH 7.4, 10 mM NaCl, 3 mM MgCl2, 0.1% IGEPAL CA-630 (26). The nuclei pellet was re-suspended in transposase reaction mix, including 25 µl of 2xTD buffer and 2 µl of Tn5 transposase (Nextera DNA Library Prep Kit, Illumina) and incubated for 30 min at 37°C. After transposition, the fragmented sample was purified using the MinElute PCR Purification Kit (Qiagen) and subsequently PCR-amplified, (10 ul of transposed DNA, 5 µl of nuclease-free water, 5 µl of primer N70#, 5 µl of primer N50#, 25 µl of NEB High Fidelity 2 x PCR Master Mix). PCR conditions were 72 °C for 5 min; 98 °C for 30 s; and five cycles 98 °C for 10 s, 63 °C for 30 s and 72 °C for 1 min. To reduce GC and size bias in PCR, the PCR reaction was monitored using qPCR with 4 µl of the PCR-amplified library, 1 µl of PPC (Nextera DNA Library Prep Kit, Illumina) and 5 µl of 2×SyBr Green Master (Applied Biosystems). The library was amplified for a total of 18 cycles. The libraries were purified using QIAquick PCR Purification Kit (Qiagen) and quantified using Qubit High Sensitivity dsDNA Kit (Invitrogen Life Science). Library quality was assessed using the Agilent Bioanalyzer High-Sensitivity DNA kit (Agilent Technologies). Libraries were sequenced on the Illumina HiSeq 2500, with 2×100 bp reads by the Einstein Epigenomics Core.

The raw reads of ATAC sequencing were adapter- and quality-trimmed using Trim Galore (version 0.3.7). Reads before and after trimming were subjected to quality checking using FastQC (version 0.11.4). Alignment to human reference genome (GRCh37.73) was performed using bowtie2 (version 2.2.3; option: -X 2000). Duplications were removed using Picard tools (version 1.119). Reads with low mapping quality (MapQ<30) were discarded. Open chromatin regions as ATAC sequencing peaks were called using MACS2 (version 2.1.1; option: callpeak -g hs --nomodel --shift -100 --extsize 200) (27).

Mapabilities of all the peaks were estimated using Mapability score obtained from the USCS genome browser and >95% of peaks of both samples were in regions with highest mapability (Mapability score=100%). We used bedtools to determine if reads overlap with the peaks (requiring >= 1 bp overlap), and then checked if the peaks overlap with known TF binding regions reported in ENCODE (requiring 50% bp of peaks overlap with TF binding region; SI Appendix, Table S5). To check the consistency between our ATAC sequencing and RNA sequencing results, we compared enrichment of ATAC seq peaks at TSS of transcribed and untranscribed genes (FPKM>=1 and FPKM<1 respectively, SI Appendix, Fig. S15b). The peak enrichment at TSS was calculated using HOMER (http://homer.ucsd.edu/homer/).

Finally, we merged the open chromatin peaks called from sample F1 and M2 using bedtools (version 2.25.0) (28) to annotate somatic mutations.

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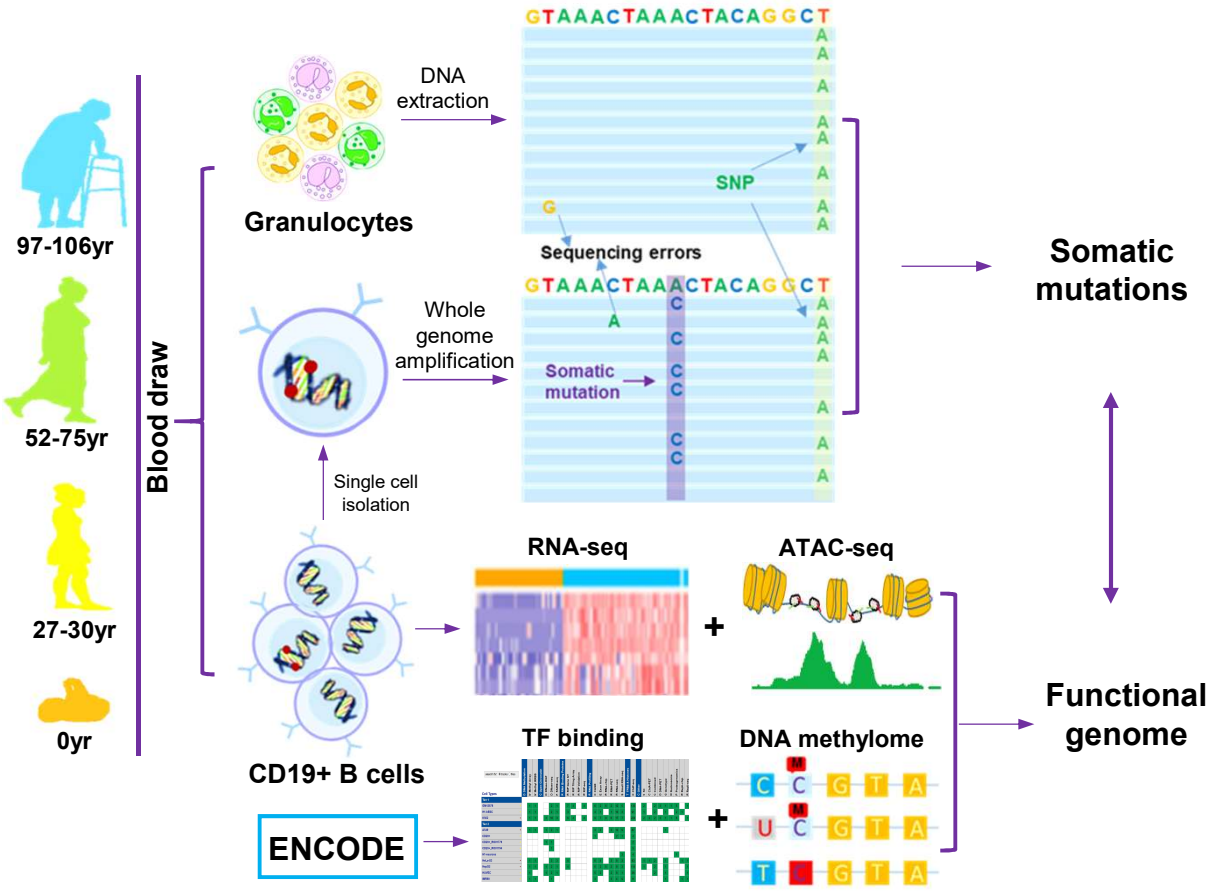


Fig. S1. Study design. A schematic illustration of the single-cell approach to characterize the somatic mutational landscape as a function of age in human B lymphocytes.

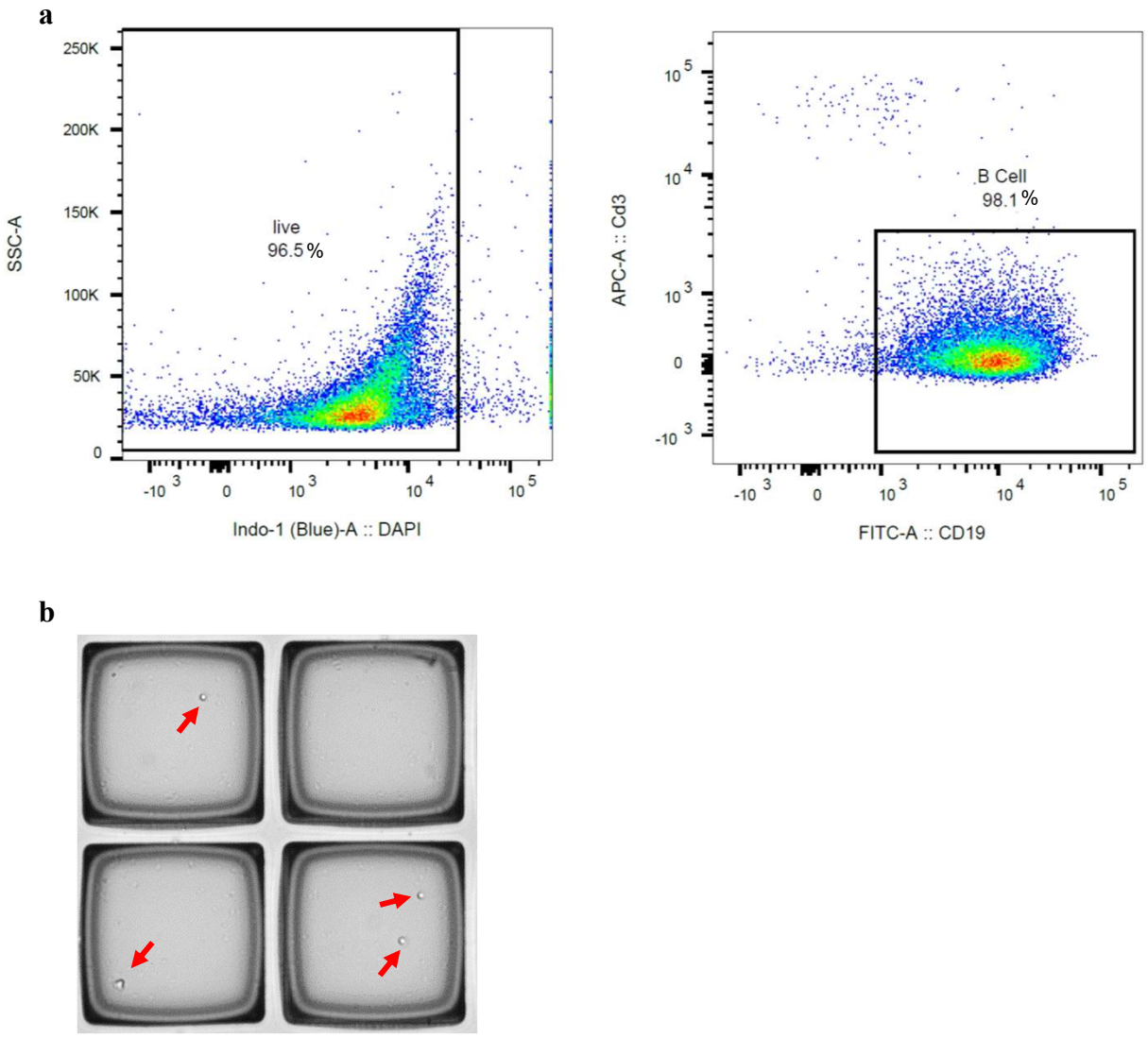


Fig. S2. Isolating single B lymphocytes. a. Specificity of B cells isolated using MACS was validated using FACS with DAPI staining for viability checking as well as APC CD3 and FITC CD19 staining for B cell checking. **b.** Isolating single B cells using CellRaft. The red arrows indicate single cells.

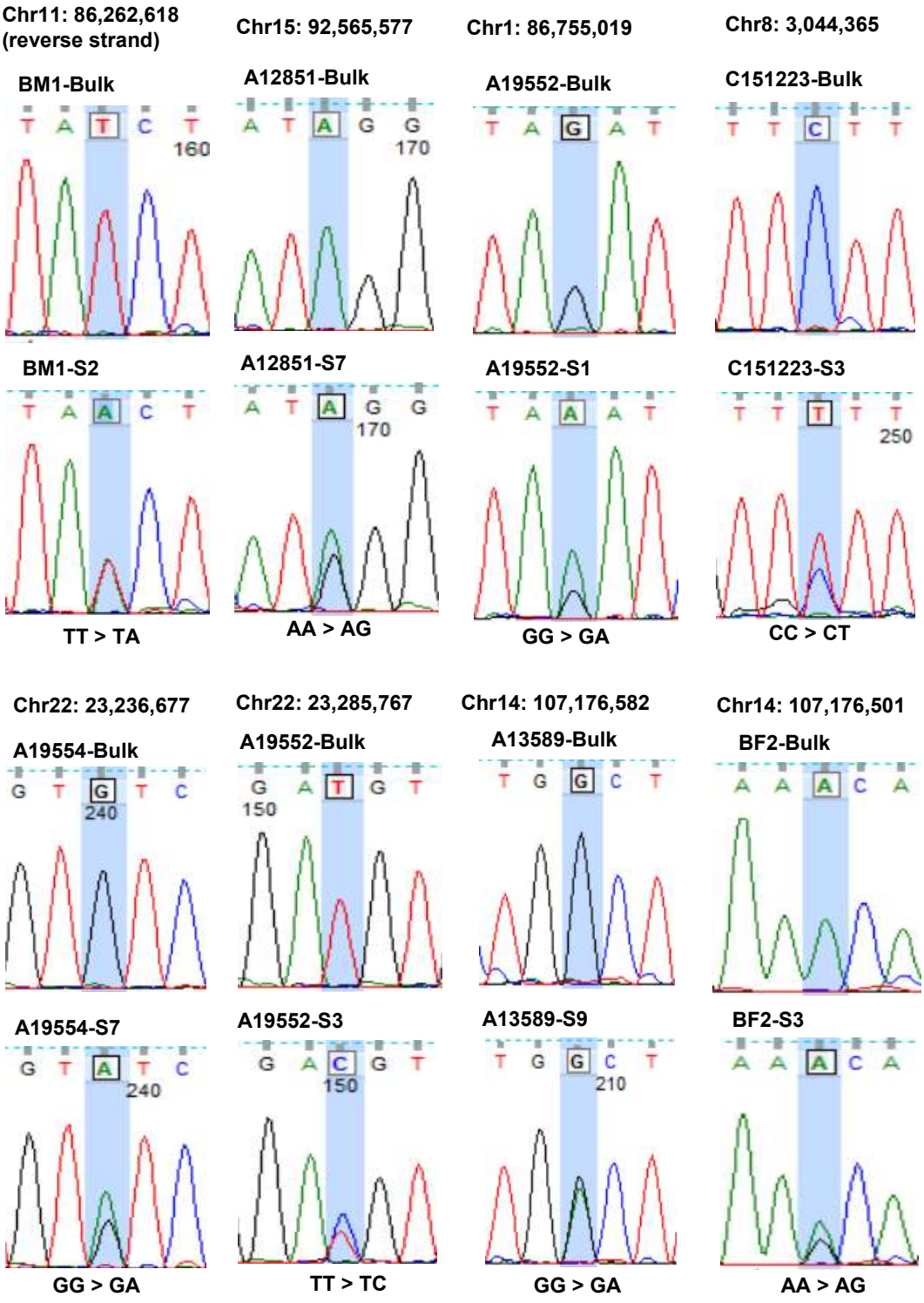


Fig. S3. Sanger sequencing of randomly selected SNVs. The genome coordinates of mutations are provided at the top, followed by results of bulk, and results of the single cell.

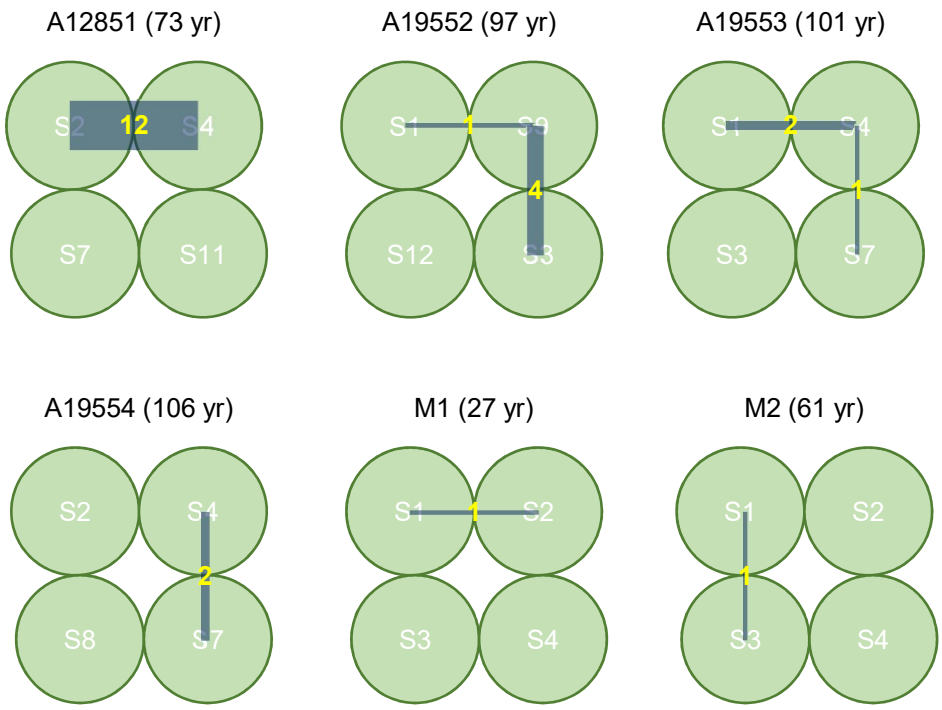


Fig. S4. Recurrent mutations. A circle presents a single cell. A line between two cells with a number indicates the number of recurrent mutations found in the two cells.

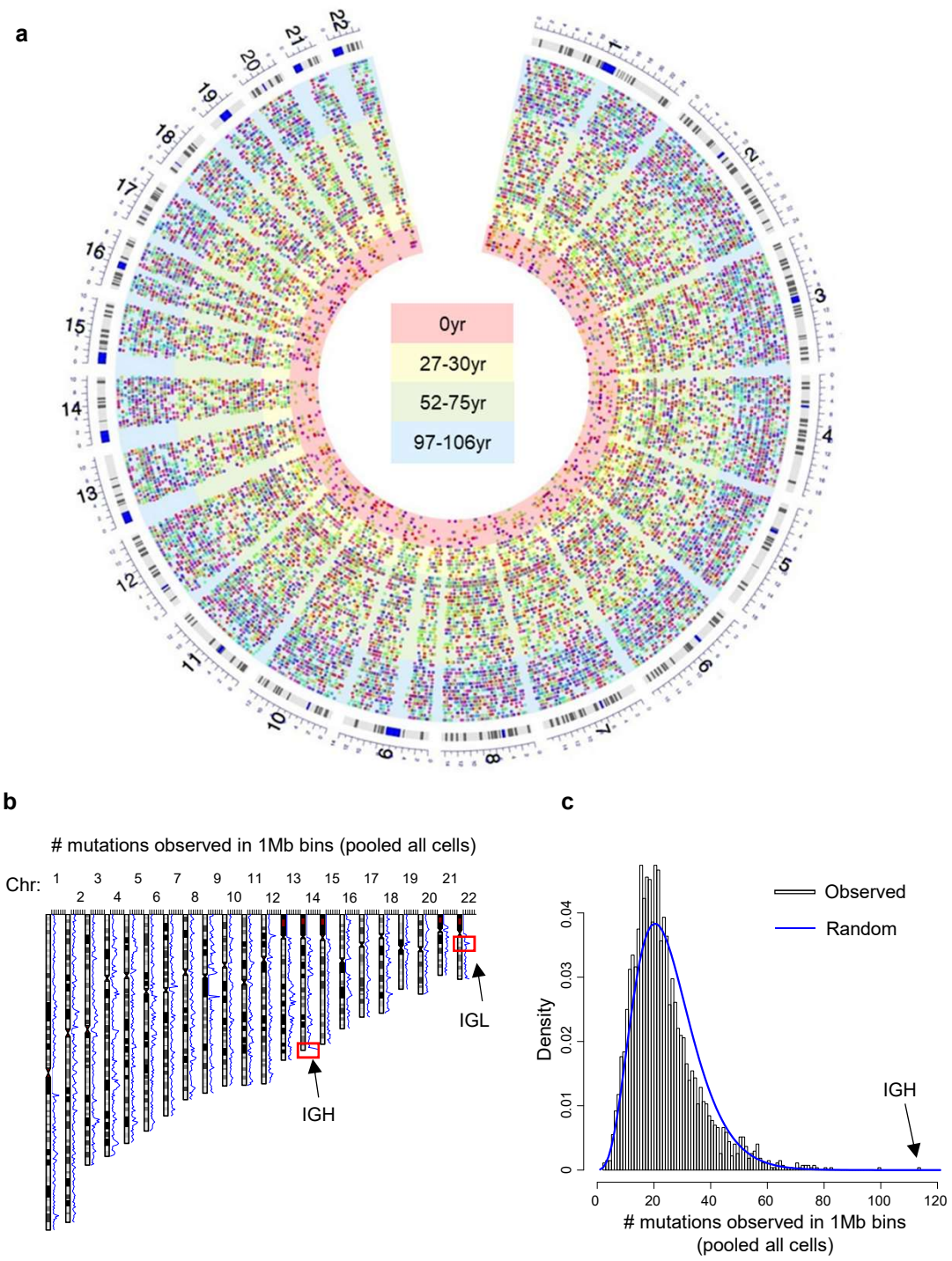


Fig. S5. Distribution of somatic mutations at Mb scale. a. Circus diagram illustrates genome-wide distribution of SNVs. Each circle represents one cell. Dots present SNVs. Neighboring SNVs are plotted with different colors. Panels correspond to age groups of donors. **b.** Number of mutations (the blue lines) observed in Mb bins across the genome. Mutations from all 56 B cells were pooled in this analysis. **c.** Distribution of the numbers of mutation per Mb bin. The blue line represents the expected negative binomial distribution, which describes random distribution.

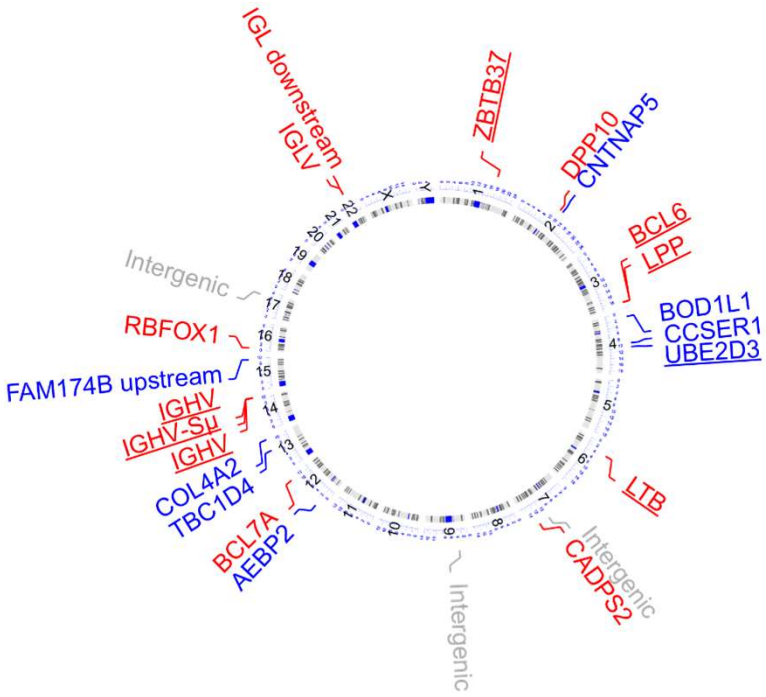


Fig. S6. Distribution of mutation hotspots across the genome.
Hotspot names in red and blue indicate the hotspots that previously reported in human studies and those that have been reported separately (Table S4 for details). Hotspot names underlined indicates the hotspots that were discovered in mouse an AID ChIP-sequencing study (see Fig. S8).

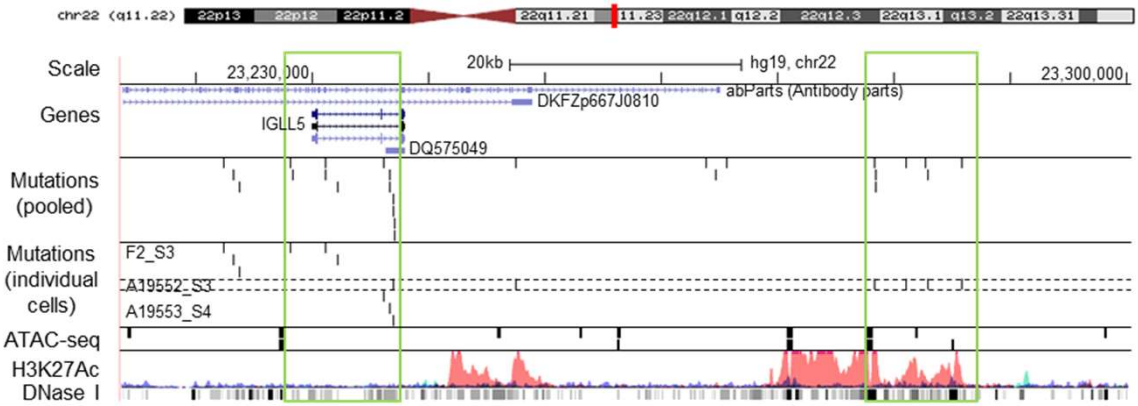


Fig. S7. Mutation hotspots in IGL regions visualized using the UCSC genome browser. The legend is the same as Fig. 1c.

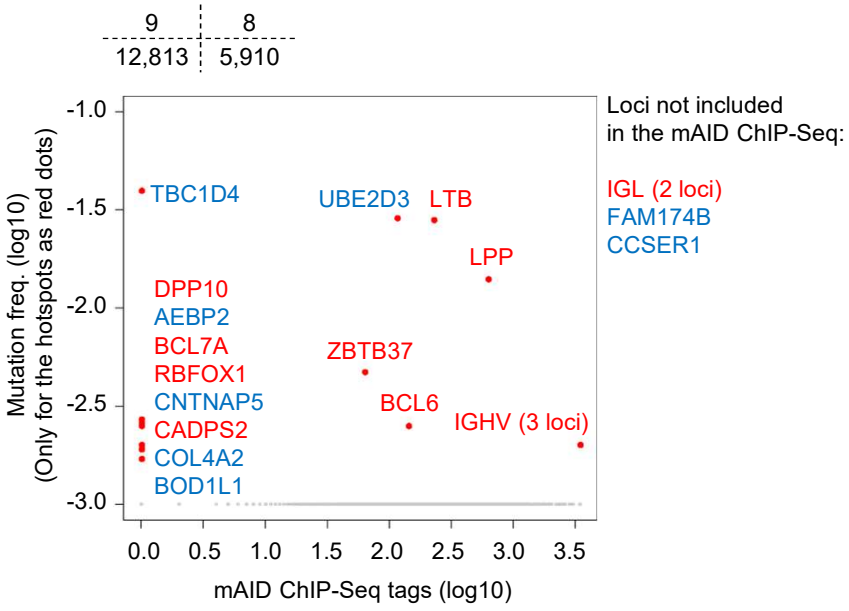
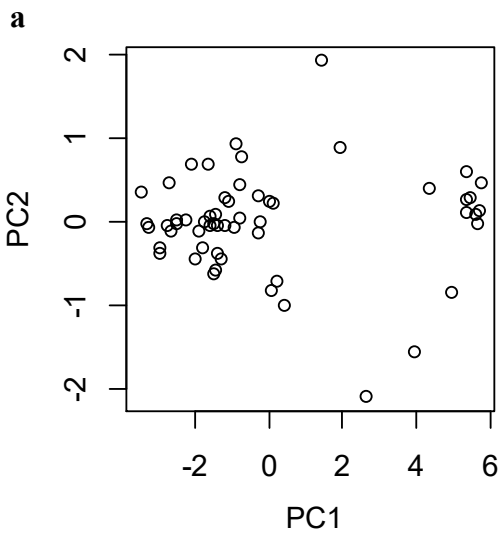
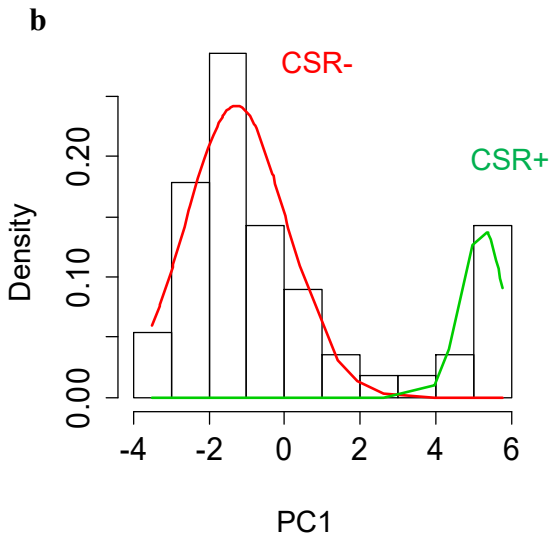


Fig. S8. Comparing the hotspots with mAID ChIP-sequencing data. The red dots indicate hotspots identified in this study. The blue dots indicates all the other genes with the mouse AID ChIP-sequencing data. The red and blue color code of hotspot name is the same as Fig. S6.





c

SHM+ cells | CSR+ cells

Cell ID	Prob. of CSR-	Prob. of CSR+
C151223_S1	1.00E+00	1.21E-26
C151223_S2	1.00E+00	2.63E-30
C151223_S3	1.00E+00	1.90E-19
C151223_S4	9.99E-01	6.33E-04
C70007_S1	1.00E+00	2.90E-17
C70007_S10	1.00E+00	2.38E-33
C70007_S3	1.00E+00	1.28E-34
C70007_S5	1.00E+00	5.52E-36
BM1_S1	4.50E-06	1.00E+00
BM1_S2	1.00E+00	1.60E-07
BM1_S3	1.00E+00	1.33E-29
BM1_S4	1.00E+00	1.57E-43
BF1_S1	2.89E-06	1.00E+00
BF1_S2	1.00E+00	2.85E-38
BF1_S3	1.00E+00	7.88E-28
BF1_S4	1.00E+00	4.33E-34
BF2_S1	1.00E+00	2.00E-32
BF2_S2	1.00E+00	2.34E-34
BF2_S3	5.79E-06	1.00E+00
BF2_S4	1.00E+00	2.87E-46
BM2_S1	1.00E+00	5.57E-52
BM2_S2	1.00E+00	5.85E-33
BM2_S3	1.00E+00	1.82E-30
BM2_S4	1.00E+00	1.65E-32
A19505_S1	1.00E+00	5.37E-32
A19505_S2	1.00E+00	3.02E-43
A19505_S7	1.00E+00	1.90E-10
A19505_S8	1.00E+00	2.64E-48

Cell ID	Prob. of CSR-	Prob. of CSR+
A13589_S10	1.00E+00	1.60E-45
A13589_S3	1.00E+00	4.30E-48
A13589_S6	1.00E+00	3.70E-52
A13589_S9	1.00E+00	3.29E-39
A12851_S11	1.00E+00	1.59E-32
A12851_S2	1.00E+00	4.26E-22
A12851_S4	1.00E+00	2.68E-31
A12851_S7	9.84E-03	9.90E-01
A11365_S1	1.00E+00	1.41E-22
A11365_S2	1.00E+00	3.90E-28
A11365_S3	1.00E+00	6.41E-37
A11365_S4	1.00E+00	2.10E-35
A19552_S1	1.00E+00	2.21E-26
A19552_S12	1.00E+00	1.85E-18
A19552_S3	1.91E-06	1.00E+00
A19552_S9	1.00E+00	1.16E-22
A20061_S14	1.00E+00	5.93E-41
A20061_S16	2.50E-06	1.00E+00
A20061_S2	1.00E+00	1.93E-54
A20061_S9	1.00E+00	7.79E-45
A19553_S1	1.00E+00	8.45E-27
A19553_S3	2.66E-05	1.00E+00
A19553_S4	5.66E-06	1.00E+00
A19553_S7	2.18E-06	1.00E+00
A19554_S2	6.80E-04	9.99E-01
A19554_S4	1.00E+00	9.14E-20
A19554_S7	5.43E-06	1.00E+00
A19554_S8	1.00E+00	3.58E-20

Fig. S9. Identifying CSR from single cells. a. PCA of normalized depths of IGHM and IGHD loci. **b.** Distribution and modeling of PC1 of the PCA. It virtually separates CSR+/- cells. **c.** Posterior probability of being CSR+/- cells.

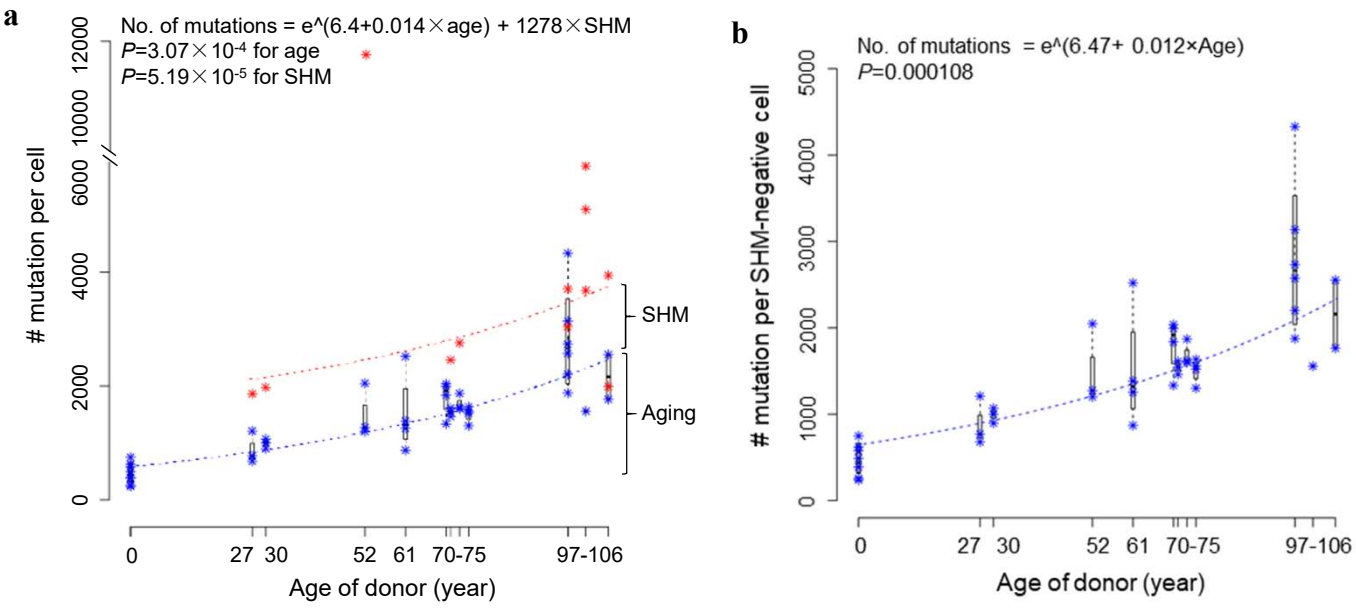
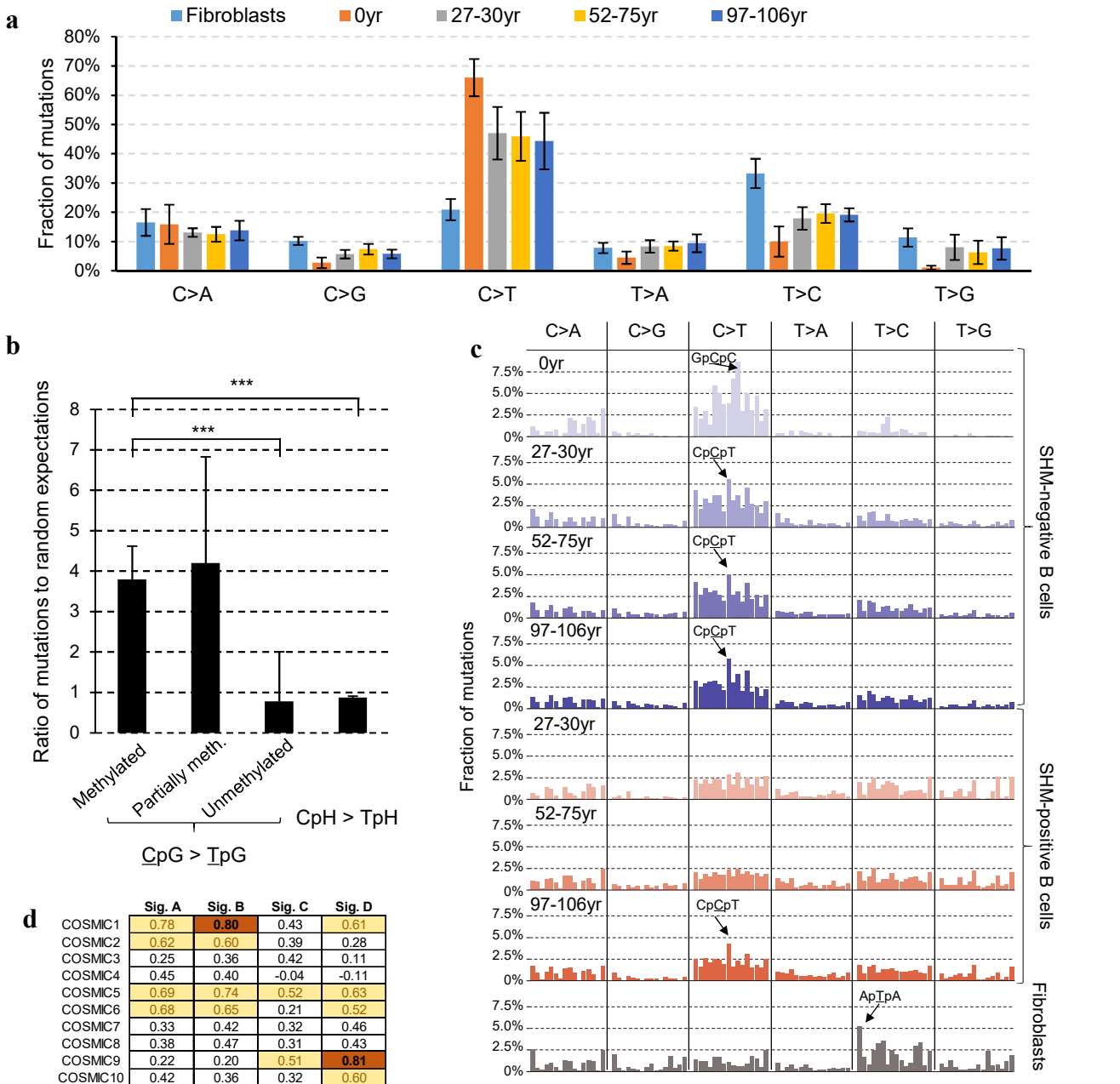


Fig. S10. Mutation frequencies of SHM+/- B cells. a. Mutation frequency with age. SHM+ (red asterisks) or SHM- (blue asterisks) cells are considered separately. Regression analyses were performed on the median mutation frequency of all cells of donors. The cell with the highest mutation frequency (from the 52-year old) was not included in the regression analysis (see supplementary text for more discussions about the "outlier" cell). **b.** Somatic SNV frequency in SHM- cells. Both regressions in **a** and **b** were performed using R with the function "nls".



d

	Sig. A	Sig. B	Sig. C	Sig. D
COSMIC1	0.78	**0.80**	0.43	0.61
COSMIC2	0.62	0.60	0.39	0.28
COSMIC3	0.25	0.36	0.42	0.11
COSMIC4	0.45	0.40	-0.04	-0.11
COSMIC5	0.69	0.74	0.52	0.63
COSMIC6	0.68	0.65	0.21	0.52
COSMIC7	0.33	0.42	0.32	0.46
COSMIC8	0.38	0.47	0.31	0.43
COSMIC9	0.22	0.20	0.51	**0.81**
COSMIC10	0.42	0.36	0.32	0.60
COSMIC11	0.68	0.71	0.23	0.33
COSMIC12	0.53	0.56	0.45	0.57
COSMIC13	0.30	0.33	0.12	0.06
COSMIC14	0.69	0.64	0.28	0.46
COSMIC15	0.73	0.66	0.33	0.49
COSMIC16	0.44	0.50	0.56	0.60
COSMIC17	0.30	0.31	0.32	0.36
COSMIC18	0.51	0.46	0.10	0.12
COSMIC19	0.75	**0.81**	0.37	0.51
COSMIC20	0.68	0.64	0.25	0.44
COSMIC21	0.48	0.56	0.30	0.46
COSMIC22	0.30	0.32	0.05	0.33
COSMIC23	0.64	0.68	0.18	0.26
COSMIC24	0.40	0.34	0.03	-0.16
COSMIC25	0.37	0.45	0.38	0.46
COSMIC26	0.51	0.56	0.41	0.54
COSMIC27	0.68	0.59	0.32	0.38
COSMIC28	0.07	0.06	0.31	0.46
COSMIC29	0.58	0.50	0.26	0.26
COSMIC30	0.39	0.38	-0.11	0.18

Color bar: <0.5 | 0.5-0.8 | >0.8

Fig. S11. Mutation spectra. a. Mutation spectra of B cells and fibroblasts. Each bar represents an average of all single cells of the group. Error bars represent s.d., **b.** Fractions of GC>AT transitions at CpG sites. Methylated, partial and unmethylated CpG sites were identified using whole-genome bisulfite sequencing data from ENCODE (Methods). Error bars indicate s.d. Both P values are smaller than 10^{-20}, using paired t test two tailed. **c.** Mutation spectra in context of their flanking base pairs. SHM+ and SHM- cells were plotted separately. The x-axis labels are in alphabetical order, i.e., in the first column C>A category from left to right, ApCpA > ApApA to TpCpT > TpApT. **d.** Spearman's correlation coefficients between our signatures A to D and COSMIC1 to 30.

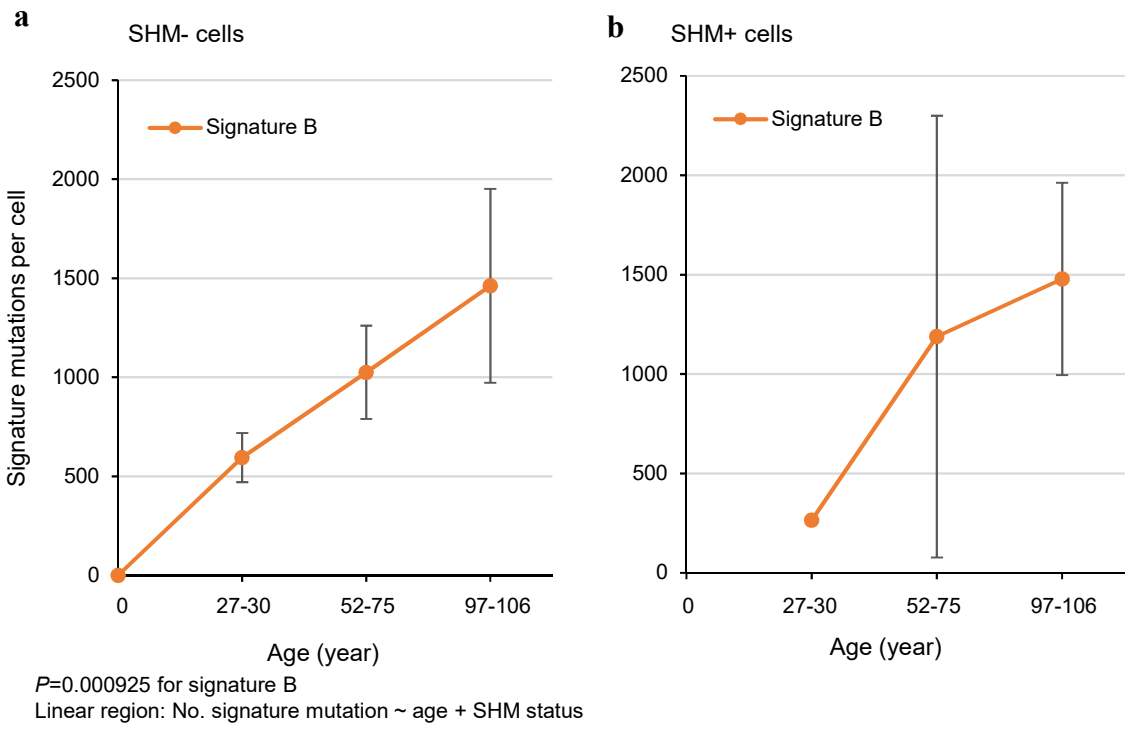


Fig. S12. Numbers of signature mutations during aging. a. SHM- cells. **b.** SHM+ cells.

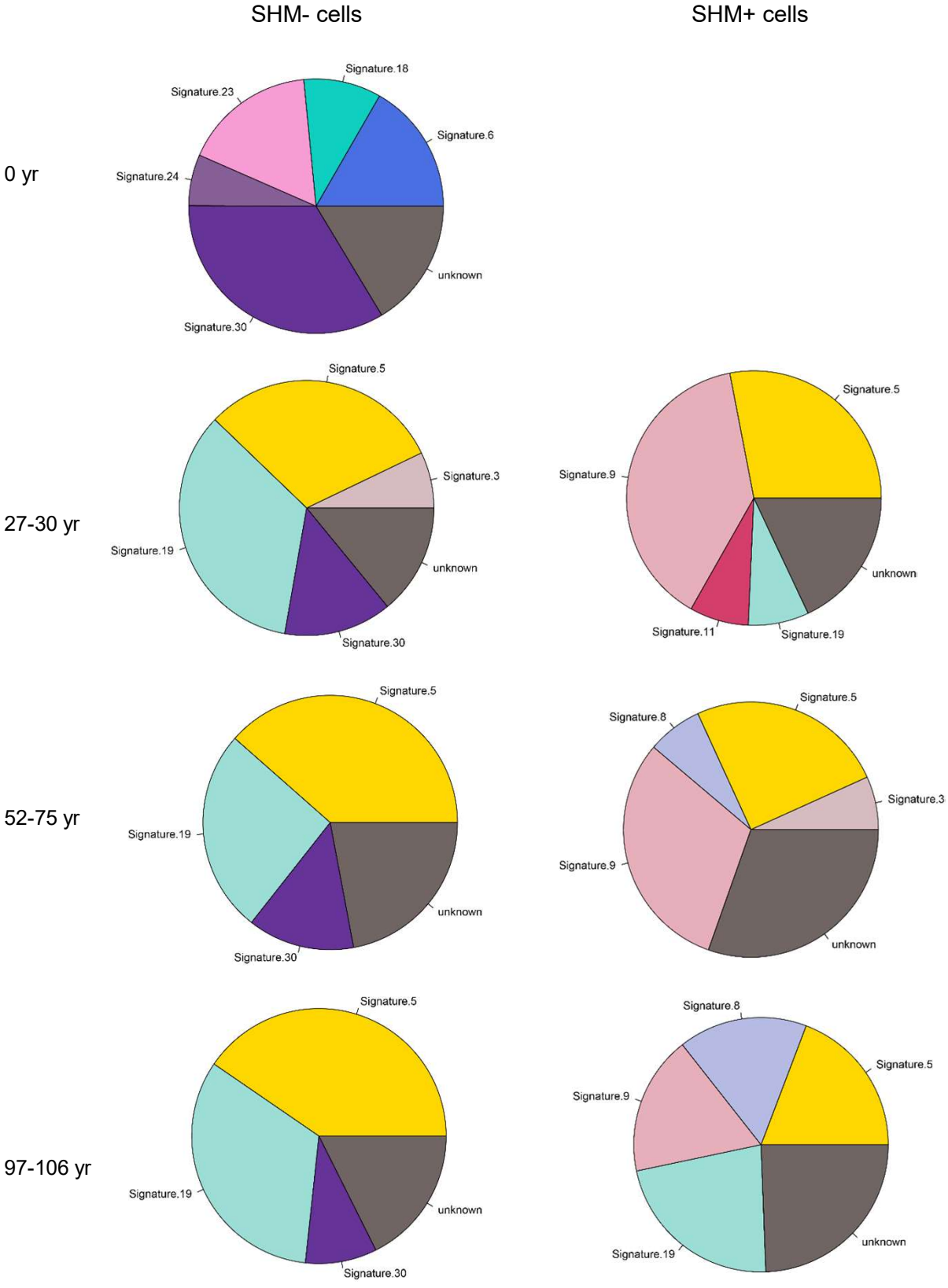


Fig. S13. Mutation signatures by refitting to the 30 COSMIC signatures.

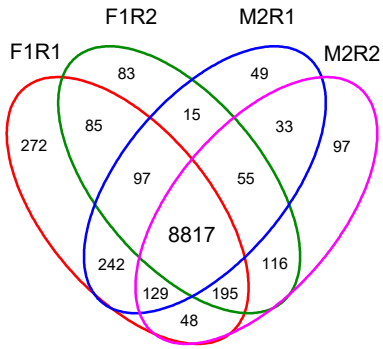


Fig. S14. Replications of RNA sequencing. A Venn diagram shows the overlap of transcribed genes between four RNA sequencing replicates.

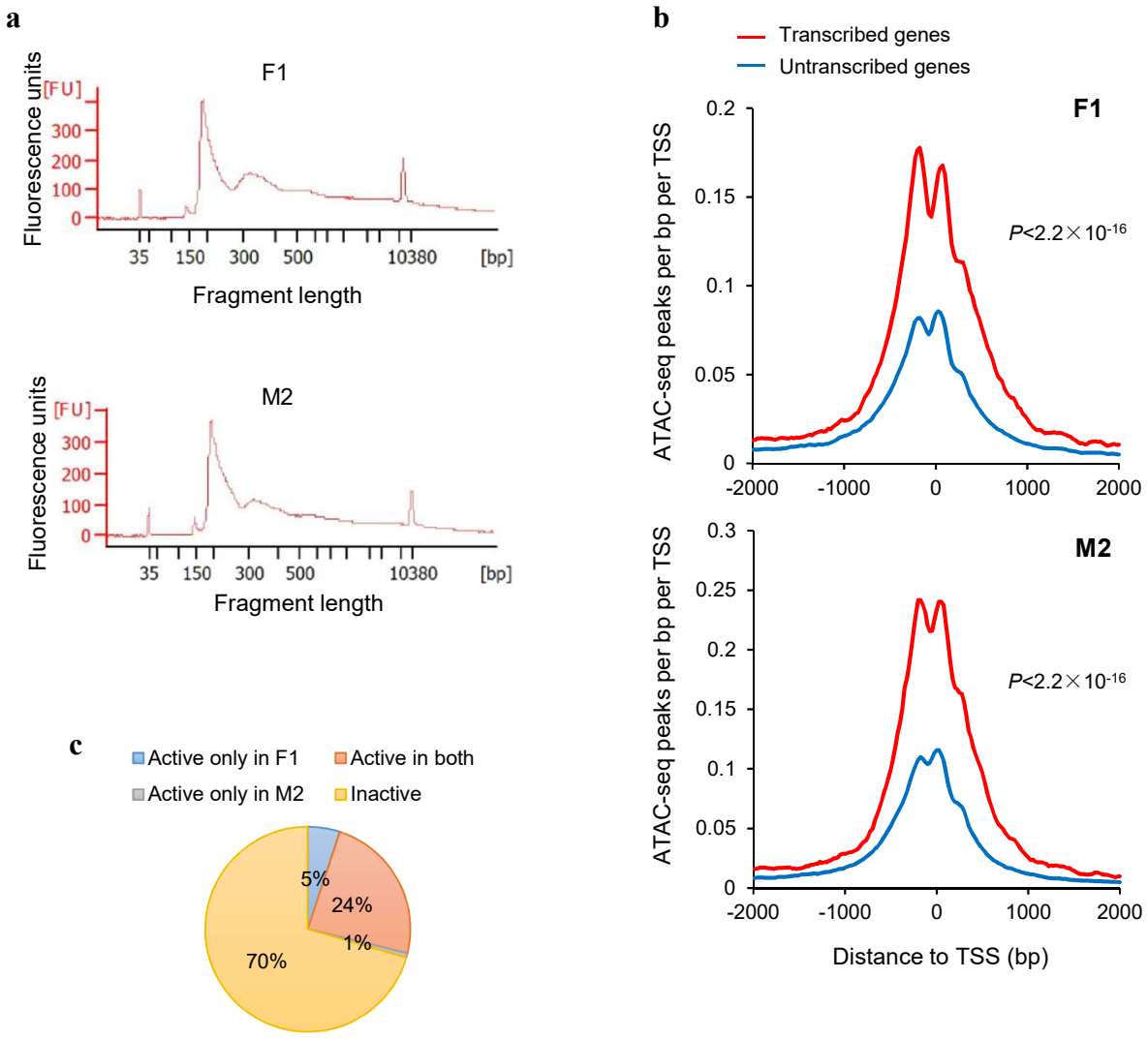


Fig. S15. ATAC sequencing. a. Bioanalyzer of ATAC sequencing library. **b.** ATAC sequencing peaks are significantly enriched in active genes than inactive genes in both of our ATAC sequencing samples (both P<2.2×10-16, Wilcoxon signed-rank test, one tailed). **c.** Fraction of active TF binding regions identified using ATAC sequencing from two replicates, F1 and M2. The total TF binding regions were identified by the ENCODE from multiple cell types.

Table S1. A summary of donor information and whole-genome sequencing statistics.

Sample	Donor	Type	Age (yr)	Gender	# raw read pairs (150bp paired)	Average depth (MapQ≥40)	% Genome (covered with reads of MapQ≥40) ≥ 20x	≥ 10x	≥ 5x	at 0x
CB151223_gDNA	C151223	Bulk	0	Female	447,118,378	29.9	87.3%	89.3%	89.7%	9.9%
C151223_S1	C151223	Single B cell	0	Female	388,942,268	27.1	53.9%	77.3%	86.0%	10.4%
C151223_S2	C151223	Single B cell	0	Female	400,781,323	27.0	48.3%	70.2%	81.7%	11.0%
C151223_S3	C151223	Single B cell	0	Female	395,046,402	26.3	48.5%	72.8%	83.9%	10.7%
C151223_S4	C151223	Single B cell	0	Female	452,383,430	30.6	54.2%	75.7%	84.9%	10.5%
CB70007_gDNA	C70007	Bulk	0	Female	369,391,632	25.8	82.3%	89.2%	89.6%	9.9%
C70007_S1	C70007	Single B cell	0	Female	446,148,531	29.7	44.8%	60.2%	70.5%	17.3%
C70007_S10	C70007	Single B cell	0	Female	366,575,784	24.4	41.8%	63.5%	76.9%	12.3%
C70007_S3	C70007	Single B cell	0	Female	409,284,627	27.8	51.6%	73.8%	83.9%	10.8%
C70007_S5	C70007	Single B cell	0	Female	360,353,854	24.9	43.4%	69.6%	83.1%	10.7%
BM1_gDNA	M1	Bulk	27	Male	356,028,466	27.7	82.3%	89.1%	90.0%	9.6%
BM1_S1	M1	Single B cell	27	Male	316,496,046	25.5	49.1%	71.4%	82.3%	11.0%
BM1_S2	M1	Single B cell	27	Male	306,310,518	25.3	51.3%	75.5%	85.2%	10.3%
BM1_S3	M1	Single B cell	27	Male	306,943,395	25.4	49.6%	72.1%	82.6%	11.1%
BM1_S4	M1	Single B cell	27	Male	375,482,752	31.0	61.9%	81.4%	87.4%	10.1%
BF1_gDNA	F1	Bulk	30	Female	314,798,478	24.2	79.6%	88.8%	89.4%	10.1%
BF1_S1	F1	Single B cell	30	Female	302,215,091	24.7	48.6%	71.6%	82.3%	11.4%
BF1_S2	F1	Single B cell	30	Female	350,226,628	28.4	54.3%	74.9%	83.9%	11.0%
BF1_S3	F1	Single B cell	30	Female	306,804,490	25.2	46.5%	68.8%	80.7%	11.6%
BF1_S4	F1	Single B cell	30	Female	353,910,036	28.7	51.3%	71.8%	82.1%	11.4%
BF2_gDNA	F2	Bulk	52	Female	308,228,315	23.8	78.5%	88.7%	89.4%	10.1%
BF2_S1	F2	Single B cell	52	Female	417,393,265	33.6	59.2%	77.3%	84.8%	11.0%
BF2_S2	F2	Single B cell	52	Female	317,430,742	25.6	52.4%	77.5%	86.2%	10.6%
BF2_S3	F2	Single B cell	52	Female	317,446,881	24.8	48.1%	71.7%	82.6%	11.3%
BF2_S4	F2	Single B cell	52	Female	327,061,166	25.3	49.2%	71.7%	82.1%	11.5%
BM2_gDNA	M2	Bulk	61	Male	338,247,300	26.3	80.9%	89.0%	90.0%	9.6%
BM2_S1	M2	Single B cell	61	Male	314,058,864	26.0	49.8%	71.9%	82.5%	11.1%
BM2_S2	M2	Single B cell	61	Male	302,780,471	24.9	54.9%	80.1%	87.4%	10.1%
BM2_S3	M2	Single B cell	61	Male	332,546,538	27.3	60.8%	82.1%	87.7%	10.1%
BM2_S4	M2	Single B cell	61	Male	320,199,875	26.3	51.2%	72.9%	83.0%	11.0%
A19505_gDNA	A19505	Bulk	70	Female	306,472,703	22.8	74.0%	88.9%	89.5%	10.0%
A19505_S1	A19505	Single B cell	70	Female	340,510,527	27.4	52.2%	73.4%	83.1%	11.1%
A19505_S2	A19505	Single B cell	70	Female	375,306,516	30.1	55.8%	75.7%	84.4%	10.8%
A19505_S7	A19505	Single B cell	70	Female	364,565,885	29.6	57.7%	77.1%	84.9%	10.8%
A19505_S8	A19505	Single B cell	70	Female	353,243,881	28.8	43.0%	57.5%	67.5%	19.7%
A13589_gDNA	A13589	Bulk	71	Male	302,722,849	23.6	73.5%	87.9%	89.7%	9.6%
A13589_S10	A13589	Single B cell	71	Male	352,853,899	27.7	51.8%	74.9%	84.8%	10.4%
A13589_S3	A13589	Single B cell	71	Male	316,476,183	25.9	45.9%	67.4%	78.8%	12.9%
A13589_S6	A13589	Single B cell	71	Male	357,301,294	27.9	48.9%	69.3%	80.3%	11.5%
A13589_S9	A13589	Single B cell	71	Male	349,908,666	27.6	49.7%	72.2%	83.0%	10.8%
A12851_gDNA	A12851	Bulk	73	Female	302,604,577	23.5	71.4%	87.8%	89.2%	10.1%
A12851_S11	A12851	Single B cell	73	Female	355,985,717	29.0	55.0%	77.0%	85.5%	10.7%
A12851_S2	A12851	Single B cell	73	Female	302,247,455	24.7	48.3%	72.6%	83.3%	11.2%
A12851_S4	A12851	Single B cell	73	Female	300,416,996	24.5	44.8%	67.8%	80.1%	11.8%
A12851_S7	A12851	Single B cell	73	Female	317,254,981	25.8	48.8%	73.0%	83.8%	10.9%
A11365_gDNA	A11365	Bulk	75	Male	302,455,601	22.1	70.0%	88.0%	89.9%	9.5%
A11365_S1	A11365	Single B cell	75	Male	361,916,064	28.9	56.8%	77.3%	85.5%	10.2%
A11365_S2	A11365	Single B cell	75	Male	342,679,387	27.7	52.2%	73.5%	83.4%	10.6%
A11365_S3	A11365	Single B cell	75	Male	360,320,205	29.0	55.2%	75.9%	84.7%	10.4%
A11365_S4	A11365	Single B cell	75	Male	329,245,422	26.5	49.2%	71.5%	82.5%	10.8%
A19552_gDNA	A19552	Bulk	97	Female	308,223,015	24.4	74.3%	88.1%	89.2%	10.1%
A19552_S1	A19552	Single B cell	97	Female	356,839,719	27.9	48.3%	71.6%	83.4%	10.8%
A19552_S12	A19552	Single B cell	97	Female	346,435,985	28.3	50.0%	72.6%	83.4%	10.9%
A19552_S3	A19552	Single B cell	97	Female	403,047,551	31.7	54.2%	74.0%	83.3%	11.2%
A19552_S9	A19552	Single B cell	97	Female	404,247,709	31.5	55.7%	77.5%	86.1%	10.5%
A20061_gDNA	A20061	Bulk	97	Female	371,214,240	28.9	83.4%	88.6%	89.4%	10.1%
A20061_S14	A20061	Single B cell	97	Female	453,045,813	37.5	53.2%	70.1%	80.2%	11.9%
A20061_S16	A20061	Single B cell	97	Female	368,446,853	30.6	52.7%	73.1%	82.9%	11.2%
A20061_S2	A20061	Single B cell	97	Female	307,497,525	25.5	43.8%	65.9%	78.9%	11.8%
A20061_S9	A20061	Single B cell	97	Female	453,195,484	37.6	63.1%	80.5%	86.7%	10.5%
A19553_gDNA	A19553	Bulk	101	Female	316,400,667	24.8	80.4%	89.0%	89.5%	10.0%
A19553_S1	A19553	Single B cell	101	Female	361,537,188	29.2	55.8%	75.9%	84.4%	10.9%
A19553_S3	A19553	Single B cell	101	Female	387,102,070	30.8	56.9%	76.1%	84.3%	10.9%
A19553_S4	A19553	Single B cell	101	Female	371,715,143	29.7	55.5%	73.4%	81.6%	12.1%
A19553_S7	A19553	Single B cell	101	Female	367,441,847	29.7	53.4%	72.1%	81.5%	11.7%
A19554_gDNA	A19554	Bulk	106	Female	340,186,669	26.4	82.5%	89.0%	89.5%	9.9%
A19554_S2	A19554	Single B cell	106	Female	349,720,246	28.2	51.4%	72.4%	82.5%	11.2%
A19554_S4	A19554	Single B cell	106	Female	331,479,239	25.5	48.7%	70.6%	81.5%	11.5%
A19554_S7	A19554	Single B cell	106	Female	321,763,064	24.9	48.2%	71.0%	82.0%	11.3%
A19554_S8	A19554	Single B cell	106	Female	314,807,986	24.0	46.1%	69.2%	81.1%	11.5%

Table S2. Sanger sequencing validation of randomly selected somatic SNVs.

Sample ID	Chr	Position	Reference	Genotype by Sanger		Genotype by Sccaller		Confirmed in sanger
				Bulk	Single cell	Bulk	Single cell	
Mutations in non SHM regions (n=20)								
A13589_S3	8	67,218,116	G	G/G	G/A	G/G	G/A	Yes
A19553_S3	9	1,849,367	T	T/T	T/G	T/T	T/G	Yes
A19553_S4	7	82,146,651	G	G/G	G/A	G/G	G/A	Yes
BF1_S2	18	67,884,384	C	C/C	C/T	C/C	C/T	Yes
A20061_S9	5	134,576,475	G	G/G	G/A	G/G	G/A	Yes
A19552_S1	1	86,755,019	G	G/G	G/A	G/G	G/A	Yes
BM1_S2	11	86,262,618	A	A/A	A/T	A/A	A/T	Yes
BF1_S2	14	42,197,923	A	A/A	A/C	A/A	A/C	Yes
A12851_S7	15	92,565,577	A	A/A	A/G	A/A	A/G	Yes
BM1_S2	5	38,503,507	C	C/C	C/A	C/C	C/A	Yes
BF2_S3	5	78,278,779	T	T/T	T/G	T/T	T/G	Yes
BF2_S3	7	46,787,006	T	T/T	T/C	T/T	T/C	Yes
BM2_S3	7	105,704,449	G	G/G	G/T	G/G	G/T	Yes
C70007_S10	19	4,354,106	G	G/G	G/A	G/G	G/A	Yes
A19554_S8	2	219,754,945	C	C/C	C/T	C/C	C/T	Yes
A19552_S9	5	61,977,544	G	G/G	G/A	G/G	G/A	Yes
A19552_S12	6	15,887,836	C	C/C	C/T	C/C	C/T	Yes
A19505_S7	5	122,114,692	T	T/T	T/A	T/T	T/A	Yes
C151223_S2	12	131,419,912	G	G/G	G/T	G/G	G/T	Yes
C151223_S3	8	3,044,365	C	C/C	C/T	C/C	C/T	Yes
Mutations in SHM regions (n=30)								
A19552_S3	22	23,285,767	T	T/T	T/C	T/T	T/C	Yes
A19554_S8	22	23,278,467	T	T/T	T/C	T/T	T/C	Yes
A19554_S8	22	23,278,462	T	T/T	T/C	T/T	T/C	Yes
A19552_S3	22	23,281,038	T	T/T	T/A	T/T	T/A	Yes
A19552_S3	22	23,278,327	T	T/T	T/C	T/T	T/C	Yes
A12851_S7	22	23,237,013	A	A/A	A/C	A/A	A/C	Yes
A12851_S7	22	23,237,006	C	C/C	C/T	C/C	C/T	Yes
A19552_S3	22	23,236,912	G	G/G	G/C	G/G	G/C	Yes
A19553_S4	22	23,236,903	A	A/A	A/G	A/A	A/G	Yes
A19554_S7	22	23,236,677	G	G/G	G/A	G/G	G/A	Yes
A19553_S4	22	23,236,114	T	T/T	T/A	T/T	T/A	Yes
BF2_S3	22	23,231,105	A	A/A	A/G	A/A	A/G	Yes
A20061_S9	22	23,231,099	C	C/C	C/T	C/C	C/T	Yes
BF2_S3	14	107,179,846	T	T/T	T/C	T/T	T/C	Yes
BF2_S3	14	107,179,752	C	C/C	C/A	C/C	C/A	Yes
BM1_S1	14	107,179,766	A	A/A	A/G	A/A	A/G	Yes
A13589_S9	14	107,176,582	G	G/G	G/A	G/G	G/A	Yes
BF2_S3	14	107,176,501	A	A/A	A/G	A/A	A/G	Yes
A19553_S3	14	106,329,284	C	C/C	C/T	C/C	C/T	Yes
A19553_S3	14	106,329,193	T	T/T	T/C	T/T	T/C	Yes
A19552_S3	14	106,327,764	T	T/T	T/A	T/T	T/A	Yes
A19553_S3	14	106,327,696	C	C/C	C/A	C/C	C/A	Yes
A19554_S7	14	106,327,631	C	C/C	C/T	C/C	C/T	Yes
A19553_S7	14	106,114,148	C	C/C	C/T	C/C	C/T	Yes
A19553_S7	14	106,112,196	G	G/G	G/A	G/G	G/A	Yes
A19553_S7	14	106,112,156	G	G/G	G/A	G/G	G/A	Yes
A19554_S7	14	106,112,113	G	G/G	G/A	G/G	G/A	Yes
A19554_S7	14	106,112,047	G	G/G	G/A	G/G	G/A	Yes
A19552_S3	14	106,326,618	G	G/G	G/G	G/G	G/A	No (not confirmed in single cell)
A19552_S3	14	106,326,599	C	C/C	C/T	C/C	C/T	Yes
Recurrent mutations (n=15)								
A12851_S2 & A12851_S4	1	213,512,146	C	C/C	C/T	C/C	C/T	Yes
A12851_S2 & A12851_S4	12	17,249,753	A	A/A	A/G	A/A	A/G	Yes
A12851_S2 & A12851_S4	12	105,146,950	A	A/A	A/G	A/A	A/G	Yes
A12851_S2 & A12851_S4	16	27,897,755	C	C/C	C/T	C/C	C/T	Yes
A12851_S2 & A12851_S4	18	52,738,117	A	A/A	A/C	A/A	A/C	Yes
A12851_S2 & A12851_S4	2	66,348,468	A	A/A	A/T	A/A	A/T	Yes
A12851_S2 & A12851_S4	22	27,976,252	T	T/T	T/C	T/T	T/C	Yes
A12851_S2 & A12851_S4	3	137,521,081	C	C/C	C/G	C/C	C/G	Yes
A12851_S2 & A12851_S4	4	188,079,357	G	G/G	G/A	G/G	G/A	Yes
A19552_S1 & A19552_S9	15	93,157,749	T	T/T	T/C	T/T	T/C	Yes
A19552_S3 & A19552_S9	10	120,845,303	T	T/T	T/C	T/T	T/C	Yes
A19552_S3 & A19552_S9	17	68,893,498	G	G/G	G/T	G/G	G/T	Yes
A19553_S1 & A19553_S4	19	53,727,460	C	C/C	C/C	C/C	C/T	No (not confirmed in single cell)
A19553_S1 & A19553_S4	3	73,231,854	T	T/T	T/T	T/T	T/C	No (not confirmed in single cell)
M2_S1 & M2_S3	9	112,192,050	T	T/T	T/C	T/T	T/C	Yes

Table S3. Estimation of mutation frequency.

Sample[1]	≥ 20x in both cell and bulk (mapq≥40)	# somatic SNVs observed	#heterozygous SNPs observed (>20x)[2]	#heterozygous SNPs expected (>20x)[3]	Sensitivity	# SNVs per cell[4]	# SNVs per cell (median by donor)
C151223_S1	1,571,404,579	74	824,244	1,324,283	62.2%	237.4	482.6
C151223_S2	1,407,517,673	96	656,434	1,189,007	55.2%	387.6	
C151223_S3	1,416,745,333	152	703,235	1,206,823	58.3%	577.7	
C151223_S4	1,573,293,541	229	819,420	1,341,803	61.1%	747.8	
C70007_S1	1,227,419,606	125	576,701	1,122,501	51.4%	621.9	438.6
C70007_S10	1,140,323,417	76	563,592	1,050,012	53.7%	389.6	
C70007_S3	1,408,519,765	70	774,251	1,279,523	60.5%	257.7	
C70007_S5	1,179,938,398	107	640,542	1,097,902	58.3%	487.7	
BM1_S1	1,456,638,254	530	743,144	1,212,073	61.3%	1861.9	988.6
BM1_S2	1,528,996,911	384	830,222	1,273,438	65.2%	1208.6	
BM1_S3	1,472,644,246	227	771,749	1,226,570	62.9%	768.6	
BM1_S4	1,840,898,270	286	1,099,974	1,529,872	71.9%	677.9	
BF1_S1	1,312,833,732	509	682,593	1,108,039	61.6%	1974.6	1033.7
BF1_S2	1,460,764,129	270	804,198	1,242,333	64.7%	895.9	
BF1_S3	1,256,329,042	260	650,707	1,069,533	60.8%	1067.2	
BF1_S4	1,381,982,739	272	724,479	1,173,466	61.7%	1000.2	
BF2_S1	1,581,655,636	423	886,492	1,344,646	65.9%	1272.7	1659.4
BF2_S2	1,427,131,060	636	822,311	1,203,368	68.3%	2046.1	
BF2_S3	1,290,332,160	3,040	682,979	1,087,033	62.8%	11764.8	
BF2_S4	1,313,122,106	313	687,569	1,103,329	62.3%	1200.1	
BM2_S1	1,457,490,563	405	784,872	1,245,017	63.0%	1382.9	1319.3
BM2_S2	1,620,472,540	455	965,499	1,376,253	70.2%	1255.7	
BM2_S3	1,785,876,994	359	1,097,220	1,513,770	72.5%	870.1	
BM2_S4	1,501,773,766	766	815,244	1,282,933	63.5%	2518.4	
A19505_S1	1,296,060,008	455	768,059	1,281,645	59.9%	1838.0	1916.6
A19505_S2	1,380,890,586	546	840,058	1,378,973	60.9%	2036.4	
A19505_S7	1,430,702,053	571	889,484	1,417,298	62.8%	1995.2	
A19505_S8	1,061,742,454	241	569,018	1,065,182	53.4%	1333.1	
A13589_S10	1,431,047,978	417	793,133	1,340,534	59.2%	1545.2	1578.7
A13589_S3	1,266,124,779	361	652,656	1,176,181	55.5%	1612.1	
A13589_S6	1,347,742,050	342	684,695	1,256,658	54.5%	1461.2	
A13589_S9	1,372,478,203	609	730,853	1,288,592	56.7%	2454.6	
A12851_S11	1,418,324,811	423	801,580	1,369,400	58.5%	1598.5	1742.8
A12851_S2	1,254,629,045	356	662,899	1,203,987	55.1%	1616.9	
A12851_S4	1,151,078,694	362	589,745	1,116,874	52.8%	1868.6	
A12851_S7	1,258,385,822	612	675,118	1,218,975	55.4%	2755.1	
A11365_S1	1,436,609,825	370	893,320	1,437,757	62.1%	1300.5	1540.0
A11365_S2	1,321,850,248	394	791,911	1,319,848	60.0%	1558.6	
A11365_S3	1,397,013,118	450	864,023	1,397,317	61.8%	1634.4	
A11365_S4	1,244,224,704	364	749,833	1,242,788	60.3%	1521.3	
A19552_S1	1,267,579,467	443	585,106	1,174,838	49.8%	2201.7	2668.7
A19552_S12	1,332,631,539	450	697,243	1,233,883	56.5%	1874.9	
A19552_S3	1,435,035,445	934	738,583	1,339,675	55.1%	3703.9	
A19552_S9	1,488,468,771	902	846,100	1,395,480	60.6%	3135.8	
A20061_S14	1,514,136,235	703	699,023	1,310,796	53.3%	2731.6	2886.4
A20061_S16	1,514,686,806	1,173	739,836	1,317,992	56.1%	4328.4	
A20061_S2	1,259,254,624	557	588,634	1,091,523	53.9%	2573.4	
A20061_S9	1,807,150,211	1,105	987,703	1,565,734	63.1%	3041.1	
A19553_S1	1,500,661,790	459	842,049	1,365,666	61.7%	1556.4	4387.6
A19553_S3	1,526,775,807	1,712	832,048	1,386,375	60.0%	5861.9	
A19553_S4	1,494,660,238	1,045	808,721	1,355,798	59.6%	3677.5	
A19553_S7	1,446,156,794	1,366	763,845	1,313,948	58.1%	5097.8	
A19554_S2	1,451,370,561	705	752,270	1,260,211	59.7%	2553.0	2270.8
A19554_S4	1,416,067,682	470	722,277	1,223,133	59.1%	1763.4	
A19554_S7	1,362,722,290	506	694,676	1,185,779	58.6%	1988.6	
A19554_S8	1,306,811,747	959	663,462	1,136,272	58.4%	3943.2	
Genome size considered	3,137,454,505						

[1]Sample ID is given as SubjectID_CellID. CellID was a randomly assigned number, which does not indicate the number of cells sequenced.

[2]Number of heterozygous germline SNPs observed in single cells with Sccaller.

[3]Number of germline SNPs called by the HaplotypeCaller from the bulk sequencing, and also the loci were sequenced with at least 20x sequencing depth in the single cells.

[4]Column 7 = Column 3 / Column 6 * Column 2 / Genome size.

Table S4. Hotspots of somatic mutations.

ClusterID	chr	start	end	size (bp)	SNV number	Cell number	Mutation frequency per cell per base pair[1]	Cell ID (SNV number)[2]	Associated gene / loci	Distance to closest ATAC-Seq peak (bp)	Closest TSS	Distance to closest TSS (bp)	Previous Off target report (AID binding, SHM associated or mutation associated in B cell related tumors)	POLR2A	YY1	C/EBP related	E-box binding TFs
Cluster#1	1	173836271	173837844	1573	4	2	$4.7x10^{-3}$ (95%CI: $2.3x10^{-3}$ – $7.1x10^{-3}$)	**A19554_S8** (3); A20061_S14 (1)	*ZBTB37*	0	*ZBTB37*	0	Qian et al., Cell 2014, PMID: 25483777	Yes	Yes	Yes	BHLHE40,MAX,MYC,TCF12,TCF3,ZEB1
Cluster#2	2	116202479	116205207	2728	4	2	$2.7x10^{-3}$ (95%CI: $1.3x10^{-3}$ – $4.1x10^{-3}$)	**F2_S3** (1); **A19553_S3** (3)	*DPP10*	90169	*DPP10*	4031	Burns et al., Leukemia 2018, PMID: 28584254	.	.	.	.
Cluster#3	2	125655504	125659376	3872	4	2	$1.9x10^{-3}$ (95%CI: $0.9x10^{-3}$ – $2.9x10^{-3}$)	**M1_S1** (3); A19554_S2 (1)	*CNTNAP5*	323016	*CNTNAP5*	676222	.	.	.	.	.
Cluster#4	3	187460619	187463603	2984	4	2	$2.5x10^{-3}$ (95%CI: $1.2x10^{-3}$ – $3.7x10^{-3}$)	**F2_S3** (1); **A19552_S3** (3)	*BCL6*	0	*BCL6*	6644	Shen et al., Science 1998, PMID: 9624052; Qian et al., Cell 2014, PMID: 25483777; many others	Yes	Yes	Yes	BHLHE40,GATA3,MAX,MYC,TCF12
Cluster#5	3	187957868	187958890	1022	4	1	$14.4x10^{-3}$ (95%CI: $7.2x10^{-3}$ – $21.8x10^{-3}$)	**F2_S3** (4)	*LPP*	683	*LPP*	216	Schwindt et al., J Neuropathol Exp Neurol. 2006, PMID: 16896311	Yes	.	.	TAL1
Cluster#6	4	13624125	13628378	4253	4	2	$1.7x10^{-3}$ (95%CI: $0.9x10^{-3}$ – $2.6x10^{-3}$)	**A19553_S3** (3); A20061_S2 (1)	*BOD1L1*	370	*BOD1L1*	8995	.	.	.	.	.
Cluster#7	4	92286679	92290096	3417	5	1	$5.4x10^{-3}$ (95%CI: $3.0x10^{-3}$ – $7.9x10^{-3}$)	**F2_S3** (5)	*CCSER1*	276003	*RP11-763F8.1*	46494	.	.	.	.	.
Cluster#8	4	103717626	103718274	648	5	1	$28.6x10^{-3}$ (95%CI: $15.7x10^{-3}$ – $41.4x10^{-3}$)	**M1_S1** (5)	*UBE2D3*	12177	*UBE2D3*	34	.	.	.	.	.
Cluster#9	6	31549576	31549841	265	4	2	$28.0x10^{-3}$ (95%CI: $13.9x10^{-3}$ – $42.0x10^{-3}$)	**F2_S3** (1); A19552_S8 (3)	*LTB*	239	*LTB*	1175	Warzocha et al., Biochem Biophys Res Commun. 1997. PMID: 9299492	Yes	.	.	.
Cluster#10	7	89556243	89560623	4380	4	4	$0.8x10^{-3}$ (95%CI: $0.4x10^{-3}$ – $1.3x10^{-3}$)	M1_S2 (1); **A13589_S9** (1); A20061_S16 (1); **A20061_S9** (1)	.	222936	*STEAP1*	223066	.	.	.	.	.
Cluster#11	7	122432807	122437692	4885	5	2	$1.9x10^{-3}$ (95%CI: $1.0x10^{-3}$ – $2.8x10^{-3}$)	**F2_S3** (4); **A19554_S8** (1)	*CADPS2*	118617	*RNF148*	91083	Burns et al., Leukemia 2018, PMID: 28584254	.	.	.	.
Cluster#12	9	30538593	30542103	3510	4	2	$2.1x10^{-3}$ (95%CI: $1.0x10^{-3}$ – $3.2x10^{-3}$)	**F2_S3** (3); **A19554_S8** (1)	.	32455	*ACO1*	1842515	.	.	.	.	.
Cluster#13	12	19566409	19569174	2765	4	2	$2.6x10^{-3}$ (95%CI: $1.3x10^{-3}$ – $4.0x10^{-3}$)	A11365_S3 (1); **A19554_S7** (3)	*AEBP2*	22998	*AEBP2*	9409	.	.	Yes	.	.
Cluster#14	12	122457912	122462446	4534	6	2	$2.5x10^{-3}$ (95%CI: $1.4x10^{-3}$ – $3.5x10^{-3}$)	**F2_S3** (5); A19552_S9 (1)	*BCL7A*	0	*BCL7A*	0	Kato et al., Proc Natl Acad Sci U S A. 2012, PMID: 22308462; Qian et al., Cell 2014, PMID: 25483777; many others	Yes	Yes	Yes	BHLHE40,GATA3,MAX,MYC
Cluster#15	13	75983796	75984265	469	5	1	$39.5x10^{-3}$ (95%CI: $21.9x10^{-3}$ – $57.1x10^{-3}$)	**A19553_S7** (5)	*TBC1D4*	14264	*TBC1D4*	96878	.	Yes	.	.	.
Cluster#16	13	111053494	111057470	3976	4	2	$1.9x10^{-3}$ (95%CI: $0.9x10^{-3}$ – $2.8x10^{-3}$)	**A19552_S3** (3); A19554_S2 (1)	*COL4A2*	7184	*COL4A2*	24928	.	Yes	.	.	.
Cluster#17	14	106112047	106114148	2101	7	3	$4.1x10^{-3}$ (95%CI: $2.5x10^{-3}$ – $5.7x10^{-3}$)	**A19553_S3** (2); **A19553_S7** (3); **A19554_S7** (2)	*IGH*	562	*TMEM121*	117086	Not applicable	Yes	.	.	.
Cluster#18	14	106324287	106329284	4997	11	4	$2.0x10^{-3}$ (95%CI: $1.4x10^{-3}$ – $2.7x10^{-3}$)	**A19552_S3** (3); **A19553_S3** (3); **A19554_S7** (1); **A20061_S9** (4)	*IGH - Sμ*	0	*KIAA0125*	54554	Not applicable	Yes	Yes	Yes	BHLHE40,MAX,TCF12,TCF3
Cluster#19	14	107175732	107179846	4114	10	5	$1.8x10^{-3}$ (95%CI: $1.2x10^{-3}$ – $2.4x10^{-3}$)	**F2_S3** (6); **M1_S1** (1); **A13589_S9** (1); **A19553_S7** (1); **A20061_S9** (1)	*IGH*	5139	*KIAA0125*	787755	Not applicable	Yes	Yes	.	.
Cluster#20	15	93157391	93160422	3031	4	4	$1.2x10^{-3}$ (95%CI: $0.6x10^{-3}$ – $1.8x10^{-3}$)	C70007_S3 (1); A19505_S2 (1); A19552_S1 (1); A19552_S9 (1)	*FAM174B*	180029	*FAM174B*	251	.	.	.	.	GATA3
Cluster#21	16	6414678	6417154	2476	4	3	$2.0x10^{-3}$ (95%CI: $1.0x10^{-3}$ – $3.0x10^{-3}$)	A11365_S4 (1); **A19554_S8** (2); A20061_S16 (1)	*RBFOX1*	1265963	*RBFOX1*	116026	Ramsay et al., Leukemia. 2013, PMID: 23187293	.	.	.	.
Cluster#22	17	60259020	60261519	2499	4	1	$5.9x10^{-3}$ (95%CI: $2.9x10^{-3}$ – $8.9x10^{-3}$)	A19554_S4 (4)	.	71821	*RP11-51L5.7*	88329	.	.	.	.	.
Cluster#23	22	23228043	23237013	8970	12	7	$0.7x10^{-3}$ (95%CI: $0.5x10^{-3}$ – $0.9x10^{-3}$)	**F2_S3** (3); **M1_S1** (1); **A12851_S7** (2); **A19552_S3** (1); **A19553_S4** (3); **A19554_S7** (1); **A20061_S9** (1)	*IGL - IGLL5*	458	*IGLL5*	0	Not applicable	Yes	Yes	.	.
Cluster#24	22	23278327	23285767	7440	7	3	$1.1x10^{-3}$ (95%CI: $0.7x10^{-3}$ – $1.6x10^{-3}$)	**F1_S1** (1); **A19552_S3** (4); **A19554_S8** (2)	*IGL*	0	*IGLL5*	0	Not applicable	Yes	Yes	Yes	BHLHE40,MAX,MYC,TCF12,TCF3,ZEB1

FDR of mutation hotspots.

#SNVs in cluster	FDR
≥4	0.0568
≥5	0.0057
≥6	0.0003
≥7	<1E-4

[1]Mutation frequencies per cell per base pair were adjusted by sensitivity shown in Table S3.

[2]SHM+ cells are written in bold.

Table S5. Summary of bisulfite, RNA and ATAC sequencing.

Bisulfite sequencing

Sample ID	Description	Data resource	Donor ID	Gender	Age (years)	Cell type	Other	# Reads	# Mapped reads	Duplication rate	Bisulfite conversion rate[1]	# C on CpG covered (≥5x)	Link to data
WGBS01	Whole genome bisulfite sequencing	ENCODE	-	Male	37	B cells (CD19+)	Read end #1	412,829,914	331,338,617	15.30%	99.30%	38,173,877	https://www.encodeproject.org/experiments/ENCSR284TCU
							Read end #2	412,829,914	329,630,675	17.43%	99.00%		

RNA sequencing

Sample ID	Description	Data resource	Donor ID	Gender	Age (years)	Cell type	Other	# Reads (pairs)	# Mapped reads (pairs)	Duplication rate	-	-	Link to data
F1RNA1	rRNA-depletion RNA-seq	New data	F1	Female	30	B cells (CD19+)	Replicate #1[2]	39,208,302	36,415,872	43.84%	-	-	-
F1RNA2	rRNA-depletion RNA-seq	New data					Replicate #2	30,520,174	28,846,722	21.82%	-	-	-
M2RNA1	rRNA-depletion RNA-seq	New data	M2	Male	61		Replicate #1	21,782,492	20,458,640	6.85%	-	-	-
M2RNA2	rRNA-depletion RNA-seq	New data					Replicate #2	20,446,244	19,165,901	7.27%	-	-	-

ATAC sequencing

Sample ID	Description	Data resource	Donor ID	Gender	Age (years)	Cell type	Other	# Reads (pairs)	# Useful reads (pairs)[3]	# Peaks called	% Peaks overlap with TF (>50%)[4]	% Reads in peaks	% peaks in Mapability=100% regions
F1ATAC	ATAC sequencing	New data	F1	Female	30	B cells (CD19+)	-	29,281,560	8,934,824	53,934	89.58%	42.69%	95.42%
M2ATAC	ATAC sequencing	New data	M2	Male	61		-	95,351,699	12,127,499	38,212	90.49%	18.66%	95.54%

[1]Bisulfite conversion rate was estimated as 1 - % of nonCpG methylation.

[2]Replicates #1 and #2 were from two separate blood draws.

[3]After filtering out reads which are duplications, mapq<=30, discoordinate aligned pairs or aligned to MT .chromosome

[4]Fraction of peaks overlap with TF binding regions identified with ChIP sequencing or array by ENCODE (http://hgdownload.cse.ucsc.edu/goldenpath/hg19/encodeDCC/wgEncodeRegTfbsClustered/).

Table S6. Average number of functional SNVs per cell.

Type	Age: 0 year		27-30 years		52-75 years		97-106 years	
	Total	Active[d]	Total	Active	Total	Active	Total	Active
Total	463.4±179.0	-	1181.9±484.7	-	2101.7±2106.1	-	3127.0±1237.1	-
TF binding region (ENCODE)	79.6±39.8	-	169.4±57.4	-	300.1±302.3	-	435.9±133.3	-
Open chromatin region (ATAC-Seq)	-	5.4±5.8	-	11.5±4.4	-	17.6±24.9	-	24.5±15.8
Promoter [From -1500 to +500bp of TSS]	30.9±16.5	17.7±10.1	43.6±14.4	19.6±7.4	70.6±63.8	33.1±34.9	114.3±47.8	56.9±26.9
5' UTR	3.6±4.8	2.1±3.5	3.7±5.4	2.5±4.0	7.5±7.1	3.9±5.7	11.2±9.1	4.9±5.7
Nonsynonymous	3.8±4.7	2.2±4.1	4.8±5.3	1.7±2.5	11.4±8.5	5.4±5.3	21.1±11.4	9.2±6.8
Synonymous	2.4±3.3	1.5±2.1	4.3±4.1	1.8±3.0	4.3±4.8	1.8±2.8	10.1±6.5	4.3±4.0
Ka/Ks ratio	0.5	0.53	0.35	0.32	0.83	0.87	0.68	0.7
LOF SNV[a]	0.4±1.1	0.4±1.1	0.4±1.2	0.0±0.0	0.6±1.7	0.6±1.7	1.5±2.8	0.5±1.4
Damaging[b]	3.4±3.0	1.3±2.8	4.0±5.3	1.7±2.5	9.1±8.2	4.0±5.0	14.7±8.5	6.5±5.5
Tolerated[c]	0.9±1.6	0.9±1.6	1.3±2.9	0.5±1.5	3.5±3.7	2.0±2.6	7.6±6.1	3.4±3.3
Intronic	184.6±72.3	-	407.8±153.8	-	682.3±674.4	-	1021.4±384.7	-
3' UTR	8.7±6.2	4.6±5.9	15.3±10.4	11.0±11.9	22.5±23.7	10.9±11.2	29.8±11.4	13.6±6.5

[a] Loss of function SNVs, including stop gain, stop loss and splicing alterations

[b] SNVs annotated as damaging by SIFT or Deleterious by PROVEAN

[c] SNVs annotated as tolerated by SIFT and Neutral by PROVEAN

[d] The number of mutations in transcribed or open chromatin regions in B lymphocytes

Table S7. Prediction of functionally of SNVs on proteins using SIFT and PROVEAN.

Chr	Pos	Ref	Mut	Cell	PROTEIN_ID	GENE_NAME	LENGTH	STRAND	CODON_CHANGE	POS	RESIDUE_REF	RESIDUE_ALT	TYPE	PROVEAN.SCORE	PROVEAN.PREDICTION (cutoff=-2.5)	SIFT.SCORE	SIFT.PREDICTION (cutoff=0.05)
1	8397997	G	A	A19552_S1	ENSP00000366699	SLC45A1	782	1	GGC GT[G/A] ACC	607	V	V	Synonymous	0	Neutral	1	Tolerated
1	9109178	G	C	A12851_S11	ENSP00000440688	SLC2A5	442	-1	TTG [C/G]TT CTG	33	L	V	Single AA Change	-0.39	Neutral	0	Damaging
1	16065109	G	A	A19553_S3	ENSP00000294454	SLC25A34	304	1	AGC TG[G/A] CTG	206	W	*	Nonsense	NA	NA	NA	NA
1	18809069	G	A	M1_S2	ENSP00000383505	KLHDC7A	777	1	CGG [G/A]GC TGT	532	G	S	Single AA Change	-5.52	Deleterious	0.006	Damaging
1	18809112	C	A	M1_S2	ENSP00000383505	KLHDC7A	777	1	GTG T[C/A]C GGC	546	S	Y	Single AA Change	-3.19	Deleterious	0.024	Damaging
1	37945960	C	T	A20061_S2	ENSP00000362174	ZC3H12A	599	1	CGG GG[C/T] CAC	171	G	G	Synonymous	0	Neutral	1	Tolerated
1	44820656	G	A	A19552_S1	ENSP00000361331	ERI3	337	-1	CGG [C/T]CC TGG	15	P	S	Single AA Change	-0.15	Neutral	0.09	Tolerated
1	47400169	T	G	A12851_S2	ENSP00000360971	CYP4A11	520	-1	AAG [A/C]GG AAG	286	R	R	Synonymous	0	Neutral	0.475	Tolerated
1	62190933	C	T	A19553_S4	ENSP00000360222	TM2D1	269	-1	CAC [G/A]GG CAG	16	G	R	Single AA Change	-0.22	Neutral	0.564	Tolerated
1	78248986	G	A	F2_S1	ENSP00000359827	FAM73A	632	1	GCA [G/A]CG CTA	49	A	T	Single AA Change	-1.24	Neutral	0.028	Damaging
1	113059977	C	A	A19554_S8	ENSP00000358698	WNT2B	391	1	TCT [C/A]CA GAT	306	P	T	Single AA Change	-7.07	Deleterious	0.001	Damaging
1	117944899	G	A	A11365_S1	ENSP00000348959	MAN1A2	641	1	GAG [G/A]AA ATT	132	E	K	Single AA Change	-1.17	Neutral	0.086	Tolerated
1	145584218	G	C	M2_S4	ENSP00000376765	PIAS3	628	1	TCA [G/C]AT GAG	457	D	H	Single AA Change	-4.08	Deleterious	0	Damaging
1	147231031	G	A	F2_S3	ENSP00000271348	GJA5	358	-1	AAG [C/T]GC AAG	106	R	C	Single AA Change	-6.24	Deleterious	0.008	Damaging
1	149857828	C	T	A19552_S3	ENSP00000358151	HIST2H2BE	126	-1	ACC AA[G/A] TAC	121	K	K	Synonymous	0	Neutral	1	Tolerated
1	151271294	C	T	A19552_S12	ENSP00000271657	PI4KB	828	-1	CAA [G/A]TC AAG	681	V	I	Single AA Change	-0.95	Neutral	0.043	Damaging
1	151503174	G	A	A19552_S9	ENSP00000271636	CGN	1203	1	CTG GA[G/A] GAG	841	E	E	Synonymous	0	Neutral	1	Tolerated
1	153916844	C	T	A19554_S2	ENSP00000354597	DENND4B	1496	-1	GCG [G/A]AG GAG	3	E	K	Single AA Change	-3.1	Deleterious	0.002	Damaging
1	154516452	G	A	A19505_S2	ENSP00000357465	TDRD10	366	1	CTG [G/A]TG CTG	173	V	M	Single AA Change	-0.91	Neutral	0.01	Damaging
1	157667480	T	A	F2_S3	ENSP00000357169	FCRL3	742	-1	GAA GT[A/T] ACT	176	V	V	Synonymous	0	Neutral	0.606	Tolerated
1	161068386	G	A	F2_S3	ENSP00000356990	KLHDC9	349	1	GTG [G/A]CG CGG	21	A	T	Single AA Change	-0.66	Neutral	0.009	Damaging
1	162344004	C	A	A19553_S7	ENSP00000356912	C1orf111	261	-1	TTC A[G/T]G GAG	207	R	M	Single AA Change	-3.53	Deleterious	0.002	Damaging
1	165175230	T	C	F2_S4	ENSP00000294816	LMX1A	382	-1	ATC [A/G]TG AAC	287	M	V	Single AA Change	-1.38	Neutral	0.039	Damaging
1	168073904	C	T	A19505_S1	ENSP00000441039	GPR161	549	-1	CTC A[G/A]C AAC	82	S	N	Single AA Change	-2.17	Neutral	0.002	Damaging
1	176738833	G	T	A19553_S3	ENSP00000356634	PAPPA2	1791	1	TTG [G/T]TG AAC	1472	V	L	Single AA Change	-2.01	Neutral	0.007	Damaging
1	180910339	G	A	A19554_S4	ENSP00000356560	KIAA1614	1190	1	CGC A[G/A]C TAC	1026	S	N	Single AA Change	-2.28	Neutral	0.006	Damaging
1	181762879	G	T	A12851_S4	ENSP00000356545	CACNA1E	2313	1	CAT [G/T]CG GGA	1993	A	S	Single AA Change	-0.44	Neutral	0.796	Tolerated
1	201061166	A	G	A19552_S9	ENSP00000355192	CACNA1S	1873	-1	GGC [T/C]TG GAT	159	L	L	Synonymous	0	Neutral	0.344	Tolerated
1	204224800	A	T	A19554_S8	ENSP00000407638	PLEKHA6	151	-1	GAA C[T/A]T TTA	74	L	H	Single AA Change	-1.94	Neutral	0.007	Damaging
1	206634596	G	A	C70007_S3	ENSP00000295713	SRGAP2	985	1	GCT G[G/A]G GAC	930	G	E	Single AA Change	-1	Neutral	0.016	Damaging
1	208390671	G	C	A19552_S9	ENSP00000356000	PLXNA2	1894	-1	CTG TC[C/G] AGC	199	S	S	Synonymous	0	Neutral	1	Tolerated
1	209799154	G	C	A19554_S8	ENSP00000348384	LAMB3	1172	-1	AAT GC[C/G] ACC	605	A	A	Synonymous	0	Neutral	1	Tolerated
1	210856914	G	A	A19553_S7	ENSP00000271751	KCNH1	989	-1	GAC AA[C/T] GTG	893	N	N	Synonymous	0	Neutral	0.804	Tolerated
1	225707039	G	A	A19552_S3	ENSP00000284563	ENAH	817	-1	GAA CG[C/T] CTG	240	R	R	Synonymous	0	Neutral	1	Tolerated
1	228467712	G	A	C151223_S4	ENSP00000455507	OBSCN	8678	1	CTC CG[G/A] CTC	2713	R	R	Synonymous	0	Neutral	0.547	Tolerated
1	228482627	C	T	A19552_S12	ENSP00000455507	OBSCN	8678	1	AGC [C/T]TG AGG	4032	L	L	Synonymous	0	Neutral	1	Tolerated
1	232534982	T	A	A20061_S9	ENSP00000262861	SIPA1L2	1722	-1	GTG C[A/T]G CAC	1687	Q	L	Single AA Change	-2.79	Deleterious	0.062	Tolerated
1	235634178	G	T	A11365_S3	ENSP00000355559	B3GALNT2	500	-1	GTT [C/A]TC AGA	250	L	I	Single AA Change	-0.48	Neutral	0.426	Tolerated
1	236906246	G	A	A13589_S10	ENSP00000355537	ACTN2	894	1	TAC GA[G/A] GAG	386	E	E	Synonymous	0	Neutral	1	Tolerated
2	27282256	G	C	A19553_S3	ENSP00000353249	AGBL5	886	1	CGG GT[G/C] CTG	691	V	V	Synonymous	0	Neutral	NA	NA
2	27465683	T	C	M2_S1	ENSP00000405416	CAD	293	1	ATG [T/C]GG GTT	176	W	R	Single AA Change	-0.5	Neutral	0.461	Tolerated
2	43452619	G	C	A19553_S1	ENSP00000282388	ZFP36L2	494	-1	GGC GG[C/G] GGC	108	G	G	Synonymous	0	Neutral	1	Tolerated
2	110372351	G	C	A19552_S3	ENSP00000365830	ANKRD57	525	1	CCG CC[G/C] CGA	95	P	P	Synonymous	0	Neutral	1	Tolerated
2	136570529	T	A	A11365_S2	ENSP00000388225	LCT	1003	-1	[A/T]AG GTG	1	K	*	Nonsense	NA	NA	NA	NA
2	175939372	C	T	F1_S3	ENSP00000264110	ATF2	505	-1	ATG [G/A]CT CCT	495	A	T	Single AA Change	-0.1	Neutral	0.407	Tolerated
2	179638333	G	C	A19552_S12	ENSP00000343764	TTN	33423	-1	GAA [C/G]AA ATC	2484	Q	E	Single AA Change	-1.86	Neutral	1	Tolerated
2	215301356	T	C	F2_S3	ENSP00000308976	VWC2L	222	1	CCC [T/C]CT CCA	132	S	P	Single AA Change	-3.67	Deleterious	0.004	Damaging
2	219754945	C	T	A19554_S8	ENSP00000258411	WNT10A	417	1	CTG [C/T]AG GAC	206	Q	*	Nonsense	NA	NA	NA	NA
2	220162755	G	A	F2_S1	ENSP00000295718	PTPRN	979	-1	CTC A[C/T]T CTG	580	T	I	Single AA Change	-4.51	Deleterious	0.095	Tolerated
2	220409590	G	A	M1_S3	ENSP00000343507	TMEM198	360	1	TGT TT[G/A] TTT	47	L	L	Synonymous	0	Neutral	1	Tolerated
2	238287663	G	T	A11365_S2	ENSP00000295550	COL6A3	3177	-1	GGT [C/A]AT CTG	705	H	N	Single AA Change	-3.66	Deleterious	0.259	Tolerated
3	7503306	G	C	A19554_S8	ENSP00000434573	GRM7	924	1	AAC G[G/C]G GAT	471	G	A	Single AA Change	-5.74	Deleterious	0.01	Damaging
3	7620638	G	A	A19505_S1	ENSP00000434573	GRM7	924	1	TAT C[G/A]C ATA	682	R	H	Single AA Change	-4.56	Deleterious	0	Damaging
3	10016121	G	C	A12851_S11	ENSP00000245046	TMEM111	261	-1	CTC C[C/G]T ATG	120	P	R	Single AA Change	-8.85	Deleterious	0	Damaging
3	25502732	C	T	A19554_S8	ENSP00000385865	RARB	455	1	CCC C[C/T]A TCT	76	P	L	Single AA Change	-6.3	Deleterious	0.024	Damaging
3	38307443	T	G	A11365_S1	ENSP00000310241	SLC22A13	551	1	TTC C[T/G]G TCT	31	L	R	Single AA Change	-4.44	Deleterious	0.004	Damaging
3	47033174	G	A	A19505_S2	ENSP00000415034	NBEAL2	2754	1	AGC AT[G/A] CTC	307	M	I	Single AA Change	-2.34	Neutral	0.162	Tolerated
3	52835066	C	A	A20061_S16	ENSP00000415769	ITIH3	890	1	GGC AA[C/A] AAT	429	N	K	Single AA Change	-1.6	Neutral	0.277	Tolerated
3	58319336	G	A	F2_S1	ENSP00000418831	PXK	113	1	GGT CT[G/A] CAG	20	L	L	Synonymous	0	Neutral	1	Tolerated
3	113375453	G	A	C70007_S3	ENSP00000320794	KIAA2018	2245	-1	GGT TC[C/T] AGA	1692	S	S	Synonymous	0	Neutral	1	Tolerated
3	113441762	T	C	A19554_S2	ENSP00000240922	NAA50	169	-1	GAC A[A/G]C ATT	108	N	S	Single AA Change	0.46	Neutral	1	Tolerated
3	123688909	T	C	A13589_S9	ENSP00000184183	ROPN1	212	-1	ATG CT[A/G] AAC	184	L	L	Synonymous	0	Neutral	1	Tolerated
3	128341246	C	T	A12851_S4	ENSP00000296255	RPN1	607	-1	CCA [G/A]CC GCA	468	A	T	Single AA Change	-1.82	Neutral	0.017	Damaging
3	129152803	G	A	C151223_S3	ENSP00000249910	MBD4	580	-1	AAA G[C/T]C TTT	434	A	V	Single AA Change	-1.35	Neutral	0.065	Tolerated
3	183210322	G	C	A20061_S16	ENSP00000341342	KLHL6	621	-1	AAA TG[C/G] ATC	508	C	W	Single AA Change	-7.6	Deleterious	0	Damaging
3	184086059	C	T	A13589_S10	ENSP00000415536	POLR2H	175	1	TCT C[C/T]T GAT	165	P	L	Single AA Change	0.54	Neutral	0	Damaging
3	196509567	G	C	A20061_S14	ENSP00000314067	PAK2	524	1	GTG C[G/C]A ATG	17	R	P	Single AA Change	-5.97	Deleterious	0	Damaging
4	6374374	G	T	A19554_S4	ENSP00000335083	PPP2R2C	447	-1	AGG AT[C/A] TTT	167	I	I	Synonymous	0	Neutral	0.853	Tolerated
4	36345255	C	T	F2_S3	ENSP00000424426	DTHD1	821	1	GAT [C/T]TC ACA	759	L	F	Single AA Change	-2.41	Neutral	0.032	Damaging
4	69535669	A	T	A20061_S2	ENSP00000341045	UGT2B15	530	-1	GAC T[T/A]T TGG	223	F	Y	Single AA Change	-1.99	Neutral	0.281	Tolerated
4	71508941	T	C	A19554_S2	ENSP00000379383	ENAM	1142	1	TTC [T/C]AC CCT	600	Y	H	Single AA Change	-4.71	Deleterious	0.02	Damaging
4	79831960	C	T	F2_S1	ENSP00000334836	BMP2K	1161	1	AAG AG[C/T] AGT	753	S	S	Synonymous	0	Neutral	1	Tolerated
4	134072028	G	T	A20061_S16	ENSP00000264360	PCDH10	1040	1	AAT [G/T]AC AAT	245	D	Y	Single AA Change	-8.67	Deleterious	0	Damaging
4	143226864	G	A	A19553_S3	ENSP00000421065	INPP4B	686	-1	ATC [C/T]TA CCC	9	L	L	Synonymous	0	Neutral	0	Damaging
4	153893618	C	T	A19505_S8	ENSP00000260008	FHDC1	1143	1	GAA GA[C/T] AAA	436	D	D	Synonymous	0	Neutral	1	Tolerated
4	154533494	T	G	F2_S3	ENSP00000386787	KIAA0922	1610	1	AAG A[T/G]T CAC	1170	I	S	Single AA Change	-0.01	Neutral	0.098	Tolerated
5	2749717	C	T	F1_S1	ENSP00000307006	IRX2	471	-1	AAG G[G/A]C GAG	145	G	D	Single AA Change	-6.92	Deleterious	0	Damaging
5	35790268	G	A	F2_S2	ENSP00000303843	SPEF2	619	1	CAG AT[G/A] AAA	265	M	I	Single AA Change	0.02	Neutral	0.077	Tolerated
5	54945139	G	A	M1_S3	ENSP00000316596	SLC38A9	561	-1	GGC A[C/T]A GTG	319	T	I	Single AA Change	-5.03	Deleterious	0.005	Damaging
5	70308644	C	T	M2_S3	ENSP00000428657	NAIP	1403	-1	GTT CA[G/A] TTG	33	Q	Q	Synonymous	0	Neutral	1	Tolerated
5	70945031	G	A	C151223_S4	ENSP00000343657	MCCC2	563	1	ATT [G/A]GG GGC	442	G	R	Single AA Change	-7.62	Deleterious	0	Damaging
5	80408468	C	T	A19552_S1	ENSP00000265080	RASGRF2	1237	1	ATT TG[C/T] TTC	626	C	C	Synonymous	0	Neutral	0.198	Tolerated
5	137089318	G	A	M1_S2	ENSP00000316042	HNRNPA0	305	-1	TAT TT[C/T] CAG	146	F	F	Synonymous	0	Neutral	1	Tolerated
5	149410394	G	A	F2_S1	ENSP00000421917	HMGXB3	1292	1	ACT [G/A]TC ACA	609	V	I	Single AA Change	-0.31	Neutral	0	Damaging
5	150075134	T	C	A19553_S4	ENSP00000199814	RBM22	420	-1	CCA G[A/G]G GAT	227	E	G	Single AA Change	-4.97	Deleterious	0.005	Damaging
5	150887123	G	A	A19505_S7	ENSP00000261800	FAT2	4349	-1	ACT [C/T]CC GAG	4037	P	S	Single AA Change	-1.54	Neutral	0.016	Damaging
5	159344800	G	A	A19505_S2	ENSP00000306662	ADRA1B	520	1	ACG TT[G/A] GGC	296	L	L	Synonymous	0	Neutral	1	Tolerated
5	167921592	A	G	M2_S2	ENSP00000231572	RARS	660	1	GTA TC[A/G] GAA	172	S	S	Synonymous	0	Neutral	0.947	Tolerated
5	169805738	C	G	M2_S3	ENSP00000274629	KCNMB1	191	-1	AAC CA[G/C] TAC	182	Q	H	Single AA Change	-3.64	Deleterious	0.001	Damaging
5	176797643	C	T	A19552_S9	ENSP00000386229	RGS14	566	1	CGG [C/T]TG GAA	369	L	L	Synonymous	0	Neutral	1	Tolerated
6	28473550	G	A	F2_S3	ENSP00000354581	GPX6	221	-1	GTC C[C/T]C AGT	130	P	L	Single AA Change	-9.51	Deleterious	0	Damaging
6	30652616	G	A	C151223_S4	ENSP00000274853	PPP1R18	613	-1	CTG [C/T]AG AAC	394	Q	*	Nonsense	NA	NA	NA	NA
6	31692391	A	G	A11365_S4	ENSP00000364964	C6orf25	241	1	CGA CC[A/G] CTC	176	P	P	Synonymous	0	Neutral	1	Tolerated
6	32096870	C	A	A20061_S9	ENSP00000364298	FKBPL	349	-1	GCT [G/T]CC CGA	230	A	S	Single AA Change	-0.3	Neutral	0.089	Tolerated
6	32134776	C	T	M2_S4	ENSP00000333380	EGFL8	293	1	TGT [C/T]AT GTG	142	H	Y	Single AA Change	-2.75	Deleterious	0.008	Damaging
6	41304104	T	A	A19554_S2	ENSP00000362181	NCR2	276	1	AGA A[T/A]C TAC	111	I	N	Single AA Change	-4.18	Deleterious	0.073	Tolerated
6	41903609	G	A	A13589_S6	ENSP00000425986	CCND3	195	-1	CTC [C/T]AG GAA	190	Q	*	Nonsense	NA	NA	NA	NA
6	43141611	G	A	A13589_S9	ENSP00000265354	SRF	508	1	ACA GG[G/A] ACA	180	G	G	Synonymous	0	Neutral	1	Tolerated
6	46661268	G	T	A20061_S16	ENSP00000346065	TDRD6	2096	1	CAT CT[G/T] GTT	1801	L	L	Synonymous	0	Neutral	1	Tolerated
6	55443789	A	C	A19505_S7	ENSP00000381654	HMGCLL1	370	-1	CAT C[T/G]C TGG	22	L	R	Single AA Change	-0.95	Neutral	0.003	Damaging
6	134496694	G	A	F2_S3	ENSP00000396242	SGK1	445	-1	CTG [C/T]TG AGC	36	L	L	Synonymous	0	Neutral	0.533	Tolerated
6	149699587	T	C	A12851_S7	ENSP00000286332	TAB2	693	1	ATG G[T/C]A ACT	179	V	A	Single AA Change	-1.08	Neutral	0.005	Damaging
7	2252879	C	T	F1_S3	ENSP00000265854	MAD1L1	718	-1	TGG GA[G/A] AGA	318	E	E	Synonymous	0	Neutral	1	Tolerated
7	31592752	G	T	M1_S4	ENSP00000395835	CCDC129	1062	1	TGG CT[G/T] CCC	64	L	L	Synonymous	0	Neutral	1	Tolerated
7	82584448	A	G	A19554_S8	ENSP00000334319	PCLO	5142	-1	GTG [T/C]TT GAA	1941	F	L	Single AA Change	-1.95	Neutral	0.28	Tolerated
7	103048347	T	C	A19505_S7	ENSP00000377328	SLC26A5	746	-1	AAT G[A/G]G AGA	280	E	G	Single AA Change	-2.9	Deleterious	0.041	Damaging
7	123197355	G	A	A19505_S7	ENSP00000341719	NDUFA5	239	-1	GCC [C/T]TT AAT	57	L	F	Single AA Change	-2.37	Neutral	NA	NA
7	127240385	G	A	A19554_S2	ENSP00000265825	FSCN3	498	1	CGA [G/A]CC GAC	477	A	T	Single AA Change	-1.98	Neutral	0.003	Damaging
7	137593015	G	C	A11365_S4	ENSP00000329140	CREB3L2	520	-1	CCT [C/G]TC CTC	251	L	V	Single AA Change	-1.73	Neutral	0.078	Tolerated
7	138720552	G	A	A13589_S9	ENSP00000275766	ZC3HAV1L	300	-1	GGC G[C/T]G GTG	71	A	V	Single AA Change	-0.48	Neutral	0.31	Tolerated
7	142640096	C	T	A19554_S2	ENSP00000347409	KEL	732	-1	CAT [G/A]CC CTC	603	A	T	Single AA Change	-0.57	Neutral	0.174	Tolerated
7	147914502	G	A	A19553_S3	ENSP00000354778	CNTNAP2	1331	1	CCG [G/A]AC CTG	1045	D	N	Single AA Change	0.63	Neutral	0.301	Tolerated
7	156956539	A	C	F2_S4	ENSP00000309198	UBE3C	1083	1	CAG GA[A/C] GAA	34	E	D	Single AA Change	-1.46	Neutral	0.189	Tolerated
8	6793655	T	A	A12851_S4	ENSP00000297435	DEFA4	97	-1	ACA [A/T]GG GGC	61	R	W	Single AA Change	-5.07	Deleterious	0.014	Damaging
8	16032769	G	T	F2_S3	ENSP00000405453	MSR1	469	-1	AAG TC[C/A] TTC	66	S	S	Synonymous	0	Neutral	1	Tolerated

8	30538444	C	T	C151223_S4	ENSP00000221130	GSR	522	-1	ATG [G/A]TC TGT	466	V	I	Single AA Change	-0.47	Neutral	0.238	Tolerated
8	30699707	A	G	A19553_S7	ENSP00000256246	TEX15	2789	-1	AAT A[T/C]T CAT	2276	I	T	Single AA Change	-0.37	Neutral	0.796	Tolerated
8	87165102	T	A	A11365_S3	ENSP00000285393	ATP6V0D2	350	1	GCA [T/A]AT GTA	317	Y	N	Single AA Change	-5.99	Deleterious	0	Damaging
8	100515147	G	A	A20061_S16	ENSP00000351346	VPS13B	4022	1	ATA [G/A]AG AGT	1376	E	K	Single AA Change	-0.84	Neutral	0.231	Tolerated
8	103335670	A	C	A19553_S7	ENSP00000429084	UBR5	2799	-1	TCA AT[T/G] AGT	551	I	M	Single AA Change	-1.25	Neutral	0.08	Tolerated
8	133083722	A	G	A19552_S9	ENSP00000407107	HHLA1	543	-1	CTC T[T/C]C AAG	481	F	S	Single AA Change	-0.93	Neutral	0.009	Damaging
8	133492494	G	C	A19552_S12	ENSP00000373648	KCNQ3	872	-1	CGC [C/G]CA GTC	96	P	A	Single AA Change	-1.12	Neutral	0.039	Damaging
8	143995831	T	C	A20061_S2	ENSP00000325822	CYP11B2	503	-1	GGT G[A/G]C AAC	268	D	G	Single AA Change	-4.8	Deleterious	0.012	Damaging
8	144378779	C	T	A19553_S7	ENSP00000328515	ZNF696	374	1	CAC [C/T]GC CGC	312	R	C	Single AA Change	-5.08	Deleterious	0	Damaging
9	1052032	G	T	A12851_S2	ENSP00000305785	DMRT2	561	1	AAG C[G/T]C TTC	140	R	L	Single AA Change	-5.92	Deleterious	0	Damaging
9	4605402	T	A	M2_S2	ENSP00000404277	C9orf68	392	-1	ATC C[A/T]T GAG	345	H	L	Single AA Change	-5.1	Deleterious	0.004	Damaging
9	8449728	G	A	A12851_S2	ENSP00000348812	PTPRD	1912	-1	ACA [C/T]CG GGT	1329	P	S	Single AA Change	-6.12	Deleterious	0.002	Damaging
9	34557981	C	A	A20061_S2	ENSP00000242338	CNTFR	372	-1	GGC TT[G/T] CCG	107	L	F	Single AA Change	0.91	Neutral	0.601	Tolerated
9	78855540	C	T	A19553_S3	ENSP00000446280	PCSK5	1860	1	GTC [C/T]AA GAC	1028	Q	*	Nonsense	NA	NA	NA	NA
9	78947398	C	T	A20061_S2	ENSP00000446280	PCSK5	1860	1	GAG GA[C/T] AGC	1513	D	D	Synonymous	0	Neutral	1	Tolerated
9	86241370	C	T	A20061_S14	ENSP00000434673	C9orf103	106	1	CTG T[C/T]G CCC	16	S	L	Single AA Change	-2.05	Neutral	0.357	Tolerated
9	98211436	T	C	M2_S4	ENSP00000332353	PTCH1	1447	-1	CGG C[A/G]C TAC	1240	H	R	Single AA Change	-1.39	Neutral	0.518	Tolerated
9	102595675	T	C	A20061_S14	ENSP00000333122	NR4A3	637	1	TGC A[T/C]G ATG	409	M	T	Single AA Change	-3.44	Deleterious	0.001	Damaging
9	112694221	A	C	A13589_S10	ENSP00000363654	PALM2-AKAP2	1103	1	TAC [A/C]TT TCC	137	I	L	Single AA Change	-0.57	Neutral	0.023	Damaging
9	115421642	C	T	M1_S4	ENSP00000440504	KIAA1958	744	1	ATT [C/T]GC CGA	510	R	C	Single AA Change	1.22	Neutral	0.192	Tolerated
9	127572254	G	A	A19552_S3	ENSP00000362682	OLFML2A	652	1	TAT [G/A]AG GAC	508	E	K	Single AA Change	-3.27	Deleterious	0.03	Damaging
9	130258259	G	A	A19553_S3	ENSP00000300417	LRSAM1	723	1	GAG C[G/A]C CAG	572	R	H	Single AA Change	-0.78	Neutral	0.243	Tolerated
9	130286100	G	A	M2_S1	ENSP00000362409	FAM129B	746	-1	AGT GC[C/T] CCC	149	A	A	Synonymous	0	Neutral	1	Tolerated
9	133951251	T	A	A20061_S16	ENSP00000347156	LAMC3	1587	1	GCC AC[T/A] GCT	1176	T	T	Synonymous	0	Neutral	0.92	Tolerated
10	8100451	C	T	F2_S3	ENSP00000368632	GATA3	444	1	TTG T[C/T]G GGG	142	S	L	Single AA Change	-2.33	Neutral	0.094	Tolerated
10	52008300	G	C	A19554_S4	ENSP00000378897	ASAH2	780	-1	ATC A[C/G]A GTG	24	T	R	Single AA Change	-1.57	Neutral	0.002	Damaging
10	63852247	G	A	M1_S2	ENSP00000279873	ARID5B	1188	1	GCG [G/A]CG CGG	1009	A	T	Single AA Change	-0.67	Neutral	0.001	Damaging
10	70333116	G	A	M2_S1	ENSP00000362748	TET1	2136	1	GGT [G/A]CT AAA	341	A	T	Single AA Change	-0.86	Neutral	0.162	Tolerated
10	75264630	G	T	C151223_S4	ENSP00000345216	USP54	1684	-1	GAA G[C/A]T CCG	1430	A	D	Single AA Change	-0.8	Neutral	0.004	Damaging
10	97116729	C	T	A19553_S4	ENSP00000360272	RP11-476E15.3.1	533	-1	ATT TC[G/A] GAA	36	S	S	Synonymous	0	Neutral	1	Tolerated
10	97181818	A	G	F1_S1	ENSP00000355136	SORBS1	1292	-1	AGG C[T/C]T TCT	114	L	P	Single AA Change	-3.4	Deleterious	0.079	Tolerated
10	101089965	C	T	C151223_S2	ENSP00000349147	CNNM1	951	1	CAG G[C/T]C GTT	274	A	V	Single AA Change	-1.21	Neutral	0.001	Damaging
10	102685780	T	G	F2_S3	ENSP00000359294	FAM178A	758	1	AGG TT[T/G] GTT	682	F	L	Single AA Change	1.27	Neutral	1	Tolerated
10	103587690	G	A	A19554_S2	ENSP00000420040	KCNIP2	285	-1	GCA [C/T]TC CGG	235	L	F	Single AA Change	-3.05	Deleterious	0.004	Damaging
10	104459137	T	A	M2_S4	ENSP00000260746	ARL3	182	-1	ACC G[A/T]T ATT	86	D	V	Single AA Change	-8.45	Deleterious	0	Damaging
10	112343279	T	C	A19554_S7	ENSP00000354720	SMC3	1217	1	CAA GA[T/C] GAA	314	D	D	Synonymous	0	Neutral	1	Tolerated
10	120085734	C	T	A12851_S11	ENSP00000358170	FAM204A	233	-1	ATA [G/A]AC CAG	159	D	N	Single AA Change	-2.55	Deleterious	0.124	Tolerated
10	129906708	T	C	A19553_S7	ENSP00000357643	MKI67	3256	-1	TCT CC[A/G] CCA	1132	P	P	Synonymous	0	Neutral	1	Tolerated
11	562273	C	T	A19552_S1	ENSP00000344226	RASSF7	373	1	TGC [C/T]TA ATT	107	L	L	Synonymous	0	Neutral	1	Tolerated
11	13427289	C	T	A19554_S2	ENSP00000431186	BTBD10	483	-1	GAA T[G/A]T CAT	316	C	Y	Single AA Change	-10.3	Deleterious	0	Damaging
11	18332432	T	C	F2_S3	ENSP00000265967	HPS5	1129	-1	GGG AA[A/G] CCG	111	K	K	Synonymous	0	Neutral	1	Tolerated
11	45931665	G	A	A19553_S7	ENSP00000241041	PEX16	346	-1	CCA C[C/T]A GCG	339	P	L	Single AA Change	-0.05	Neutral	0	Damaging
11	57319882	T	C	A11365_S2	ENSP00000287156	UBE2L6	153	-1	TTC AG[A/G] AAG	137	R	R	Synonymous	0	Neutral	0.395	Tolerated
11	58034921	A	G	A20061_S16	ENSP00000378516	OR10W1	305	-1	GTT G[T/C]G GCA	137	V	A	Single AA Change	-0.53	Neutral	1	Tolerated
11	59611404	G	A	F1_S2	ENSP00000257248	GIF	417	-1	TAC AA[C/T] TTG	68	N	N	Synonymous	0	Neutral	1	Tolerated
11	61543837	C	T	A19552_S9	ENSP00000278836	C11orf9	1151	1	GGG [C/T]GG CTG	478	R	W	Single AA Change	-7.65	Deleterious	0	Damaging
11	64681874	G	A	A19552_S3	ENSP00000410522	ATG2A	1940	-1	CTG CT[C/T] ACC	90	L	L	Synonymous	0	Neutral	1	Tolerated
11	74547437	A	G	A19552_S3	ENSP00000299563	RNF169	708	1	TTA [A/G]AT CAT	597	N	D	Single AA Change	-0.67	Neutral	0.023	Damaging
11	76072049	C	T	A20061_S14	ENSP00000260045	PRKRIR	761	-1	ACC A[G/A]T CAT	90	S	N	Single AA Change	-1.26	Neutral	0.014	Damaging
11	86749116	A	G	A19552_S9	ENSP00000306344	TMEM135	458	1	CCT C[A/G]T AAC	10	H	R	Single AA Change	-0.79	Neutral	0.365	Tolerated
11	93862575	G	T	A19552_S9	ENSP00000227638	PANX1	426	1	CTG [G/T]CT GTG	33	A	S	Single AA Change	-0.82	Neutral	0.236	Tolerated
11	115085495	A	T	A19552_S9	ENSP00000329797	CADM1	471	-1	CCT G[T/A]G ATG	276	V	E	Single AA Change	2.21	Neutral	1	Tolerated
11	123601440	G	A	A20061_S16	ENSP00000337724	ZNF202	648	-1	TTC [C/T]GC TAC	53	R	C	Single AA Change	0.03	Neutral	0.122	Tolerated
11	123894447	A	G	A19554_S2	ENSP00000364164	OR10G9	311	1	TCC C[A/G]C TGC	243	H	R	Single AA Change	-7.8	Deleterious	0	Damaging
12	6554717	C	G	A20061_S9	ENSP00000266557	CD27	260	1	TGT AA[C/G] TCT	88	N	K	Single AA Change	-2.78	Deleterious	0.007	Damaging
12	10046108	G	A	A20061_S16	ENSP00000438244	KLRF2	207	1	TGG AT[G/A] TGG	149	M	I	Single AA Change	-1.1	Neutral	0.101	Tolerated
12	13906630	C	T	M2_S2	ENSP00000279593	GRIN2B	1484	-1	GAC [G/A]AT GGA	211	D	N	Single AA Change	-2.1	Neutral	0.156	Tolerated
12	32717218	C	T	A12851_S7	ENSP00000449273	FGD4	903	1	AAG C[C/T]A CAA	105	P	L	Single AA Change	-3.51	Deleterious	0	Damaging
12	40076714	A	T	F1_S3	ENSP00000317671	C12orf40	652	1	GAT [A/T]CT TGT	330	T	S	Single AA Change	-1.19	Neutral	0.287	Tolerated
12	46244505	G	A	A13589_S3	ENSP00000335044	ARID2	1835	1	TCA [G/A]TA CAG	867	V	I	Single AA Change	-0.36	Neutral	0	Damaging
12	49418427	A	G	C151223_S3	ENSP00000301067	MLL2	5537	-1	GAG C[T/C]G CCA	5329	L	P	Single AA Change	-6.72	Deleterious	0.024	Damaging
12	52629007	G	A	F2_S3	ENSP00000329243	KRT7	469	1	AAG TC[G/A] GCC	131	S	S	Synonymous	0	Neutral	0.448	Tolerated
12	52754670	G	A	A19554_S2	ENSP00000257901	KRT85	507	-1	TTC AG[C/T] TGC	497	S	S	Synonymous	0	Neutral	1	Tolerated
12	52941644	C	T	A12851_S4	ENSP00000267119	KRT71	523	-1	AAG AA[G/A] CAG	367	K	K	Synonymous	0	Neutral	1	Tolerated
12	52943122	G	T	M2_S1	ENSP00000267119	KRT71	523	-1	GAA AT[C/A] AAC	224	I	I	Synonymous	0	Neutral	1	Tolerated
12	53086288	G	C	A19553_S4	ENSP00000342710	KRT77	578	-1	CGT GA[C/G] TAC	448	D	E	Single AA Change	0.02	Neutral	1	Tolerated
12	54106917	G	T	A11365_S3	ENSP00000449960	CALCOCO1	691	-1	CTT C[C/A]T GAA	622	P	H	Single AA Change	-2.13	Neutral	0.011	Damaging
12	54332796	G	A	A19553_S3	ENSP00000243056	HOXC13	330	1	GGA [G/A]GC GGC	36	G	S	Single AA Change	-0.2	Neutral	0.38	Tolerated
12	56215823	C	T	A20061_S9	ENSP00000316240	DNAJC14	702	-1	ACA [G/A]TA CCC	683	V	I	Single AA Change	-0.41	Neutral	0.144	Tolerated
12	56559279	C	T	A20061_S16	ENSP00000449396	SMARCC2	1245	-1	GCT [G/A]TG GCT	1019	V	M	Single AA Change	0.11	Neutral	0.185	Tolerated
12	57974739	C	T	A19553_S1	ENSP00000408979	KIF5A	1032	1	CAG [C/T]TG GTA	847	L	L	Synonymous	0	Neutral	1	Tolerated
12	91502646	A	G	A19505_S2	ENSP00000266718	LUM	338	-1	AAC TG[T/C] GCA	37	C	C	Synonymous	0	Neutral	1	Tolerated
12	102117102	G	A	F2_S1	ENSP00000229266	CHPT1	406	1	TTA [G/A]TG GTA	313	V	M	Single AA Change	-2.73	Deleterious	0.001	Damaging
12	104350514	C	A	F2_S3	ENSP00000367330	C12orf73	71	-1	AT[G/T] CCC	1	M	I	Single AA Change	-3.77	Deleterious	0	Damaging
12	112630465	G	A	A19553_S3	ENSP00000449784	C12orf51	4272	-1	TAC C[C/T]G CGG	2918	P	L	Single AA Change	-3.51	Deleterious	0	Damaging
12	130847323	C	T	A19505_S7	ENSP00000245255	PIWIL1	861	1	TCA CG[C/T] TGC	661	R	R	Synonymous	0	Neutral	1	Tolerated
12	133810797	C	T	A19552_S3	ENSP00000409950	AC226150.2.1	379	-1	GAC A[G/A]C CAG	49	S	N	Single AA Change	-1.2	Neutral	0.003	Damaging
13	19751563	G	T	A19553_S4	ENSP00000382982	TUBA3C	450	-1	AAC T[C/A]C ATC	187	S	Y	Single AA Change	-3.59	Deleterious	NA	NA
13	33703573	C	G	A19553_S3	ENSP00000338785	STARD13	1113	-1	GAA A[G/C]C CTC	414	S	T	Single AA Change	-1.88	Neutral	0.016	Damaging
13	41800635	C	A	A20061_S14	ENSP00000400031	MTRF1	468	-1	TTG A[G/T]A GCT	366	R	I	Single AA Change	-6.33	Deleterious	0.008	Damaging
13	43175042	G	A	F2_S2	ENSP00000239849	TNFSF11	317	1	TTA [G/A]AT CTG	153	D	N	Single AA Change	-0.65	Neutral	0.277	Tolerated
13	45008947	G	A	F1_S3	ENSP00000397435	TSC22D1	1073	-1	GAA [C/T]TA ATA	1013	L	L	Synonymous	0	Neutral	1	Tolerated
13	46717522	A	G	A13589_S10	ENSP00000315757	LCP1	627	-1	GCC C[T/C]G GTC	424	L	P	Single AA Change	-5.93	Deleterious	0	Damaging
13	52548213	G	A	C70007_S3	ENSP00000242839	ATP7B	1465	-1	ATG AT[C/T] TCC	381	I	I	Synonymous	0	Neutral	1	Tolerated
13	77625979	A	G	A19552_S3	ENSP00000384288	MYCBP2	4678	-1	CTC AT[T/C] TGT	4574	I	I	Synonymous	0	Neutral	0.721	Tolerated
13	98018755	C	A	A19553_S7	ENSP00000267287	MBNL2	367	1	GCA G[C/A]A ACA	346	A	E	Single AA Change	-2.85	Deleterious	0.001	Damaging
13	113656248	G	A	A12851_S4	ENSP00000405639	MCF2L	1123	1	TCA CT[G/A] CTG	8	L	L	Synonymous	0	Neutral	0.927	Tolerated
14	20937852	C	T	F2_S4	ENSP00000452421	PNP	221	1	CGG [C/T]AG AGT	16	Q	*	Nonsense	NA	NA	NA	NA
14	23992544	C	G	A19553_S4	ENSP00000413418	ZFHX2	2572	-1	AAG [G/C]CC CCA	2203	A	P	Single AA Change	-1.15	Neutral	0.016	Damaging
14	23995327	C	T	F2_S3	ENSP00000413418	ZFHX2	2572	-1	ACT C[G/A]C TCT	1275	R	H	Single AA Change	-3.3	Deleterious	0.001	Damaging
14	24632246	G	A	M1_S3	ENSP00000380073	IRF9	393	1	CGC CT[G/A] CGC	84	L	L	Synonymous	0	Neutral	1	Tolerated
14	33292497	G	A	M1_S1	ENSP00000280979	AKAP6	2319	1	ATG AA[G/A] GGC	1826	K	K	Synonymous	0	Neutral	1	Tolerated
14	51239095	A	G	A19553_S4	ENSP00000245441	NIN	2133	-1	GGG A[T/C]G GGC	302	M	T	Single AA Change	-0.33	Neutral	1	Tolerated
14	54417201	G	T	A13589_S9	ENSP00000245451	BMP4	408	-1	TTA C[C/A]T CAA	259	P	H	Single AA Change	2.98	Neutral	0.324	Tolerated
14	55369196	C	T	A19553_S4	ENSP00000378890	GCH1	250	-1	GAG GA[G/A] GAT	62	E	E	Synonymous	0	Neutral	1	Tolerated
14	58673875	C	G	F1_S3	ENSP00000452135	ACTR10	90	1	CTT [C/G]AG CCT	87	Q	E	Single AA Change	-0.21	Neutral	0	Damaging
14	60976225	C	T	A19553_S4	ENSP00000328596	SIX6	246	1	TCG [C/T]TG CCC	37	L	L	Synonymous	0	Neutral	1	Tolerated
14	70037686	G	T	A19552_S3	ENSP00000438285	C14orf162	88	-1	AGC [C/A]AC GCC	22	H	N	Single AA Change	-7	Deleterious	NA	NA
14	75248662	C	A	A11365_S3	ENSP00000324463	YLPM1	2146	1	GTT C[C/A]A CAA	639	P	Q	Single AA Change	-1.2	Neutral	NA	NA
14	91927818	A	G	A19552_S9	ENSP00000450883	SMEK1	833	-1	CTG CC[T/C] GGT	766	P	P	Synonymous	0	Neutral	0.869	Tolerated
14	92404743	G	A	F2_S1	ENSP00000267620	FBLN5	489	-1	GCT [C/T]AC TGC	60	H	Y	Single AA Change	0.19	Neutral	0	Damaging
14	95560340	A	G	M2_S2	ENSP00000343745	DICER1	1922	-1	GCT G[T/C]A AAG	1750	V	A	Single AA Change	-3.69	Deleterious	0.005	Damaging
15	39544389	C	T	A19554_S8	ENSP00000323686	C15orf54	183	1	AGG G[C/T]T GAG	18	A	V	Single AA Change	-4	Deleterious	NA	NA
15	57731679	G	A	A19552_S3	ENSP00000281282	CGNL1	1302	1	AAG GA[G/A] GAG	494	E	E	Synonymous	0	Neutral	1	Tolerated
15	73621914	C	A	A19505_S2	ENSP00000261917	HCN4	1203	-1	GAA AA[G/T] TAC	530	K	N	Single AA Change	-4.75	Deleterious	0.003	Damaging
15	88726711	C	T	A20061_S16	ENSP00000354207	NTRK3	839	-1	ATC AA[G/A] AAC	111	K	K	Synonymous	0	Neutral	0.971	Tolerated
15	93518140	G	T	A20061_S16	ENSP00000377747	CHD2	1828	1	ATC C[G/T]A AAA	846	R	L	Single AA Change	-6.56	Deleterious	0	Damaging
15	99759191	C	A	A19553_S3	ENSP00000262074	TTC23	447	-1	ATT [G/T]TG CCT	123	V	L	Single AA Change	-0.14	Neutral	0.506	Tolerated
15	100252922	G	A	F2_S2	ENSP00000337202	MEF2A	506	1	ACT GA[G/A] GAC	489	E	E	Synonymous	0	Neutral	1	Tolerated
16	4257695	C	T	A11365_S1	ENSP00000333285	SRL	931	-1	GAG [G/A]AG ACT	158	E	K	Single AA Change	-1.73	Neutral	0.008	Damaging
16	4933413	A	G	C70007_S1	ENSP00000340510	PPL	1756	-1	GAG C[T/C]G GCG	1748	L	P	Single AA Change	-3.79	Deleterious	0.002	Damaging
16	5108533	G	A	A19554_S4	ENSP00000283478	C16orf89	440	-1	TAC TG[C/T] CTG	234	C	C	Synonymous	0	Neutral	0.498	Tolerated
16	10032262	G	A	C151223_S4	ENSP00000332549	GRIN2A	1464	-1	TTC GT[C/T] AAG	187	V	V	Synonymous	0	Neutral	1	Tolerated
16	30500454	G	A	A12851_S7	ENSP00000349252	ITGAL	1170	1	AGC G[G/A]C ATC	353	G	D	Single AA Change	-6.46	Deleterious	0	Damaging
16	34256839	C	T	F2_S3	ENSP00000318279	CTD-2144E22.5.1	173	1	GTG G[C/T]G CCG	28	A	V	Single AA Change	-2	Neutral	NA	NA
16	55536728	C	T	A19553_S3	ENSP00000219070	MMP2	660	1	TTC [C/T]CC AAG	603	P	S	Single AA Change	-5.81	Deleterious	0.012	Damaging
16	58314356	G	A	A19553_S7	ENSP00000219301	PRSS54	395	-1	ACC AT[C/T] ACG	320	I	I	Synonymous	0	Neutral	0.635	Tolerated
16	66551693	T	C	A19552_S9	ENSP00000299697	TK2	307	-1	TTG AT[A/G] GTT	221	I	M	Single AA Change	-2.65	Deleterious	0.032	Damaging

16	67472983	T	C	M1 S2	ENSP00000441282	ATP6V0D1	392	-1	GAG G[A/G]C CGT	277	D	G	Single AA Change	-5.12	Deleterious	0.005	Damaging
16	72139506	G	C	A13589 S10	ENSP00000268482	DHX38	1227	1	TCT [G/C]GT TAT	824	G	R	Single AA Change	-7.37	Deleterious	0	Damaging
16	77225429	A	G	A13589_S3	ENSP00000248248	MON1B	547	1	GCG G[A/G]G GAC	16	E	G	Single AA Change	-0.96	Neutral	0.006	Damaging
16	84523014	C	T	A11365 S3	ENSP00000343635	KIAA1609	456	-1	GAT CT[G/A] GTT	133	L	L	Synonymous	0	Neutral	1	Tolerated
16	85022431	G	A	A20061 S14	ENSP00000341681	ZDHHC7	345	-1	GGG [C/T]TG GAC	122	L	L	Synonymous	0	Neutral	1	Tolerated
16	87446685	C	T	A19552 S3	ENSP00000268616	ZCCHC14	949	-1	TCC [G/A]AC AGC	437	D	N	Single AA Change	-1.73	Neutral	0.002	Damaging
17	2599795	G	A	M2 S2	ENSP00000320468	KIAA0664	1310	-1	GCG TG[C/T] AAG	702	C	C	Synonymous	0	Neutral	1	Tolerated
17	4719200	G	A	A12851 S7	ENSP00000263088	PLD2	933	1	CTT [G/A]GA GAC	476	G	R	Single AA Change	-4.27	Deleterious	0.001	Damaging
17	4875547	G	A	F2 S2	ENSP00000412886	CAMTA2	1241	-1	CCA [C/T]AG GCT	953	Q	*	Nonsense	NA	NA	NA	NA
17	5486124	A	G	A19552 S3	ENSP00000269280	NLRP1	1473	-1	CAC C[T/C]G GGG	105	L	P	Single AA Change	-1.92	Neutral	0.004	Damaging
17	7950975	C	T	A19552 S9	ENSP00000369530	ALOX15B	676	1	AGT G[C/T]A GGG	558	A	V	Single AA Change	-2.43	Neutral	0.003	Damaging
17	9765339	T	A	A20061 S9	ENSP00000379509	GLP2R	554	1	GGG [T/A]GC TGG	330	C	S	Single AA Change	-9.32	Deleterious	0	Damaging
17	10248858	G	A	A19552 S1	ENSP00000252172	MYH13	1938	-1	AAC [C/T]AG CAG	447	Q	*	Nonsense	NA	NA	NA	NA
17	17682065	A	T	F2_S3	ENSP00000438627	SMCR5	140	-1	CCT CT[T/A] GGC	109	L	L	Synonymous	0	Neutral	NA	NA
17	27959764	G	T	A19552 S9	ENSP00000444743	SSH2	1450	-1	CTG CT[C/A] CTT	816	L	L	Synonymous	0	Neutral	0.264	Tolerated
17	31618815	G	T	A20061 S9	ENSP00000225823	ACCN1	563	-1	AAC [C/A]GC TTG	107	R	S	Single AA Change	-3.72	Deleterious	0.054	Tolerated
17	36485967	C	T	C151223 S3	ENSP00000345060	GPR179	2367	-1	ACC A[G/A]C AGG	1162	S	N	Single AA Change	-1.56	Neutral	0	Damaging
17	36625519	C	T	F1 S1	ENSP00000393539	ARHGAP23	1491	1	GGA [C/T]GC CAT	595	R	C	Single AA Change	-5.5	Deleterious	0	Damaging
17	39538458	G	A	A20061 S2	ENSP00000251648	KRT34	436	-1	CGC A[C/T]C AGC	56	T	I	Single AA Change	-2.32	Neutral	0.017	Damaging
17	43367953	T	A	A19552 S3	ENSP00000342059	MAP3K14	946	-1	TGC GG[A/T] AAG	53	G	G	Synonymous	0	Neutral	1	Tolerated
17	43922875	C	A	A19552 S12	ENSP00000332488	AC217771.1	684	1	GCA GG[C/A] GGC	201	G	G	Synonymous	0	Neutral	1	Tolerated
17	46132474	C	T	A11365 S1	ENSP00000445811	NFE2L1	616	1	GCC [C/T]AG CCC	32	Q	*	Nonsense	NA	NA	NA	NA
17	46703346	G	A	A13589 S10	ENSP00000309439	HOXB9	250	-1	CTC [C/T]GC ACC	96	R	C	Single AA Change	-6.61	Deleterious	0	Damaging
17	46993534	G	A	A19552 S9	ENSP00000354201	UBE2Z	354	1	AAT GA[G/A] CCC	225	E	E	Synonymous	0	Neutral	1	Tolerated
17	56060216	C	A	A19554 S8	ENSP00000258963	VEZF1	521	-1	AAT C[G/T]A CAC	191	R	L	Single AA Change	-6.72	Deleterious	0.033	Damaging
17	70645336	G	A	A13589 S9	ENSP00000445829	SLC39A11	342	-1	GGG G[C/T]A GGC	255	A	V	Single AA Change	-2.47	Neutral	0.042	Damaging
17	73237531	C	T	A19554 S2	ENSP00000245541	GGA3	723	-1	GAA G[G/A]G CAG	299	G	E	Single AA Change	-5.72	Deleterious	0.074	Tolerated
18	67684672	G	C	A19505_S8	ENSP00000255674	RTTN	2226	-1	AGT C[C/G]T GCA	2131	P	R	Single AA Change	-1.6	Neutral	0.072	Tolerated
19	2222166	G	A	A20061 S2	ENSP00000221482	DOT1L	1740	1	CCT [G/A]CC TCT	1000	A	T	Single AA Change	-1.2	Neutral	0.014	Damaging
19	2251673	T	G	A13589 S3	ENSP00000221496	AMH	560	1	GAG C[T/G]C AGC	467	L	R	Single AA Change	-5.68	Deleterious	0	Damaging
19	4354106	G	A	C70007 S10	ENSP00000262966	MPND	471	1	ATG CT[G/A] GGC	243	L	L	Synonymous	0	Neutral	1	Tolerated
19	5456606	C	T	A12851 S4	ENSP00000222033	ZNRF4	429	1	TAC AG[C/T] TTC	368	S	S	Synonymous	0	Neutral	1	Tolerated
19	7172411	G	A	A19554 S4	ENSP00000303830	INSR	1382	-1	CTC GG[C/T] CTC	386	G	G	Synonymous	0	Neutral	1	Tolerated
19	8056686	T	A	A12851 S7	ENSP00000264073	ELAVL1	353	-1	GGT T[A/T]T GAA	32	Y	F	Single AA Change	-0.8	Neutral	0.467	Tolerated
19	9074112	G	A	A12851 S7	ENSP00000381008	MUC16	14507	-1	CCT C[C/T]C TCT	4445	P	L	Single AA Change	-2.41	Neutral	0.004	Damaging
19	10097414	G	A	A20061 S14	ENSP00000264828	COL5A3	1745	-1	CGG GG[C/T] CTC	722	G	G	Synonymous	0	Neutral	1	Tolerated
19	15549915	G	A	A12851 S7	ENSP00000373933	WIZ	1651	-1	ACC TC[C/T] GAG	582	S	S	Synonymous	0	Neutral	1	Tolerated
19	18331076	G	A	F1 S3	ENSP00000444263	PDE4C	821	-1	CGC TC[C/T] GGG	363	S	S	Synonymous	0	Neutral	1	Tolerated
19	19038632	A	T	A11365_S3	ENSP00000247003	DDX49	483	1	ACA C[A/T]G GTC	387	Q	L	Single AA Change	-4.84	Deleterious	0.01	Damaging
19	31770312	G	A	M1 S2	ENSP00000240587	TSHZ3	1081	-1	AAC TC[C/T] TAC	129	S	S	Synonymous	0	Neutral	1	Tolerated
19	36120554	C	G	A20061 S16	ENSP00000262633	RBM42	480	1	ATT AT[C/G] GCG	87	I	M	Single AA Change	-0.9	Neutral	0	Damaging
19	41073572	G	A	F2 S3	ENSP00000263373	SPTBN4	2564	1	ATC [G/A]AG AAA	2114	E	K	Single AA Change	-2.5	Deleterious	0.063	Tolerated
19	44117140	G	A	A13589 S6	ENSP00000432514	SRRM5	730	1	AGA AG[G/A] TCA	304	R	R	Synonymous	0	Neutral	1	Tolerated
19	51504410	C	T	A20061 S14	ENSP00000375682	KLK8	305	-1	CCC C[G/A]A CCT	5	R	Q	Single AA Change	-0.03	Neutral	0.106	Tolerated
19	51602294	C	T	A19553 S7	ENSP00000390011	CTU1	348	-1	GAG G[G/A]G GGC	204	G	E	Single AA Change	-0.07	Neutral	0.451	Tolerated
19	54756825	C	T	A19554 S8	ENSP00000414225	LILRB5	622	-1	GTT GT[G/A] ACT	452	V	V	Synonymous	0	Neutral	0.581	Tolerated
19	55451097	C	T	A19552 S1	ENSP00000414273	NLRP7	1065	-1	CCC [G/A]CG GTG	392	A	T	Single AA Change	-1.44	Neutral	0.413	Tolerated
19	57005558	T	G	A19553 S4	ENSP00000299997	AC004696.1	76	1	ATG A[T/G]C GCA	2	I	S	Single AA Change	-2	Neutral	0	Damaging
19	58420358	G	A	A19553 S3	ENSP00000311319	ZNF417	575	-1	CTT [C/T]AC ACT	430	H	Y	Single AA Change	-5.9	Deleterious	0	Damaging
19	58420399	G	A	A19553 S3	ENSP00000311319	ZNF417	575	-1	AAA T[C/T]A TTT	416	S	L	Single AA Change	-2.87	Deleterious	0.133	Tolerated
19	58926982	C	A	A20061 S9	ENSP00000306756	ZNF584	421	1	GTC AG[C/A] AGA	87	S	R	Single AA Change	-0.34	Neutral	0.55	Tolerated
20	37377482	G	T	A20061 S14	ENSP00000243903	ACTR5	607	1	CTG [G/T]GT GTC	121	G	C	Single AA Change	-8.22	Deleterious	0	Damaging
20	40040816	C	T	A20061_S14	ENSP00000362330	CHD6	2715	-1	AGA [G/A]TT CCT	2407	V	I	Single AA Change	-0.75	Neutral	0	Damaging
20	43541343	G	T	M2 S1	ENSP00000217073	PABPC1L	614	1	AAA G[G/T]C CAG	79	G	V	Single AA Change	-8.04	Deleterious	0	Damaging
20	47991214	C	T	F2 S3	ENSP00000360806	KCNB1	858	-1	CGC [G/A]TG GTC	295	V	M	Single AA Change	-2.82	Deleterious	0	Damaging
20	50140350	C	A	A20061 S9	ENSP00000379330	NFATC2	925	-1	GCC [G/T]GG GTG	144	G	W	Single AA Change	-0.98	Neutral	0.316	Tolerated
20	58318314	A	G	A20061 S9	ENSP00000360054	PHACTR3	559	1	CAG [A/G]CA ACG	91	T	A	Single AA Change	-3.71	Deleterious	0.005	Damaging
20	62594513	A	G	A19552 S9	ENSP00000217130	ZNF512B	892	-1	CAC [T/C]GT GGC	635	C	R	Single AA Change	-10.7	Deleterious	0.001	Damaging
21	35186297	G	A	A19552 S1	ENSP00000370685	ITSN1	1721	1	CCA A[G/A]T GCC	883	S	N	Single AA Change	-1.02	Neutral	0.031	Damaging
21	38877699	G	A	A19552 S12	ENSP00000381932	DYRK1A	763	1	TTG AA[G/A] TTC	451	K	K	Synonymous	0	Neutral	1	Tolerated
22	20126721	C	G	A12851 S4	ENSP00000384716	ZDHHC8	778	1	TGC [C/G]CG TGG	37	P	A	Single AA Change	-5.19	Deleterious	0.016	Damaging
22	26317227	G	A	A19552 S12	ENSP00000386096	MYO18B	2568	1	ATT [G/A]GC CAT	1791	G	S	Single AA Change	-3.33	Deleterious	0.111	Tolerated
22	51017936	C	G	A20061 S9	ENSP00000384400	CHKB	395	-1	AGT CG[G/C] TAT	344	R	R	Synonymous	0	Neutral	1	Tolerated