Subject (Frequency)	***IG Genes***	***Epigenetic Subtype***	***IGHV Hypermutation***	***Mutated Drivers***	***Clinical Outcome***
Subset 1 (~2.4%)	IGHV1,-5,-7 IGHD6-19 IGHJ4 IGKV1-39	Naive-like	U-CLL	*NOTCH1* *NFKBIE* *TP53*	Very aggressive; median TTFT = 1.6 years
Subset 2 (~2.8%)	IGHV3-21 IGHJ6 IGLV3-21	Intermediate	U-CLL and M-CLL	IGLV3-21^{R110} *SF3B1* del(11q) Rarely *TP53*	Very aggressive; median TTFT = 1.9 years
Subset 4 (~1%)	IGHV4-34 IGHD5-18 IGHJ6 IGKV2-30	Memory-like	M-CLL Ongoing somatic hypermutation	None	Very indolent; median TTFT = 11 years
Subset 6 (~0.9%)	IGHV1-69 IGHJ3	ND	U-CLL	*NOTCH1*	Very aggressive; median TTFT = 1.6 years
Subset 8 (~0.5%)	IGHV4-39 IGHD6-13 IGHJ5 IGKV1-39	ND	U-CLL	*NOTCH1* Trisomy 12 Rarely *TP53*	Very aggressive; median TTFT = 1.5 years; Richter transformation

Supplementary Table 2: Chronic lymphocytic leukemia (CLL) subgroups defined by stereotyped B-cell receptor.

This table is reproduced from Nadeu F, Diaz-Navarro A, Delgado J, Puente XS, Campo E. Genomic and epigenomic alterations in chronic lymphocytic leukemia. *Annual Review of Pathology: Mechanisms of Disease*. 2020;15(1):149-177.[1]

Data from references [2-4].

Abbreviations: del, deletion; IG, immunoglobulin; IGHV, immunoglobulin heavy variable; M-CLL, IGHV-mutated chronic lymphocytic leukemia; ND, no data; U-CLL, IGHV-unmutated chronic lymphocytic leukemia; TTFT, time to first treatment.

Gene	***Mutation***	***Impact***	***Agent***	***Reference(s)***
BTK	C481S	Kinase active, loss of binding	Covalent BTK i§	[5,6]
	C481G	Kinase weak, loss of binding	Covalent BTK i§	[7]
	C481F	Kinase dead	Covalent BTK i§¶	[8,9]
	C481Y	Kinase dead	Covalent BTK i§¶	[8,9]
	C481R	Kinase dead	Covalent BTK i§¶&	[8,9]
	C481W	Kinase dead	Covalent BTK i§¶&	[8,9]
	C481T	Kinase active, loss of binding	Covalent BTK i§¶	[8,9]
	V416L	Loss inhibition	Non-covalent BTKi‡	[10]
	A428D	Loss inhibition	Non-covalent BTKi, Covalent BTKi	[10]
	M437R	Loss inhibition	Non-covalent BTKi	[10]
	T474I	Loss inhibition	Non-covalent BTKi, Covalent BTKi	[8,10]
	T474S	Loss inhibition	Covalent BTKi§¶	[8]
	L528W	Loss inhibition	Non-covalent BTKi, Ibrutinib, Zanubrutinib	[8,10]
PLCG2†	T495C	Gain of Function	BTKi&	[11]
	R742P	Gain of Function	BTKi	[8]
	P664S	Gain of Function	BTKi	[11]
	R665W	Gain of Function	BTKi	[5,10]
	R742P	Gain of Function	BTKi	[8]
	S707P	Gain of Function	BTKi	[8]
	S707F	Gain of Function	BTKi	[8]
	S707Y	Gain of Function	BTKi∞	[12]
	L845F	Gain of Function	BTKi	[5]
	L845G	Gain of Function	BTKi	[11]
	L845fs	Gain of Function	BTKi	[13]
	L845-846 del	Gain of Function	BTKi	[11]
	D993G	Gain of Function	BTKi&	[11]
	D993H	Gain of Function	BTKi	[11]
	D993Y	Gain of Function	BTKi	[11]
	D1140G	Gain of Function	BTKi	[8]
	M1141R	Gain of Function	BTKi	[11]
	M1141K	Gain of Function	BTKi	[11]
	T495C	Gain of Function	BTKi&	[11]
CARD11	N280-L283del	Gain of Function	BTKi	[14]
	D401Y	Gain of Function	BTKi	[14]
	Various	Gain of Function	BTKi*	[11]
BCL2	G101V	Loss of binding	Venetoclax	[15,16]
	D103Y	Loss of binding	Venetoclax	[17]

SMARCA4		Intrinsic resistance	Ibrutinib + venetoclax combination	[18]
ARID2		Intrinsic resistance	Venetoclax	[18]

Supplementary Table 3: Negative impact of gene mutations on response to targeted agents in chronic lymphocytic leukemia (CLL)

§Covalent BTKi tested include: ibrutinib, acalabrutinib, zanubrutinib

‡Non-covalent BTKi tested include: pirtobrutinib, fenebrutinib, vecabrutinib, nemtabrutinib

¶Information on non-covalent BTKi not available

&Based on constructs of these mutations, not reported in patients

†Not all *PLCG2* mutations have been reported with non-covalent BTKi but are included based on mechanism of action

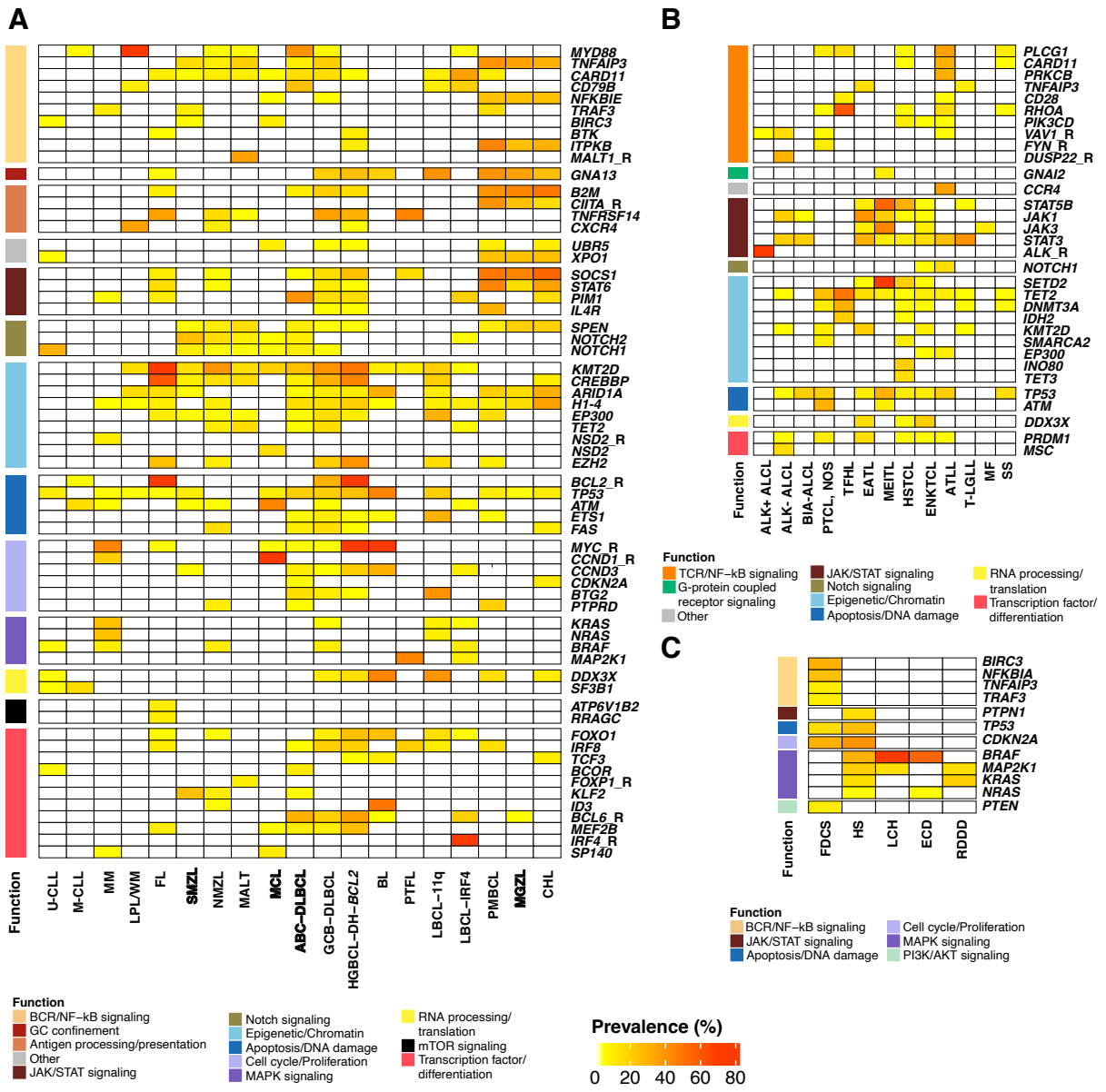
∞Also described as a germline mutation[19]

**CARD11* mutation is uncommon in CLL. Additional gain-of-function mutations of *CARD11* in MCL are associated with broad resistance to BTKi.

***SMARCA4* and *ARID2* mutations have been associated with resistance in mantle cell lymphoma, not yet described in CLL

Technique	*Profiling*	*Sample material*	*Coverage*	*Refs*
scRNA-seq	Transcriptome	Viable cells	Genome-wide	20
Spatial-seq	Topographical transcriptome	Frozen tissue	Genome-wide	21-23
snRNA-seq	Transcriptome	Viable nuclei	Genome-wide	24,25
CITE-seq ECCITE-seq	Cellular indexing of transcriptomes and epitopes by sequencing	Viable cells	Genome-wide	26,27
GoT	Genotyping of transcripts	Viable cells	Targeted mutations	28
scDNA-seq	Genome	Viable cells	Genome-wide or targeted	29,30
scATAC-seq	Chromatin accessibility	Viable cells, frozen tissue	Genome-wide	31
scDNAme-seq	Epigenome	Viable cells	Genome-wide	32
CyToF	Protein/epitopes	Viable cells	Targeted (~40 markers)	33
Spatial-proteomics	Topographical protein/epitope mapping (IMC, CODEX multiplex imaging, MIBI, CyCIF imaging, MxIF,..)	Frozen, FFPE tissue	targeted (~50 markers)	34-37

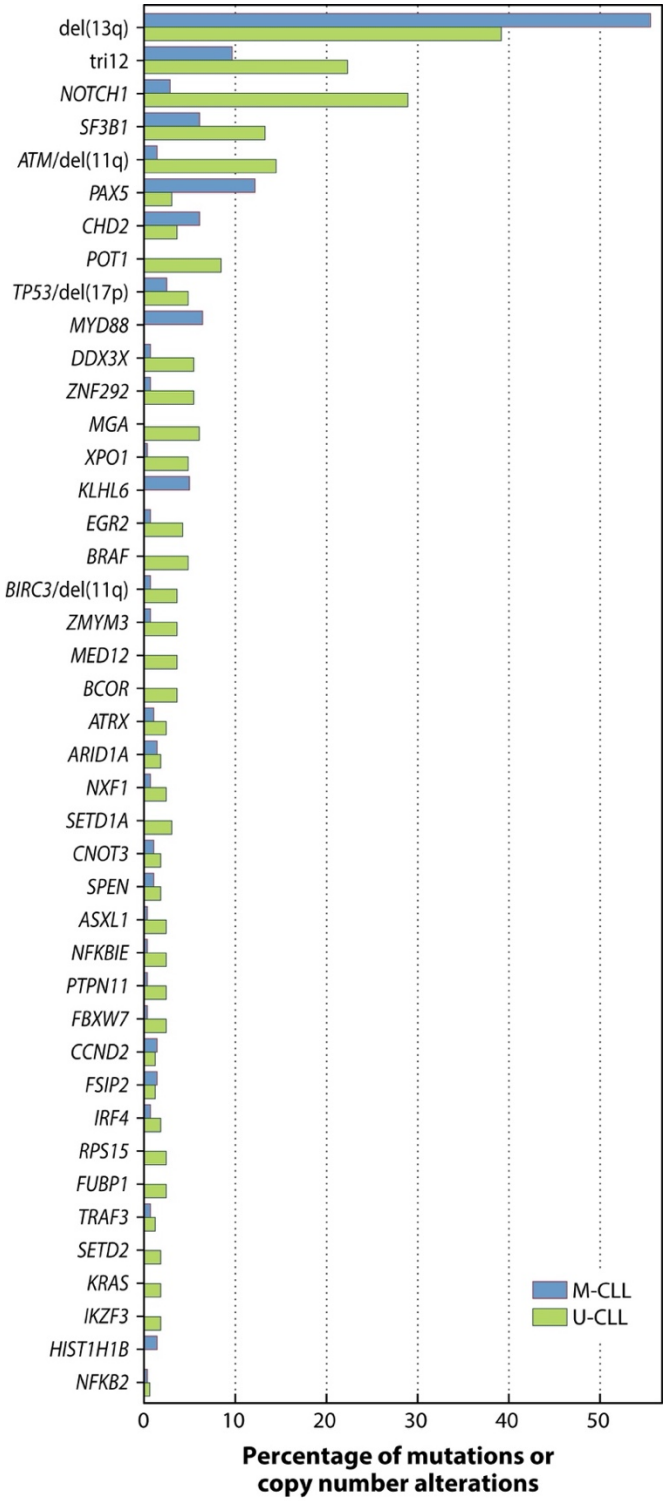
Supplementary Table 4: Single cell technologies
Abbreviations: ATACseq: assay for transposase-accessible chromatin with high-throughput sequencing; CITE: cellular indexing of transcriptomes and epitopes by sequencing; CODEX: codetection by indexing;; CyCIF: cyclic immunofluorescence; CyToF: cytometry by time of flight; DNAme-seq: DNA methylation sequencing; ECCITE: expanded CRISPR-compatible CITE-seq; IMC: imaging mass spectrometry; MIBI: multiplex ion beam imaging; MxIF: multiplexed immunofluorescence; scRNA-seq: single cell RNA-sequencing; snRNA-seq: single nucleus RNA sequencing



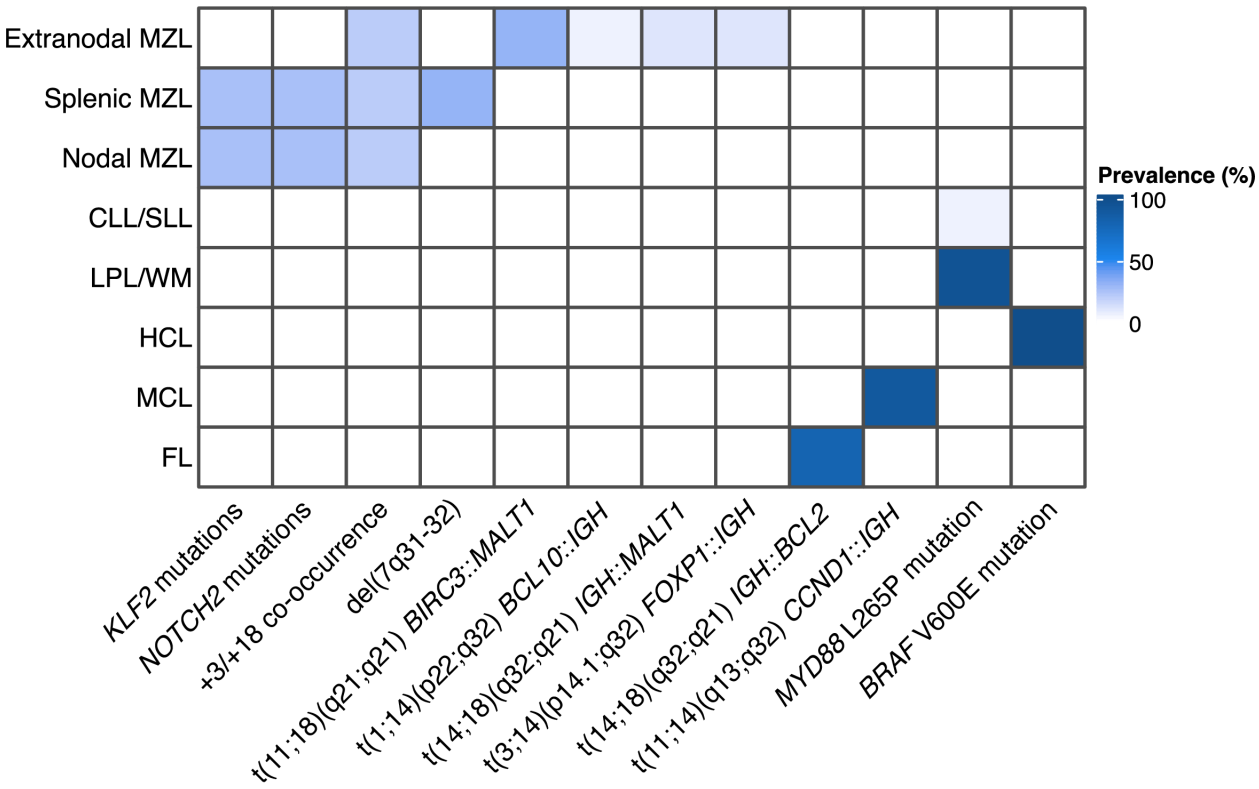
Supplemental Figure 1: Mutational landscape of mature lymphoid and histiocytic and dendritic cell neoplasms.

Frequency of selected single nucleotide variants/indels and rearrangements (R) are shown in the form of a heat map for mature B-cell neoplasms (Panel A), NK- and T-cell neoplasms (Panel B) and histiocytic and dendritic neoplasms (Panel C) along with inferred functional groups. Only genes referenced in the main text where there is a mutational frequency of at least 10% observed in one or more neoplasm are displayed - see ***Table S1*** for the full list of genes. The mutational frequencies were sourced from the literature and unpublished data, noting that different sequencing technologies and mutation callers were used across the studies. Abbreviations: U-CLL: IGHV-unmutated chronic lymphocytic leukemia; M-CLL: IGHV-mutated CLL; MM: multiple myeloma; LPL/WM: lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; FL: follicular lymphoma; SMZL: splenic marginal zone lymphoma; NMZL: nodal MZL; MALT: mucosa-associated lymphoid tissue lymphoma; MCL: mantle cell lymphoma;

ABC-DLBCL: activated B-cell-like diffuse large B-cell lymphoma; GCB-DLBCL: germinal center B-cell-like DLBCL; HGBCL-DH-*BCL2*: high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements; BL: Burkitt lymphoma; PTFL: pediatric-type FL; LBCL-11q: large B-cell lymphoma with 11q aberration; LBCL-*IRF4*: LBCL with *IRF4* rearrangement; PMBCL: primary mediastinal large B-cell lymphoma; MGZL: mediastinal gray-zone lymphoma; CHL: classic Hodgkin lymphoma; ALK+ ALCL: ALK-positive anaplastic large cell lymphoma; ALK- ALCL: ALK-negative ALCL; BIA-ALCL: breast implant-associated ALCL; PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified; TFHL: follicular helper T-cell lymphoma; EATL: enteropathy-associated T-cell lymphoma; MEITL: monomorphic epitheliotropic intestinal T-cell lymphoma; HSCTL: hepatosplenic T-cell lymphoma; ENKTCL: extranodal NK/T-cell lymphoma; ATLL: adult T-cell leukemia/lymphoma; T-LGLL: T-cell large granular lymphocytic leukemia; MF: mycosis fungoides; SS: Sezary syndrome; FDCS: follicular dendritic cell sarcoma; HS: histiocytic sarcoma; LCH: Langerhans cell histiocytosis; ECD: Erdheim-Chester disease; RDDD: Rosai-Dorfman-Destombes disease.



Supplementary Figure 2: Frequency of cytogenetic and genomic lesions in chronic lymphocytic leukemia (CLL) stratified by IGHV mutation status.
This figure is reproduced from Nadeu F, Diaz-Navarro A, Delgado J, Puente XS, Campo E. Genomic and epigenomic alterations in chronic lymphocytic leukemia. *Annual Review of Pathology: Mechanisms of Disease*. 2020;15(1):149-177.



Supplementary Figure 3: Genomic features that differentiate marginal zone lymphomas from other small B-cell lymphomas.

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