Supplementary Materials

Materials and Methods

Case Selection and Data Collection

A retrospective search of the pathology archives from January 2020 to October 2021 at the University of Utah, ARUP Laboratories, Oregon Health and Science University (OHSU), University of Kansas Medical Center (KUMC), and University of Pennsylvania (UPenn) was performed for cases with pathogenic or likely pathogenic variants in *STAT3* or *STAT5B* identified by NGS testing. 118 patients (65 with lymphoid, 50 with myeloid and 2 with composite neoplasms) with presumably somatic *STAT3* or *STAT5B* variants were identified in an unselected cohort of 6690 patients with hematologic neoplasms (15% in 442 with lymphoid neoplasms and less than 1% in 6248 with myeloid neoplasms). Cases were de-identified at the time of data collection. Concomitant variants limited to the common gene list (supplementary Table 1) were strictly used for further analysis. Patient demographic features, and clinical diagnosis were recorded for each case, and corresponding flow cytometric, cytogenetic, and T-cell clonality studies were further analyzed for correlation. Further, additional 18 age-matched MDS cases with T-LGL expansion were identified at the University of Utah and no *STAT3* or *STAT5B* variants were found by NGS in these cases. The study protocol was approved by the institutional review boards of these institutions and performed according to the Declaration of Helsinki.

Next Generation Sequencing

DNA was extracted from fresh bone marrow aspirates and NGS testing was performed using a targeted NGS panel at each institution (Tab. S2). The ARUP myeloid malignancy NGS panel included 65 genes (all coding exons, Tab. S2) commonly mutated in MNs, and targeted hybrid-capture sequencing was performed using the SureselectXTHS kit (Agilent technologies,

Santa Clara, California) following the manufacturer's protocol. In brief, 1 μg of DNA was fragmented before library preparation using a Covaris E220 instrument (Covaris, Woburn). Adaptor ligated and molecular barcoded libraries were created, and solution hybridization was performed using pools of biotinylated RNA baits. Libraries were then pooled and sequenced on Illumina MiSeq. Alignment was performed using Burrows-Wheeler Aligner (BWA-MEM), with further analysis performed using GATK (version 3), Varscan2, and SNNPET (Agilent Technologies). For all samples, callers were run with default settings in individual sample analysis modes. To call a mutation, 20 × coverage of the base analyzed (as defined by the mutation caller) was required as well as coverage in both the forward and reverse directions. Annotation of variants was performed using SureCall (version 3.5.1.46; Agilent Technologies). Additionally, variants were curated using the Genome Aggregation Database (gnomAD), Exome Aggregation Consortium (EXAC), Exome Variant Server (EVS), Catalogue of Somatic Mutations in Cancer (COSMIC), and Human Gene Mutation Database (HGMD). The shared genes tested and genes listed in NGS panels at each institution were summarized in supplementary tables 1 and 2. All genes listed in each institution were sequenced with coverage of all coding exons for all institutions.

T-Cell Clonality By PCR

DNA was extracted as described above, followed by PCR and fragment analysis according to the BIOMED-2 multiplex PCR protocol, which was validated for clinical use at ARUP laboratories.[1,2] Any peak more than 2 x higher than the maximal height of the polyclonal background was considered clonal. Any reactions with three or more clonal peaks were considered oligoclonal.[1,2]

Diagnostic Criteria of T/NK LGLL and T-LGL Expansion in Myeloid Neoplasms

Flow cytometric, cytogenetic studies and myeloid malignancy panel by NGS panel were performed as parts of the standard protocol for myeloid neoplasm workup at ARUP Laboratories. At least 3 of 5 criteria[3] were required for diagnosis of T-LGLL with *STAT3/STA5B* variants: (a) presence of more than 500/μL T or NK-LGL in peripheral blood for more than 6 months;[4] (b) presence of abnormal cytotoxic T lymphocytes with an LGL phenotype expressing CD2, CD3, CD8, CD56 or CD16 or CD57 lacking or with diminished CD5;[5] (c) clonal TCR gene rearrangement by PCR; (d) characteristic LGL infiltrate in bone marrow;[6] (e) cytopenia (anemia or neutropenia) excluding other etiologies. Similar criteria were applied to the diagnosis of NK-LGLL with exceptions of aberrant NK cell phenotype by flow cytometry[7] and exclusion of clonal T-cells by germline configuration of TCR gene rearrangement by PCR. 18 MDS cases (patients #119 -136 in Tab. S3) with T-LGL clonal expansion were defined as a clone of given size with expression of LGL phenotype (commonly CD3+/ CD8+/CD57+ and/or CD16+ without apparent aberrancies) by flow cytometry that met the following criteria at the time of MDS diagnosis: (i) CD4/CD8 ratio less than 1; (ii) LGL T-cells more than 30% of total T-cells; (iii) LGL T-cells more than 10% of total leukocytes. The mean absolute LGL clone size was 289 cells/μL, less than those with an LGLL diagnosis ($P<0.05$).[3,8]

Statistics

Descriptive statistics were used for patient characteristics, number of somatic variants per case, VAFs of each variant, and percentage of large granular lymphocytes in each case, and the results were summarized as appropriate. Unpaired t-test was used for all quantitative data, and Fisher exact test or Chi square test was used for qualitative data. VAF distribution analysis was performed using the methods described by Galli et al.[9] Linear regression was used to determine

the correlation between the VAFs of *STAT3* or *STAT5B* variants and the VAFs of predominant concurrent variants as well as the percentage of LGLs by flow cytometry.

Supplementary Tables

Supplementary table 1. List of shared genes and their transcript IDs (RefSeq accession number) tested by myeloid mutation NGS panels in all institutions.

Genes	Accession	Genes	Accession	Genes	Accession	Genes	Accession	Genes	Accession	Genes	Accession
ANKRD26	NM_014915.2	*CSF3R*	NM_156039.3	*GATA1*	NM_002049.3	*KMT2C*	NM_170606.3	*PTPN11*	NM_002834.3	*STAG2*	NM_001042749.2
ASXL1	NM_015338.5	*CUX1*	NM_181552.2	*GATA2*	NM_001145661.1	*KRAS*	NM_004985.4	*RAD21*	NM_006265.2	*STAT3*	NM_139276.2
ASXL2	NM_018263.6	*DDX41*	NM_016222.4	*GNAS*	NM_000516.1	*LUC7L2*	NM_016019.1	*RUNX1*	NM_001754.4	*STAT5B*	NM_012488.4
BCOR	NM_001123385.1	*DNMT3A*	NM_175629.2	*IDH1*	NM_005896.3	*MPL*	NM_005373.2	*SETBP1*	NM_015559.2	*TET2*	NM_001127208.2
BCORL1	NM_021946.4	*ETNK1*	NM_018638.4	*IDH2*	NM_002168.3	*NF1*	NM_000267.3	*SF3B1*	NM_012433.3	*TP53*	NM_000546.5
BRAF	NM_004333.4	*ETV6*	NM_001987.4	*JAK2*	NM_004972.3	*NOTCH1*	NM_017617.3	*SH2B3*	NM_005475.3	*U2AF1*	NM_006758.2
CALR	NM_004343.3	*EZH2*	NM_004456.4	*JAK3*	NM_000215.3	*NPM1*	NM_002520.6	*SMC1A*	NM_006306.2	*U2AF2*	NM_007279.2
CBL	NM_005188.3	*FBXW7*	NM_018315.5	*KDM6A*	NM_001291415.1	*NRAS*	NM_002524.5	*SMC3*	NM_005445.3	*WT1*	NM_024426.4
CEBPA	NM_004364.4	*FLT3*	NM_004119.2	*KIT*	NM_000222.2	*PHF6*	NM_001015877.1	*SRSF2*	NM_003016.4	*ZRSR2*	NM_005089.3

Supplemental table 2. Complete list of genes on NGS panels at each institution.

Institutions	Complete gene list
OHSU	*ABL1, AKT1, ANKRD26, ARID1A, ARID1B, ASXL1, ASXL2, ATG2B, ATM, ATRX, BCL2, BCL6, BCOR, BCORL1, BIRC3, BIRC6, BLM, BRAF, BRCA1, BRCA2, BRCC3, BRD4, BTK, CALR, CARD11, CASP10, CBL, CBLB, CBLC, CCND1, CCND3, CCR4, CD27, CD79A, CD79B, CDH11, CDKN2A, CDKN2C, CEBPA, CHD2, CHEK2, CREBBP, CRLF2, CSF1R, CSF3R, CTCF, CTLA4, CUX1, CXCR4, DAXX, DDX41, DDX54, DHX15, DHX29, DIS3, DNAH5, DNAH9, DNAJC21, DNM2, DNMT1, DNMT3A, DOCK8, DTX1, EED, EFTUD1, EGFR, ELANE, EP300, ERBB4, ETNK1, ETV6, EZH2, FAM47A, FAM5C, FAS, FAT1, FAT4, FBXO11, FBXW7, FLT3, FOXO1, FYN, GATA1, GATA2, GATA3, GNA13, GNAS, GNB1, GSKIP, HAX1, HIST1H1E, HNRNPK, HRAS, HVCN1, ID3, IDH1, IDH2, IGLL5, IKZF1, IKZF3, IL7R, IRF4, JAK1, JAK2, JAK3, KDM6A, KIT, KLF2, KLHL6, KMT2A, KMT2C, KMT2D, KRAS, LLGL2, LRRC4, LUC7L2, MAGT1, MAML1, MAP2K1, MECOM, MED12, MEF2B, MGA, MLH1, MPL, MSH2, MSH6, MYC, MYD88, NAF1, NBN, NF1, NFKBIE, NOTCH1, NOTCH2, NPAT, NPM1, NRAS, NT5C2, NXF1, PAX5, PCLO, PDGFRA, PHF6, PIGA, PIK3CD, PIM1, PLCG1, PLCG2, PMS2, POT1, PPM1D, PRDM1, PRKCB, PRPF40B, PRPF8, PRPS1, PSMB5, PTCH1, PTEN, PTPN11, RAD21, RB1, RBBP6, RELN, RHOA, RIT1, RPS15, RTEL1, RUNX1, RYR1, RYR2, SAMD9, SAMD9L, SAMHD1, SBDS, SETBP1, SETD2, SETDB1, SF1, SF3A1, SF3B, SH2B3, SMARCA2, SMARCB1, SMC1A, SMC3, SOCS1, SPEN, SPI1, SRP72, SRSF2, STAG2, STAT3, STAT5B, STXBP2, SUZ12, SYK, SYNE1, TBL1XR1, TCF3, TCF4, TERC, TERT, TET2, TNFAIP3, TNFRSF14, TP53, TRAF3, U2AF1, U2AF2, UBR5, USH2A, VAV1, WAS, WHSC1, WT1, XPO1, ZBTB7A, ZRSR2*
ARUP	*ANKRD26, ASXL1, ASXL2, BCOR, BCORL1, BRAF, CALR, CBL, CBLB, CEBPA, CSF3R, CUX1, DDX41, DNMT1, DNMT3A, ELANE, ETNK1, ETV6, EZH2, FBXW7, FLT3, GATA1, GATA2, GNAS, HNRNPK, IDH1, IDH2, IL7R, JAK1, JAK2, JAK3, KDM6A, KIT, KMT2A, KMT2C, KRAS, LUC7L2, MPL, NF1, NOTCH1, NPM1, NRAS, NSD1, PHF6, PIGA, PRPF40B, PRPF8, PTPN11, RAD21, RUNX1, SETBP1, SF3B1, SH2B3, SMC1A, SMC3, SRSF2, STAG2, STAT3, STAT5B, SUZ12, TET2, TP53, U2AF1, U2AF2, WT1, ZRSR2*
KUMC	*ABL1, ADA, ANKRD26, ASXL1, ASXL2, ATM, ATRX, BCL6, BCOR, BCORL1, BCR, BIRC3, BLM, BRAF, BRCA1, BRCA2, BRINP3, C17orf97, CALR, CARD11, CBL, CBLB, CBLC, CDKN2A, CEBPA, CHEK2, CREBBP, CRLF2, CSF1R, CSF3R, CTCF, CUX1, DAXX, DDX41, DNM2, DNMT1, DNMT3A, EED, EGFR, ELANE, EP300, ETNK1, ETV6, EZH2, FAM154B, FAM47A, FAS, FBXW7, FLRT2, FLT3, GATA1, GATA2, GJB3, GNAS, HNRNPK, HRAS, IDH1, IDH2, IKZF1, IKZF3, IL7R, JAK1, JAK2, JAK3, KAT6A, KCNA4, KCNK13, KDM6A, KDR, KIT, KLHDC8B, KLHL6, KMT2A, KMT2C, KRAS, LRRC4, LUC7L2, MAP2K1, MLH1, MPL, MSH2, MSH6, MYC, MYD88, NBN, NF1, NOTCH1, NPAT, NPM1, NRAS, NSD1, NTRK3, OR13H1, OR8B12, P2RY2, PAX5, PCDHB1, PDGFRA, PHF6, PML, PMS2, PRAMEF2, PRF1, PRPF40B, PRPF8, PTEN, PTPN11, RAD21, RB1, RELN, RUNX1, SETBP1, SF1, SF3A1, SF3B1, SH2B3, SH2D1A, SMARCB1, SMC1A, SMC3, SRP72, SRSF2, STAG2, STAT3, STXBP2, SUZ12, TAL1, TERC, TERT, TET2, TNFRSF13B, TP53, TPMT, TUBA3C, U2AF1, U2AF2, WAS, WRN, WT1, XPO1, ZRSR2*
UPenn	*ABL1, ASXL2, ATM, B2M, BCL2, BCOR, BCORL1, BIRC3, BRAF, BRCA2, BRINP3, BRINP3, BRIP1, BTK, CALR, CARD11, CBL, CD79A, CD79B, CDKN2A, CEBPA, CIITA, CREBBP, CSF1R, CSF3R, CXCR4, DDX3X, DDX41, DICER, DNMT3A,EGR2, ERCC4, ETV6, EZH2,FANCA, FANCC, FANCD2, FANCE, FANCF, FANCL, FANCM, FBXW7, FLT3, GATA2, GNA13, GNAS, HNRNPK, ID3, IDH1, IDH2, IKZF1, IL7R, JAK2, JAK3, KIT, KLF2, KLHL6, KRAS, MAP2K1, MAPK1, MIR142, MPL, MYC, MYCN, MYD88, NF1, NFKBIE, NOTCH1, NOTCH2, NPM1, NRAS, PALB2, PDGFRA, PHF6, PLCG1, PLCG2, POT1, PRPF40B, PTEN, PTPN11, RAD21, RAD51, RAD51C, RHOA1, RIT1, RPS15, RRAGC, RUNX1, SETBP1, SF1, SF3A1, SF3B1, SLX4, SMC1A, SOCS1, SRSF2, STAG2, STAT3, STAT5B, TNFRSF14, TP53, TPMT, TRAF3, U2AF1, U2AF2, WT1, XPO1, XRCC2, ZMYM3, ZRSR2*

Supplemental Table 3. The molecular and cytogenetic profiles of 118 hematologic neoplasm patients with pathogenic/likely pathogenic *STAT3* and *STAT5B* variants and additional 18 MDS patients with expanded T-LGL population

Pts	Age	Sex	Dx	STAT	NA	AA	VAF (%)	Other variants	VAF (%)	Tiers	Cytogenetics	TCC
1	79	M	T-LGLL	STAT3	c.1919A>T	p.Y640F	7	ASXL1 c.1934dup, p.G646fs	6	1	46,XY[20]	Positive
								TET2 c.3176C>A, p.S1059*	5	1		
								TET2 c.4487dup, p.S1497fs	1	1		
2	83	M	T-LGLL	STAT3	c.1940A>T	p.N647I	12	DNMT3A c.1474+1del, p.?	13	1		Positive
								DNMT3A c.2694_2703dup, p.F902fs	14	1		
3	66	M	T-LGLL	STAT3	c.1852G>C	p.G618R	8	DNMT3A c.2645G>A, p.R882H	8	1		
								DNMT3A c.2694_2703dup, p.F902fs	2	1		
4	74	F	T-LGLL	STAT3	c.1919A>T	p.Y640F	10	DNMT3A c.2645G>A, p.R882H	12	1		
5	66	M	T-LGLL	STAT3	c.1981G>T	p.D661Y	4	DNMT3A c.1040Tdel, p.L347fs	2	1	46,XY[20]	Positive
6	84	M	T-LGLL	STAT3	c.1919A>T	p.Y640F	6	STAT3 c.1981G>T, p.D661Y	3	1		Positive
								DNMT3A c.1976G>A, p.R659H	2	2		
7	75	M	T-LGLL	STAT3	c.1982A>T	p.D661V	30	TET2 c.5618T>C, p.I1873T	32	1	46,XY[20]	
								TET2 c.1648C>T, p.R550*	30	1		
8	82	F	T-LGLL	STAT3	c.1919A>T	p.Y640F	4	STAT3 c.1852G>C, p.G618R	6	1		
								TET2 c.1630C>T, p.R544*	6	1		
9	85	F	T-LGLL	STAT3	c.1919A>T	p.Y640F	3	TET2 c.4264_4267del, p.K1422fs	7	1		
								TET2 c.2759_2766dup, p.N923*	2	1		
								TET2 c.741_742dup, p.H248fs	2	1		
10	73	M	T-LGLL	STAT3	c.1982A>T	p.D661V	30	TET2 c.1945C>T, p.Gln649*	32	1	46,XY[20]	Positive
								TET2 c.2822dup, p.Pro942fs	29	1		
11	71	F	T-LGLL	STAT3	c.1919A>T	p.Y640F	6	TET2 c.5620G>A, p.E1874K	6	1	46,XX[13]	Positive
12	83	M	T-LGLL	STAT3	c.1919A>T	p.Y640F	6	TP53 c.743G>A, p.R248Q	3	1	46,XY[20]	Positive
								STAG2 c.570_572delCAT, p.I191del	8	1		
13	53	F	T-LGLL	STAT3	c.1919A>T	p.D661Y	32	TP53 c.743G>A, p.R248Q	31	1		
14	67	M	T-LGLL	STAT3	c.1847_1849del	p.E616del	4	TP53 c.706T>C, p.Y236H	3	1		Positive
15	65	F	T-LGLL	STAT3	c.1919A>T	p.Y640F	5	CEBPA c.543C>A, p.Y181*	5	1	46,XY[20]	Positive
16	75	M	T-LGLL	STAT3	c.1982A>T	p.D661V	24				46,XY[20]	
17	70	M	T-LGLL	STAT3	c.1940A>T	p.N647I	30				46,XY[25]	Positive
18	74	M	T-LGLL	STAT3	c.1919A>T	p.Y640F	17	STAT3 c.1981G>T, p.D661Y	6	1		
19	48	M	T-LGLL	STAT3	c.1919A>T	p.Y640F	6					Positive
20	83	M	T-LGLL	STAT3	c.1842C>G	p.S614R	5				46,XY[20]	
21	67	F	T-LGLL	STAT3	c.1919A>T	p.Y640F	11					Positive
22	70	M	T-LGLL	STAT3	c.1919A>T	p.Y640F	29				46,XY[20]	Positive
23	66	M	T-LGLL	STAT3	c.1852G>C	p.G618R	4				46,XY[20]	
24	80	M	T-LGLL	STAT3	c.1981G>T	p.D661Y	15				46,XY[20]	
25	85	M	T-LGLL	STAT3	c.1919A>T	p.Y640F	4				46,XY[20]	Positive
26	51	M	T-LGLL	STAT3	c.1919A>T	p.Y640F	5				Nl	Positive
27	71	M	T-LGLL	STAT3	c.1940A>T	p.N647I	14					
28	79	M	T-LGLL	STAT3	c.1940A>T	p.N647I	6				46,XY[20]	
29	66	M	T-LGLL	STAT3	c.1229A>G	p.H410R	9				46,XY[20]	Positive
30	53	F	T-LGLL	STAT3	c.1919A>T	p.Y640F	7				46,XX[20]	Positive
31	88	M	T-LGLL	STAT3	c.1919A>T	p.Y640F	5					
32	74	M	T-LGLL	STAT3	c.1842C>G	p.S614R	8				46,XY[20]	Positive
33	61	M	T-LGLL	STAT3	c.1981G>T	p.D661Y	43				46,XY[20]	positive
34	19	F	T-LGLL	STAT3	c.1919A>T	p.Y640F	9					Positive
35	78	M	T-LGLL	STAT3	c.1982A>T	p.D661V	42					positive
36	35	M	T-LGLL	STAT3	c.1842C>G	p.S614R	3				46,XY[20]	Positive
37	69	M	T-LGLL	STAT3	c.1981G>T	p.D661Y	11					Positive
38	67	F	T-LGLL	STAT3	c.1981G>T	p.D661Y	14				45,X,-X[1]/45,sl,add(5)(p15.1)[2]/46,XX[17]	Positive
39	51	F	T-LGLL	STAT3	c.1981G>T	p.D661Y	19				47,XX,+X[3]/46,XX[17]	Positive
40	89	F	T-LGLL	STAT3	c.1919A>T	p.Y640F	9				NI	Positive
41	67	M	T-LGLL	STAT3	c.1919A>T	p.Y640F	18				45,X,-Y[14]/46,XY[6]	Positive
42	74	F	T-LGLL	STAT3	c.1919A>T	p.Y640F	8				N	Positive
43	64	M	T-LGLL	STAT3	c.1981G>T	p.D661Y	7				N	Positive
44	66	M	T-LGLL	STAT3	c.1940A>T	p.N647I	4				46,XY[20]	Positive
45	42	F	T-LGLL	STAT5B	c.1924A>C	p.N642H	5				46,XX[20]	Positive
46	75	M	T-LGLL	STAT5B	c.1810C>T	p.H604Y	5				46,XX[20]	Positive
47	38	M	NK-LGLL	STAT3	c.1973A>G	p.K658R	11	DNMT3A c.2206C>T, p.R736C	4	1	46,XY[20]	Negative
								TET2 c.3707_3718del, p.I1236_L1240delinsM	24	1		
48	71	M	NK-LGLL	STAT3	c.1852G>C	p.G618R	3	DNMT3A c.2202del, p.Y735fs	1	1	46,XY[20]	Negative
								DNMT3A c.2202del, p.Y735fs	1	1		
49	73	M	NK-LGLL	STAT3	c.1842C>G	p.S614R	5				46,XY[20]	
								DNMT3A c.1969G>A, p.V657M	4	1		
50	78	M	NK-LGLL	STAT3	c.1981G>T	p.D661Y	13	TP53, c.542G>A, p.R181H	17	1	46,XY[20]	
								KMT2C, c.11647del, p.D3883fs*3	4	1		

51	85	M	NK-LGLL	STAT3	c.1981G>T	p.D661Y	39					
52	77	M	NK-LGLL	STAT3	c.1981G>T	p.D661Y	25					
53	54	M	NK-LGLL	STAT3	c.1981G>T	p.D661Y	7					Negative
54	52	M	NK-LGLL	STAT3	c.1982A>T	p.D661V	9				46,XY[20]	Negative
55	74	M	NK-LGLL	STAT3	c.1982A>T	p.D661V	31					Negative
56	55	M	NK/T lymphoma; EBV positive	STAT5B	c.1924A>C	p.N642H	1				45,X,-Y,i(7)(q10),add(8)(p23)[8]/46,XY[3]	Positive
57	69	M	T-PLL	STAT5B	c.1994A>T	p.Y665F	3				46,XX,+8,i(8)(q10)x2-3,del(11)(q22q23),inv(14)(q11.2q32), add(15)(p11.1),der(18;21)(q10;q10)[cp3]/46,XX[20]	Positive
58	39	M	T-PLL	STAT5B	c.1924A>C	p.N642H	40	STAG2 c.1737_1738del, p.S579fs JAK1 c.2097_2108delins12, p.S703I	63 2	1 1	44,XY,add(1)(q42),add(4)(q31),inv(5)(p15.1q32),-7,t(11;13)(p11.2;q13), del(12)(p11.2),add(14)(p11.2),der(14)t(7;14)(q10;p11.2),add(16)(p13.3), -20,add(22)(p11.2)[11]/44,idem,+7,i(7)(q10),-14,-der(14)[5]/46,XY[4]	Positive
59	27	M	B-LBL	STAT3	c.1982A>T	p.D661V	3	CEBPA 322_336delinsA, p.Y108fs CEBPA c.937_939dup, p.K313dup	51 29	1 1		
60	67	M	PTLD; PBL	STAT3	c.1842C>G	p.S614R	8	STAT3 c.1842C>A, p.S614R TP53 c.743G>A, p.R248Q	5 31	1 1	46,XY,t(8;14)(q24;q32),der(13)t(1;13)(q21;q32),add(22)(p11.2)[17] /46,sl,add(1)(q23)[1]/46,XY[2]	
61	66	M	DLBCL	STAT3	c.1144C>T	p.R382W	24	MYD88 c.755T>C, p.L265P	20	1	52,Y,add(X)(q24),+Y,der(1)t(1;8)(p36.1;q11.2,add(2)(q32),der(2)add(2)(p11.2) add(2)(q33),+3,add(4)(q23),inv(4)(p15.2q27),inv(6)(p25q21),+7, add(7)(p15.1),add(7)(q22)x2,add(8)(q13),add(9)(p22),add(9)(p24),add(11)(p11.2), add(13)(q12),add(14)(q24)x2,add(17)(q21),+18,der(18)del(18)(q21)idic(18)(p11.2), +22,add(22)(q12),+mar[cp12]/53,idem,+18[2]/46,XY[6]	
62	72	F	MM	STAT3	c.1981G>T	p.D661Y	2	DNMT3A c.1949T>C, p.L650R DNMT3A c.855+1G>A, p.?	4 2	1 1	46,XX[25]	
63	53	M	CLL	STAT3	c.1982A>T	p.D661V	2					
64	55	M	MM	STAT3	c.1969_1971dup	p.Y657dup	15					Negative
65	78	M	MM	STAT5B	c.1883C>G	p.T628S	5				45,X,-Y[7]/46,XY[13]	
66	47	M	B-LBL	STAT5B	c.2135T>A	p.V712E	40	STAT5B c.1883C>G, p.T628S KDM6A c.2688del, p.N897fs	5 48	1 1	48,Y,add(X)(q24),add(8)(q13),add(11)(p11.2),add(13)(q12),add(14)(q24)x2,add(17)(q21), +18,der(27 18)del(18)(q21)idic(18)(p11.2),+22,add(22)(q12),+mar[cp12]/53,idem,+18[2]/46,XY[3]	
67	70	M	T-LGLL; MDS	STAT3	c.1919A>T	p.Y640F	3				46,XY,del(5)(q13q33)[12]/46,XY[8]	Positive
68	56	M	T-LGLL; MDS	STAT3	c.1919A>T	p.Y640F	16	SF3B1, H662Y	13	1	46,XY[20]	Positive
69	64	F	Anemia	STAT3	c.1919A>T	p.Y640F	17					Negative
70	60	F	Cytopenia	STAT3	c.1981G>T	p.D661Y	29				46,XX[20]	Negative
71	64	M	Pancytopenia	STAT3	c.1919A>T	p.Y640F	8					
72	59	F	Neutropenia	STAT3	c.1919A>T	p.Y640F	20					
73	80	M	Anemia	STAT3	c.1982A>T	p.D661V	6	STAT3 c.509A>T, p.D170V ASXL1 c.1900_1922del, p.E635fs	3 2	2 1	46,XY[20]	
74	34	M	Anemia	STAT3	c.1919A>T	p.Y640F	4	DNMT3A c.2099C>T, p.P700L	2	1	46,XY[1]//46,XX[19]	
75	76	M	AA	STAT3	c.1981G>T	p.D661Y	5	DNMT3A c.2497del, p.I833fs DNMT3A c.2259G>T, p.W753C	5 5	1 2		
76	67	M	Anemia	STAT3	c.1919A>T	p.Y640F	2	SF3B1 c.1997A>C, p.K666T CBL c.773G>A, p.W258* TET2 c.3244G>T, p.E1082* TET2 c.5698_5700del, p.V1900del	4 4 2 3	1 1 1 2		
77	78	M	MDS/MPN	STAT3	c.1981G>T	p.D661Y	4	SF3B1 c.2098A>G, p.K700E DNMT3A c.1474_1474+5del, p.?	5 11	1 1		
78	69	F	CMML	STAT3	c.1840A>C	p.S614R	5	ASXL1 c.2525del, p.N842fs STAG2 c.1798delinsAC, p.Y600fs U2AF2 c.572_586del, p.I191_K195del	6 4 5	1 1 2	46,XX[20]	
79	57	M	MDS/MPN	STAT3	c.1840A>C	p.S614R	47	ASXL1 c.1585C>T, p.Q529* SRSF2 c.284C>T, p.P95L CSF3R c.1853C>T, p.T618I STAG2 c.1551_1552insTAAA, p.E518* LUC7L2 c.838C>T, p.R280* KRAS c.38G>A, p.G13D SETBP1 c.2602G>C, p.D868H	46 45 65 41 98 44 4	1 1 1 1 1 1 1		
80	79	F	MDS/MPN	STAT3	c.1840A>C	p.S614R	1	SRSF2 c.284C>A, p.P95H ASXL1 c.2290del, p.L764fs CBL c.1247G>A, p.C416Y SETBP1 c.2608G>A, p.G870S	62 43 85 47	1 1 1 1	46,XX[20]	
81	67	M	CMML	STAT3	c.1852G>C	p.G618R	14	ASXL1 c.3055A>T, p.R1019*	35	1	46,XY[3]	

								SRSF2 c.284C>A, p.P95H	37	1		
								SETBP1 c.2602G>A, p.D868N	36	1		
								KRAS c.99T>A, p.D33E	21	1		
								KRAS c.351A>T, p.K117N	35	1		
82	70	M	MDS	STAT3	c.1919A>T	p.Y640F	5	ASXL1 c.1934dup, p.G646fs	25	1	45,XY,-7[14]/46,XY[3]	
								SETBP1 c.2602G>A, p.D868N	26	1		
								CUX1 c.558del, p.T187fs	2	1		
								EZH2 c.187C>T, p.R63*	30	1		
								ETV6 c.226del, p.E76fs	27	1		
								EZH2 c.892C>T, p.R298C	8	2		
83	48	F	MDS	STAT3	c.1144C>T	p.R382W	3	RUNX1, c.485G>A, p.R162K	27	1	46,XX,der(7)t(1;7)(q12;p12)[14]/46,XX[6]	
								IDH2 c.419G>A, p.R140Q	17	1		
								ASXL1 c.1934dup, p.G646fs	14	1		
								IDH1 c.394C>T, p.R132C	34	1		
								ASXL2 c.3565G>T, p.E1189*	12	1		
84	49	M	MDS	STAT3	c.1981G>T	p.D661Y	10	TET2 c.4960C>T, p.Q1654*	6	1	46,XY[20]	
85	85	M	MDS	STAT3	c.1981G>T	p.D661Y	21	DNMT3A c.2197G>T, p.E733*	13	1		
								TET2 c.1200del, p.P401fs	19	1		
								SF3B1 c.2098A>G, p.K700E	13	1		
86	74	M	MDS	STAT3	c.1981G>T	p.D661Y	4	TP53 c.711G>A, p.M237I	2	1		
								U2AF1 c.470A>C, p.Q157P	2	1		
								DNMT3A c.2639del, p.M880fs	14	1		
								TET2 c.3411dup, p.K1138*	2	1		
								RUNX1 c.1098_1103dup, p.I366_G367dup	36	2		
								TP53 c.467_469del, p.R156_V157delinsL	3	2		
87	84	M	MDS	STAT3	c.1840A>C	p.S614R	24	TP53 c.824G>A, p.C275Y	23	1	46,XY[20]	
								DNMT3A c.1315_1316del, p.M439fs	2	1		
88	62	M	MDS	STAT3	c.1852G>C	p.G618R	36	STAT3 c.1919A>T, p.Y640F	3	1	46,XY,del(12)(q13q15)[20]	
89	61	M	MDS	STAT3	c.1919A>T	p.Y640F	3	KIT c.1540G>T, p.E514*	3	1		Negative
90	68	M	AML	STAT3	c.1975A>C	p.I659L	21	RUNX1 c.320G>A, p.R107H	29	1	46,XY,t(3;12)(q26.2;p13)[19]/46,XY,del(12)(p11.2)[6]/46,XY[1]	Negative
								U2AF1, c.470A>C, p.Q157P	26	1		
								SETBP1 c.2602G>A, p.D868N	26	1		
								MPL c.1771_1794del, p.Y591_C598del	37	2		
91	27	F	AML	STAT3	c.1840A>C	p.S614R	45	RUNX1 c.422C>A, p.S141*	13	1		
								SETBP1 c.2602G>A, p.D868N	48	1		
								WT1 c.1105delinsGG, p.R369fs	45	1		
								GATA2 c.1186C>T, p.R396W	47	1		
								NRAS c.35G>A, p.G12D	6	1		
92	83	M	AML	STAT3	c.1919A>T	p.Y640F	3	FLT3 c.1745_1840dup, p.?	NR	1		
								FLT3 c.1732_1794dup, p.M578_E598dup	NR	1		
								RUNX1 c.402_405dup, p.N136fs	41	1		
								SF3B1 c.1998G>T, p.K666N	44	1		
								DNMT3A c.2644C>T, p.R882C	45	1		
								PHF6 c.585+2T>A, p.?	5	1		
93	80	F	AML	STAT3	c.1139+1G>A	p.?	43	FLT3 c.1751_1795dup, p.S584_E598dup		1	46,XX[20]	
								NPM1 c.860_863dup, p.W288fs		1		
								DNMT3A c.2096G>A, p.G699D		1		
								IDH2 c.419G>A, p.R140Q	30	1		
94	58	M	AML	STAT3	c.1973A>T	p.Y657F	12	DMNT3A, c.958C>T, p.R320*	50	1	46,XY[20]	
								NRAS, c.183A>C, p.Q61H	4	1		
								CEBPA, c.890G>C, p.R297P	49	1		
								CEBPA, c.539dup, p.Y181fs	43	1		
95	22	F	AML	STAT3	c.1852G>C	p.G618R	41	KRAS c.34G>C, p.G12R	41	1		
								JAK3 c.115dup, p.Q39fs	29	1		
96	88	M	AML	STAT3	c.361A>T	p.T121S	38	ASXL1 c.2077C>T, p.R693*	41	1		
								U2AF2 c.572_586del, p.I191_K195del	31	2		
97	74	F	AML	STAT3	c.1981G>T	p.D661Y	38	JAK2 c.1849G>T, p.V617F	3	1	46,XX,del(5)(q13q33)[14]/46,XX[6]	
98	53	F	MPN	STAT3	c.1842C>G	p.S614R	44	JAK2 c.1849G>T, p.V617F	96	1	47,XX,+21[3]/46,XX[17]	
								ASXL1 c.2077C>T, p.R693*	46	1		
								DNMT3A c.2645G>A, , p.R882H	48	1		
								SETBP1 c.2608G>A, p.G870S	47	1		
								WT1 c.1301G>T, p.R434L	2	1		
99	67	M	MPN	STAT3	c.1840A>C	p.S614R	49	JAK2 c.1849G>T, p.V617F	44	1	46,XY[11]	
								SRSF2 c.284_307del, p.P95_R102del	43	1		
								NRAS c.35G>A, p.G12D	46	1		
100	82	M	MPN	STAT3	c.1847_1849del	p.E616del	6	SETBP1 c.2608G>A, p.G870S	47	1	46,XY[20]	
								CSF3R c.1853C>T, p.T618I	40	1		
								EZH2 c.1200_1203del, p.E401fs	40	1		
								ASXL2 c.1222C>T, p.Q408*	49	1		
								ZRSR2 c.83dup, p.K29fs	50	1		
101	91	M	APL	STAT3	c.1842C>G	p.S614R	8	SRSF2 c.284C>A, p.P95H	2	1	46,XY,t(15;17)(q22;q21)[17]/46,XY[3]	
								TP53 c.469G>T, p.V157F	2	1		

102	74	M	AML	STAT5B	c.1924A>C	p.N642H	42	FLT3 c.1817_1818ins30, p.P606_R607ins10	NR	1		
								RUNX1 c.411_412insC, p.E138fs	48	1		
								ASXL1 c.1934dup, p.G646fs	35	1		
								U2AF1 c.470A>C, p.Q157P	47	1		
								PHF6 c.767C>G, p.S256*	94	1		
								WT1 c.1143_1144ins16, p.A382fs	3	1		
103	87	F	AML	STAT5B	c.2135T>A	p.V712E	5	RUNX1 c.372dup, p.P125fs			46,XX[1]	
								IDH2 c.515G>A, p.R172K	10	1		
								CBL c.1249C>T, p.P417S	30	1		
								TET2 c.939del, p.C314fs	3	1		
								SH2B3 c.1325_1326insCCACTCCA, p.Q442fs	1	1		
									7	1		
								SH2B3 c.1585del, p.V529fs	3	1		
								PHF6 c.803T>C, p.V268A	29	2		
104	72	M	AML	STAT5B	c.1924A>C	p.N642H	65	STAT5B c.2110A>C, p.I704L	3	1		
								U2AF1 c.101C>A, p.S34Y	47	1		
								TET2 c.1147C>T, p.Q383*	96	1		
								ASXL2 c.1840C>T, p.R614*	47	1		
105	72	M	AML	STAT5B	c.1924A>C	p.N642H	24	ASXL1 c.1900_1922del, p.E635fs	28	1	46,XX[20]	
								NPM1 c.863_864insCCAG, p.W288fs	10	1		
								U2AF1 c.467G>A, p.R156H	22	1		
								GATA2 c.685dup, p.L229fs	7	1		
								KRAS c.38G>A, p.G13D	6	1		
106	85	F	MDS	STAT5B	c.1883C>G	p.T628S	4	ASXL1 c.2385del, p.W796fs	28	1	46,XX[20]	
								TET2 c.4677_4681del, p.Y1560fs	44	1		
								TET2 c.4679dup, Y1560*	41	1		
107	73	M	MDS	STAT5B	c.1994A>T	p.Y665F	9	SRSF2 c.284_307del, p.P95_R102del	38	1	46,XY[20]	Negative
								CBL c.1258C>T, p.R420*	11	1		
								CBL c.403G>T, p.E135*	7	1		
								CUX1 c.720C>G, p.N240K	7	1		
								CUX1 c.3104dup, p.L1036fs	27	1		
								GATA2 c.913C>G, p.L305V	37	2		
108	68	F	MDS	STAT5B	c.1924A>C	p.N642H	46	SRSF2 c.284C>T, p.P95L	47	1		
								ETV6 c.1037A>G, p.Y346C	2	2		
109	73	M	MDS	STAT5B	c.1924A>C	p.N642H	4	ASXL1 c.1779dup, p.C594fs	32	1		
								SRSF2 c.284C>A, p.P95H	30	1		
110	64	M	CMML	STAT5B	c.1924A>C	p.N642H	45	ASXL1 c.1934dup, p.G646fs	37	1		
								IDH2 c.419G>A, p.R140Q	45	1		
								SRSF2 c.284C>G, p.P95R	46	1		
								NRAS c.37G>T, p.G13C	27	1		
								NRAS c.190T>G, p.Y64D	3	2		
111	70	M	CMML	STAT5B	c.1924A>C	p.N642H	3	RUNX1 c.352-1G>A, p.?	48	1		
								ASXL1 c.1934dup, p.G646fs	34	1		
								SRSF2 c.284C>A, p.P95H	41	1		
								STAG2 c.819+1G>A, p.?	52	1		
								EZH2 c.2155_2156delinsC, p.R719fs	24	1		
								TET2 c.3646C>T, p.R1216*	89	1		
								NRAS c.34G>C, p.G12R	25	1		
112	83	M	CMML	STAT5B	c.1924A>C	p.N642H	3	TET2 c.3590del, p.K1197fs	43	1	46,XY[20]	
								TET2 c.5026del, p.H1676fs	36	1		
								TET2 c.5034_5035del, p.Y1679fs	15	1		
113	63	F	MDS/MPN	STAT5B	c.1994A>T	p.Y665F	12	SF3B1 c.2098A>G, p.K700E	17	1		
								CALR c.1122_1125del, p.K374fs	12	1		
								NRAS c.436G>A, p.A146T	24	1		
								TET2 c.2737C>T, p.Q913*	47	1		
								SH2B3 c.530del, p.G177fs	21	1		
114	78	F	MPN	STAT5B	c.1924A>C	p.N642H	37	JAK2 c.1849G>T, p.V617F	11	1		
								SRSF2 c.284C>G, p.P95R	45	1		
								SMC3 c.2428-2A>G, p.?	44	1		
115	66	M	MPN	STAT5B	c.1924A>C	p.N642H	17	JAK2 c.1849G>T, p.V617F	47	1		
								SRSF2 c.284C>T, p.P95L	47	1		
								FBXW7 c.1394G>A, p.R465H	16	1		
								NRAS c.35G>T, p.G12V	4	1		
								RUNX1 c.503G>A, p.G168E	40	2		
116	64	M	ET	STAT5B	c.1924A>C	p.N642H	4	JAK2 c.1849G>T, p.V617F	24	1		
								PRPF8 c.4780T>C, p.C1594R	39	2		
117	49	M	ET	STAT5B	c.1924A>C	p.N642H	3	JAK2 c.1849G>T, p.V617F	13			
118	76	M	MN, NOS	STAT5B	c.1924A>C	p.N642H	41	RUNX1 c.967+2_967+5del, p.?	1	1		
								RUNX1 c.720_730delins10; p.H242fs	1	1		
								RUNX1 c.676_677del, p.S226*	8	1		
								DNMT3A c.2711C>T, p.P904L	45	1		

119	78	M	MDS-RS-MLD	SF3B1 c.2098A>G, p.K700E	22	1	46,XY[20]	Oligo
120	73	F	MDS-EB2	ASXL1 c.1934dup, p.G646fs	32	1	46,XX,r(7)(p?22q?22)[16]	
				SRSF2 c.283C>A, p.P95T	36	1		
				STAG2 c.1044_1047dup, p.A350fs	29	1		
				STAG2 c.3205dup, p.T1069fs	3	1		
				BCOR c.616_617delinsCCCGGTG,	3	1		
				p.F206fs	9	1		
				LUC7L2 c.736C>T, p.R246*	34	2		
				TET2 c.4121G>A, p.C1374Y				
121	58	M	MDS-SLD	CALR c.1099_1150del, p.L367fs	16	1	46,XX[20]	
122	40	M	MDS-EB2	TP53 c.994-2A>G, p.?	95	2	46-50,X,-Y,der(5)t(5;15)(q13;q11.2),-9,add(9)(p12),-15,	Negative
				NRAS c.37G>C, p.G13R	14	2	add(20)(q13.3),-21,add(21)(q22),del(21)(q22),-22,+4-8mar,inc[cp14]	
				IDH2 c.531C>G, p.D177E	11	2	/94-97,sl,x2[cp5]/46,XY[1]	
123	60	M	MDS-SLD	DNMT3A c.1758C>A, p.C586*	2	1	46,XX[20]	
124	68	M	MDS-EB2	SF3B1 c.1998G>T, p.K666N	1	1	53,XY,+1,+4,del(5)(q13q33),+8,+10,+11,+14,+14[3]	
				TP53 c.329G>C, p.R110P	1	1	/54,sl,+15[cp9]/53,sl,-11,+i(11)(q10)[7]/46,XY[1]	
125	77	M	MDS-MLD	TP53 c.832C>A, p.P278T	31	1	44,XY,add(5)(q13),del(7)(q22),-12,add(16)(q24),-17,-18,-21,-22,i(22)(q10), +2r,+mar[2]/44,sl,t(3;21)(q12;p11.2),add(6)(p21),+12, add(14)(p11.2),add(15)(p11.2),-add(16)(q24),+18,+21,-22,-i(22)(q10), -r[3]/46,XY[2] * Suboptimal mitotic index	
126	80	F	MDS-EB2	DDX41 c.3G>A, p.?	45	1	46,XX[6]	
				DDX41 c.1574G>A, p.R525H	4	1		
127	67	F	MDS-SLD				46,XX,del(5)(q13q22)[2]/47,XX,+15[2]/46,XX[17]	Negative
128	55	M	T-MDS				46,XY,+1,der(1;7)(q10;p10)[11]/46,XY[9]	Negative
129	72	F	MDS-EB1	RUNX1 c.292del, p.L98fs	23	1	44,XX,add(4)(q25),-5,add(6)(q27),-10,-12,+r[1]/45-47,XX,-2,-3,add(3)(q27), del(5)(q13q33),-7,add(8)(p11.1),-12,-16,add(21)(p11.1),+r,+3-6mar[cp19]	
130	63	F	MDS-EB2	SRSF2 c.282_284delinsGCA, p.P95H	16	1	46,XX[6]	
				ASXL1 c.1934dup, p.G646fs	16	1		
				TET2 c.2502T>A, p.C834*	14	1		
				TET2 c.3781C>T, p.R1261C	13	1		
				STAG2 c.1039dup, p.C347fs	13	1		
				CEBPA c.68del, p.P23fs	2	1		
				CEBPA c.840G>T, p.K280N	9	2		
131	72	M	MDS-EB2	U2AF1 c.470A>C, p.Q157P	27	1	46,XY[20]	Negative
				TET2 c.3717del, p.L1240fs	2	1		
				TP53 c.460G>A, p.G154S	3	2		
132	69	M	AML-MRC	ASXL1 c.1934dup, p.G646fs	23	1	46,XY[20]	
				RUNX1 c.705del, p.M236*	23	1		
				SRSF2 c.284C>G, p.P95R	26	1		
				PHF6 c.117_118insAG, p.A40fs	9	1		
133	73	F	AML-MRC	RUNX1 c.485G>C, p.R162T	27	1	46,XX[15]	
				ASXL1 c.1934dup, p.G646fs	25	1		
				IDH1 c.394C>T, p.R132C	21	1		
				KRAS c.436G>C, p.A146P	4	1		
				PHF6 c.875G>A, p.C292Y	12	2		
				CBL c.1142G>C, p.C381S	2	2		
134	84	F	MDS-EB1	SRSF2 c.281_283dup, p.R94dup	41	1	46,XX[20]	
				RUNX1 c.990delinsAGCCT, p.F330fs	42	1		
				STAG2 c.775C>T, p.R259*	43	1		
				NRAS c.37G>T, p.G13C	39	1		
				NRAS c.35G>A, p.G12D	5	1		
135	75	F	MDS-MLD	ASXL1 c.1294C>T, p.Q432*	42	1	47,XX,+8[3]/46,XX[18]	Negative
				RUNX1 c.423_441dup, p.T148fs	21	1		
				DNMT3A c.1122+1G>A, p.?	47	1		
				IDH2 c.419G>A, p.R140Q	2	1		
				EZH2 c.2197T>G, p.Y733D	80	2		
136	62	M	MDS-MLD	SRSF2 c.284C>T, p.P95L	37	1	46,XY[20]	Negative
				PHF6 c.129dup, p.K44*	49	1		
				TET2 c.2746C>T, p.Q916*	73	1		
				TET2 c.1211T>A, p.L404*	2	1		

Pts, patients; Dx, diagnosis; VAF: variant allele frequency by %; Tiers: 1, pathogenic/likely pathogenic variants; 2, variant of uncertain significance (VUS); TCC, T-cell clonality; AML, acute myeloid leukemia; AML-MRC, acute myeloid leukemia with myelodysplasia related changes; MDS, myelodysplastic syndrome; T-MDS, therapy related myelodysplastic syndrome; MDS/MPN, myelodysplastic/myeloproliferative neoplasm; MPN, myeloproliferative neoplasm; ET, essential thrombocythemia, CMML, chronic myelomonocytic leukemia; AA, aplastic anemia; T-LGLL, T-cell

large granular lymphocytic leukemia; NK-LGLL, chronic NK cells leukemia; T-PLL, T-cell prolymphocytic leukemia; PTLD, post transplant lymphoproliferative disorder; PBL, plasmablastic lymphoma; B-LBL, B-lymphoblastic leukemia/lymphoma; CLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MM, multiple myeloma; DLBCL, diffuse large B cell lymphoma.

Supplemental table 4. Demographic features of hematologic neoplasm patients with pathogenic *STAT3/5B* variants.

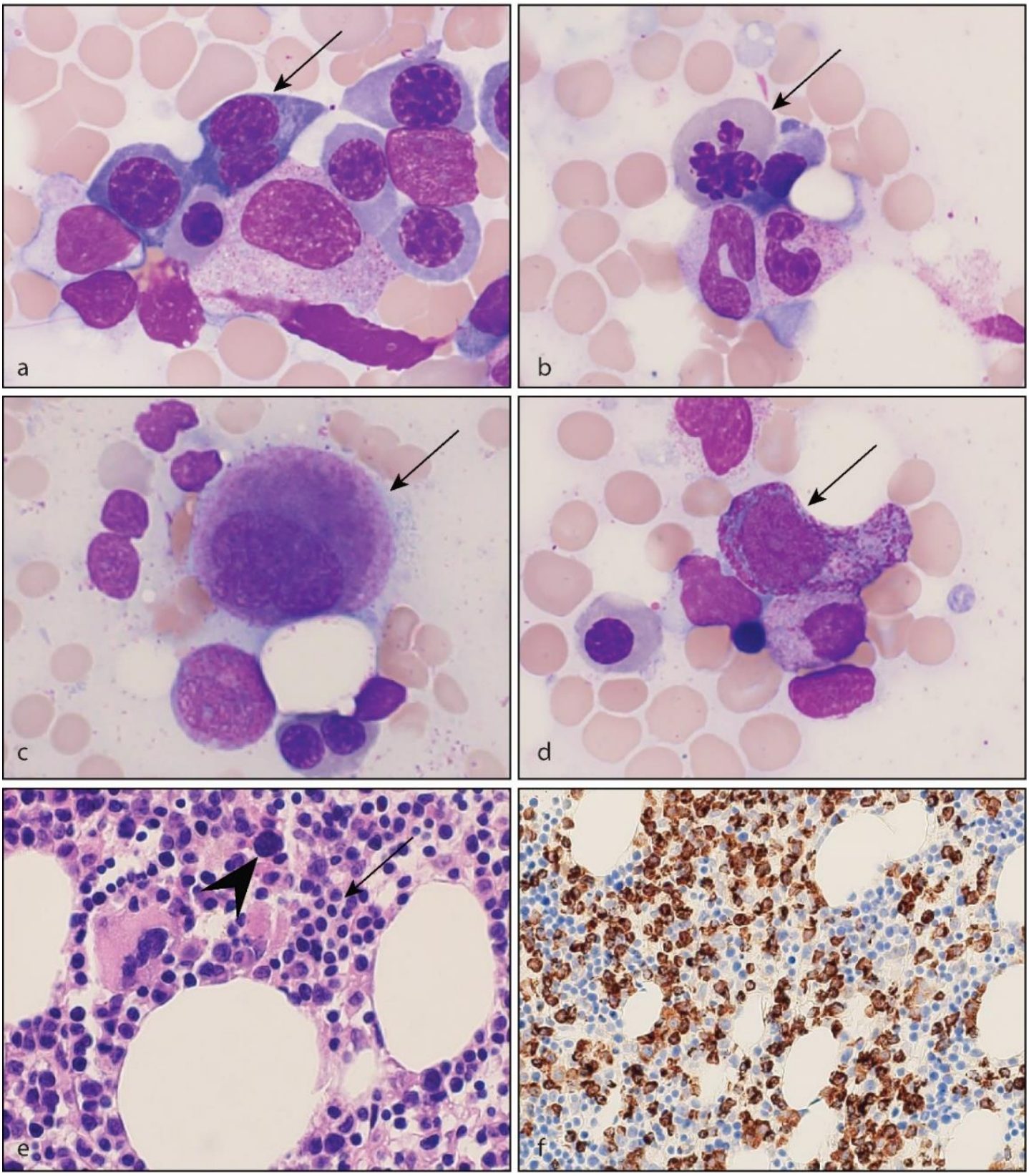
Diagnosis	T-LGLL	NK-LGLL	Other T-LPD	Other LPD	T-LGLL + MDS	MN with pathogenic *STAT3/5B*	MDS with expanded LGL[#]	Summary
Patient, n	46	9	3	8	2	50	18	135
Sex, M/F	32/14*	9/0**	3/0	7/1	2/0	26/24	10/8	88/47
Median age, Y (range)	71 (19-89)	73 (38 - 85)	54 (39-69)	61 (27-78)[@]	63 (56-70)	70 (22-91)	71 (40-84)	70 (19-91)

M, male; F, female; Y, years; * P=0.1, T-LGLL vs MN with *STAT3/5B*; ** P=0.008 NK-LGLL vs MN with *STAT3/5B*; [@], P=0.06, other LPD vs T-LGLL; [#], no *STAT3/5B* variants identified by NGS. T-LGLL, T-cell large granular lymphocytic leukemia; NK-LGLL, NK cell large granular lymphocytic leukemia or chronic lymphoproliferative disorder of NK cells; LPD, lymphoproliferative disorder; MDS, myelodysplastic syndrome; MN, myeloid neoplasm.

Supplementary Figures

Supplementary figure 1. Dysmyelopoiesis in bone marrow aspirates from patients with NK-LGLL. (a-b) Bone marrow aspirate smears from a patient with NK-LGLL showed dyserythropoiesis with nuclear membrane irregularities (arrows, 1000 X magnification). **(c)** Bone marrow aspirate smears also showed atypical megakaryocytes with small monolobulated nuclei (arrow, 1000 X magnification). **(d)** Neoplastic NK cells with coarse azurophilic granulation (arrow, 1000 X magnification) showed a sinusoidal distribution (**e**, arrow) with an atypical megakaryocyte in the background (arrowhead, H&E, 400 X magnification) **(f)** The neoplastic NK-cells were highlighted by TIA-1 immunohistochemistry (IHC, 200 X magnification).

Supplementary figure 1.



Supplementary References

1 Sandberg, Y. *et al.* BIOMED-2 multiplex immunoglobulin/T-cell receptor polymerase chain reaction protocols can reliably replace Southern blot analysis in routine clonality diagnostics. *J Mol Diagn* **7**, 495-503, doi:10.1016/S1525-1578(10)60580-6 (2005).

2 van Dongen, J. J. *et al.* Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 Concerted Action BMH4-CT98-3936. *Leukemia* **17**, 2257-2317, doi:10.1038/sj.leu.2403202 (2003).

3 Durrani, J. *et al.* Large granular lymphocytic leukemia coexists with myeloid clones and myelodysplastic syndrome. *Leukemia* **34**, 957-962, doi:10.1038/s41375-019-0601-y (2020).

4 Shi, M. *et al.* T-cell clones of uncertain significance are highly prevalent and show close resemblance to T-cell large granular lymphocytic leukemia. Implications for laboratory diagnostics. *Mod Pathol* **33**, 2046-2057, doi:10.1038/s41379-020-0568-2 (2020).

5 Ohgami, R. S. *et al.* Refining the diagnosis of T-cell large granular lymphocytic leukemia by combining distinct patterns of antigen expression with T-cell clonality studies. *Leukemia* **25**, 1439-1443, doi:10.1038/leu.2011.107 (2011).

6 O'Malley, D. P. T-cell large granular leukemia and related proliferations. *Am J Clin Pathol* **127**, 850-859, doi:10.1309/A8FHDA0VVRJ05GJP (2007).

7 Morice, W. G. *et al.* Chronic lymphoproliferative disorder of natural killer cells: a distinct entity with subtypes correlating with normal natural killer cell subsets. *Leukemia* **24**, 881-884, doi:10.1038/leu.2009.304 (2010).

8 Komrokji, R. S. *et al.* Characterization of myelodysplastic syndromes (MDS) with T-cell large granular lymphocyte proliferations (LGL). *Leukemia* **34**, 3097-3099, doi:10.1038/s41375-020-0928-4 (2020).

9 Galli, A. *et al.* Relationship between clone metrics and clinical outcome in clonal cytopenia. *Blood* **138**, 965-976, doi:10.1182/blood.2021011323 (2021).