

SUPPLEMENTAL MATERIAL

SUPPLEMENTAL FIGURE AND TABLE LEGENDS

Supplemental Figure 1. Identification of Clonal Hematopoiesis (CH) in HLH. (A) Age distribution in individuals who do not have a myeloid malignancy with and without clonal hematopoiesis in the cohort (shown are mean and S.E.M.). (B) Distribution of mutations identified in cohort. (C) Co-mutation plot depicting all mutations in which each column is a patient with clonal hematopoiesis, each row is a gene, and cells in gray reflect the presence of a mutation. (D) Frequency of CH with a VAF > 0.1 identified in HLH cohort and individuals from TOPMed cohort which utilized whole genome sequencing. Down-sampling analysis from TOPMed (Bick et al.) revealed identification of all cases of VAF > 0.1 but less than complete identification of cases with VAF > 0.02. We therefore chose a VAF > 0.1 for this analysis as our variant identification pipeline was also able to reliably detect all clones at that size.

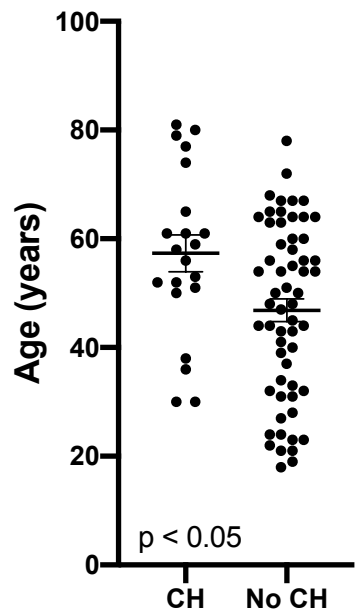
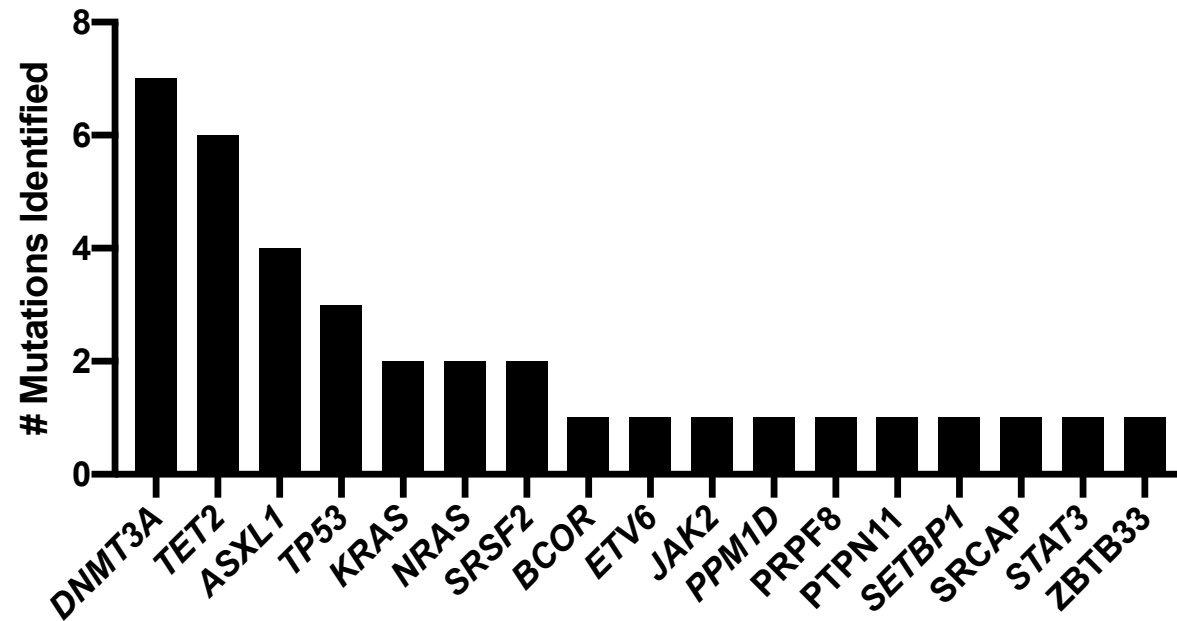
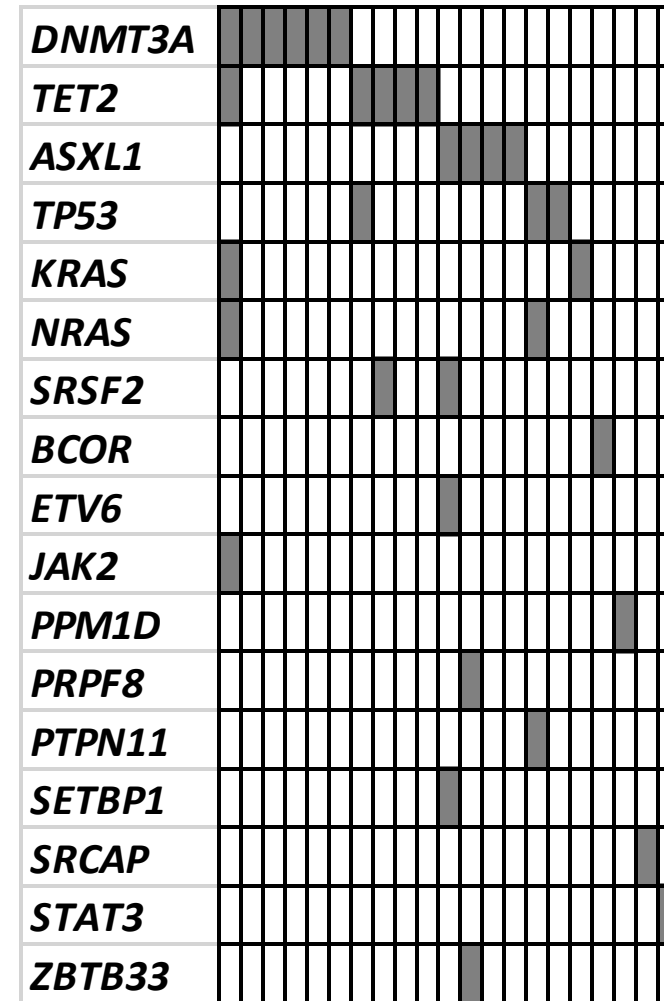
Supplemental Figure 2. Bone Marrow Derived Macrophage Response to ODN1826. (A) Log-fold change (LFC) of cytokines measured in supernatants from *Tet2*-wildtype (WT) and *Tet2*-null (*Tet2*) BMDMs 24 hours after stimulation with vehicle (PBS) or ODN1826 (ODN).

Supplemental Figure 3. Peripheral Blood and Bone Marrow Analysis of HLH Mouse Model. Peripheral blood (A) and bone marrow (B) composition in each treatment group. (C) Representative flow plot of Lin^{lo}Sca-1⁺c-Kit⁻ cell population (population gated on live, lineage low population) in *Tet2*-wild-type treated and untreated mice.

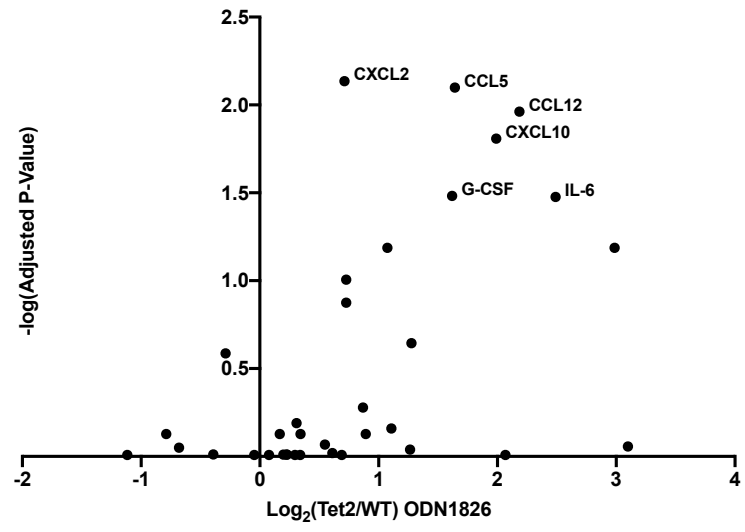
Supplemental Table 1. Genes Sequenced to Determine Presence of Clonal Hematopoiesis.

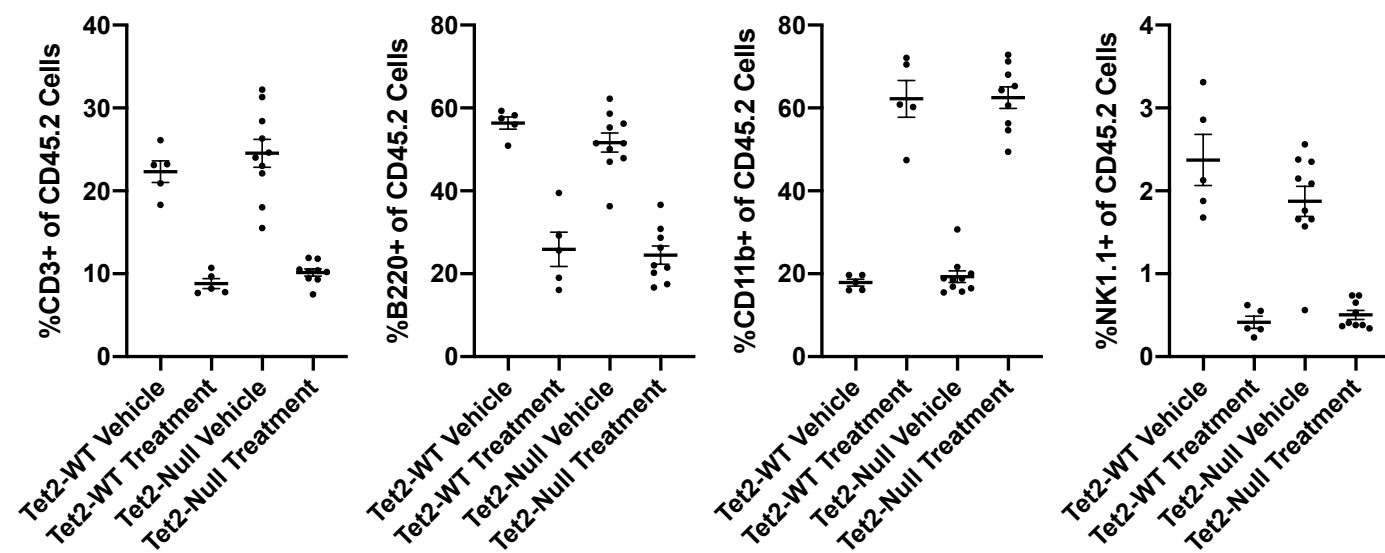
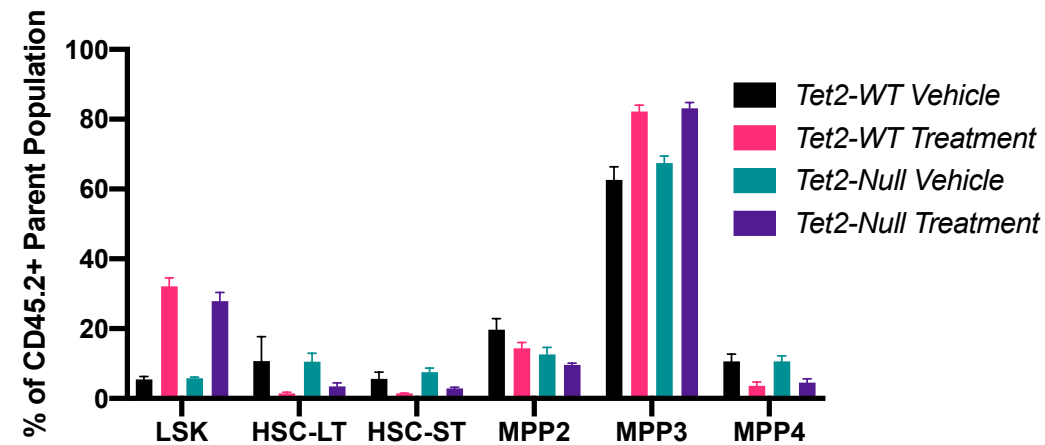
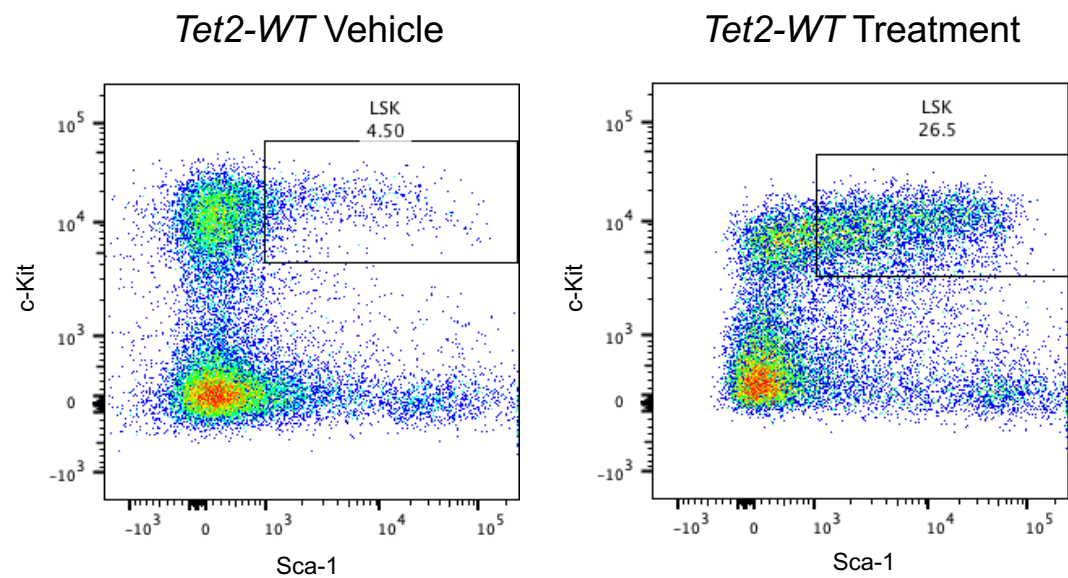
Supplemental Table 2. Clonal Hematopoietic Variants Identified in Cohort.

Supplemental Table 3. Additional Clinical Information for Cohort.

A**B****C****D**

Cohort	NGS Platform	Genes Sequenced	Frequency of CH (VAF > 0.1)		
			All	<60	>60
Adult HLH	Targeted	98	14%	9%	25%
Bick et al (2020)	Whole Genome	Whole Genome	5%	2%	9%



A**B****C**

Supplemental Table 1. Genes Sequenced to Determine Presence of Clonal Hematopoiesis.

ASXL1	CTCF	JAK2	PDS5B	SETBP1	TNFAIP3
ASXL2	CUX1	JAK3	PHF6	SETD2	TNFRSF14
ATM	DDX41	KIT	PHIP	SF1	TP53
ATRX	DNMT3A	KRAS	PIGA	SF3A1	U2AF1
B2M	EP300	LUC7L2	PIGT	SF3B1	U2AF2
BCOR	ETNK1	MIR-142	PPM1D	SH2B3	VPS45
BCORL1	ETV6	MPL	PRPF40B	SMC1A	WT1
BRAF	EZH2	MRE11A	PRPF8	SMC3	YLPM1
BRCC3	FANCL	MYC	PTEN	SRCAP	ZBTB33
CALR_E9	FLT3	MYD88	PTPN11	SRSF2	ZFHX3
CBL	GATA1	MYH9	PTPRF	STAG1	ZNF318
CBLB	GATA2	NF1	RAD21	STAG2	ZRSR2
CEBPA	GNAS	NOTCH1	RASGRF1	STAT3	
CREBBP	GNB1	NOTCH2	RIT1	STAT5B	
CSF1R	IDH1	NPM1	RPL11	TERC	
CSF3R	IDH2	NRAS	RPS7	TERT	
CSNK1A1	IKZF1	NXF1	RUNX1	TET2	

Supplemental Table 2. Clonal Hematopoietic Variants Identified in Cohort.

chrom	pos_start	pos_end	ref	var	gene	cdna	aa	result	reads1	reads2	var_freq
20	31022441	31022441	-	G	ASXL1	c.1927dupG	p.G642fs	frameshift insertion	1019	77	0.0692
20	31023008	31023011	0	-	ASXL1	c.2493_2496del	p.L831fs	frameshift deletion	1011	36	0.0344
20	31021211	31021211	C	T	ASXL1	c.C1210T	p.R404X	stopgain	540	207	0.2756
20	31022837	31022837	A	-	ASXL1	c.2322delA	p.R774fs	frameshift deletion	333	285	0.4553
X	39934363	39934363	C	-	BCOR	c.236delG	p.R79fs	frameshift deletion	480	18	0.0361
2	25467083	25467083	G	A	DNMT3A	c.C1792T	p.R598X	stopgain	545	545	0.5
2	25457243	25457243	G	A	DNMT3A	c.C2644T	p.R882C	nonsynonymous SNV	771	16	0.0203
2	25463290	25463290	A	C	DNMT3A	c.T2203G	p.Y735D	nonsynonymous SNV	888	18	0.02
2	25470582	25470582	C	A	DNMT3A	c.G892T	p.G298W	nonsynonymous SNV	306	8	0.0255
2	25466800	25466800	G	A	DNMT3A	c.C1903T	p.R635W	nonsynonymous SNV	235	37	0.136
2	25467117	25467117	G	T	DNMT3A	c.C1758A	p.C586X	stopgain	829	41	0.047
2	25463182	25463182	G	A	DNMT3A	c.C2311T	p.R771X	stopgain	265	206	0.4364
12	12006399	12006399	C	T	ETV6	c.C367T	p.Q123X	stopgain	322	258	0.4441
9	5073770	5073770	G	T	JAK2	c.G1849T	p.V617F	nonsynonymous SNV	686	46	0.0628
12	25398285	25398285	C	T	KRAS	c.G34A	p.G12S	nonsynonymous SNV	726	56	0.0714
12	25368410	25368410	C	T	KRAS	c.G535A	p.G179S	nonsynonymous SNV	263	201	0.4332
1	1.15E+08	115256528	T	G	NRAS	c.A183C	p.Q61H	nonsynonymous SNV	918	24	0.0255
1	1.15E+08	115258747	C	T	NRAS	c.G35A	p.G12D	nonsynonymous SNV	855	19	0.0217
17	58740897	58740900	0	-	PPM1D	c.1802_1805del	p.T601fs	frameshift deletion	330	250	0.431
17	1576446	1576446	C	A	PRPF8	c.G3703T	p.E1235X	stopgain	625	14	0.0219
12	1.13E+08	112940059	G	C	PTPN11	c.G1711C	p.E571Q	nonsynonymous SNV	505	95	0.1581
18	42531907	42531907	G	A	SETBP1	c.G2602A	p.D868N	nonsynonymous SNV	185	137	0.4241
16	30732137	30732137	G	T	SRCAP	c.G3091T	p.E1031X	stopgain	583	12	0.0202
17	74732959	74732959	G	A	SRSF2	c.C284T	p.P95L	nonsynonymous SNV	197	155	0.4391
17	74732959	74732959	G	A	SRSF2	c.C284T	p.P95L	nonsynonymous SNV	418	24	0.0543
17	40474482	40474482	T	A	STAT3	c.A1919T	p.Y640F	nonsynonymous SNV	564	12	0.0208
4	1.06E+08	106157649	T	-	TET2	c.2550delT	p.H850fs	frameshift deletion	959	51	0.0503
4	1.06E+08	106155982	-	C	TET2	c.884dupC	p.A295fs	frameshift insertion	662	482	0.4141
4	1.06E+08	106157012	T	-	TET2	c.1913delT	p.M638fs	frameshift deletion	492	384	0.4262
4	1.06E+08	106180774	A	T	TET2	c.3804-2A>T		splicing	507	417	0.4513
4	1.06E+08	106193728	C	T	TET2	c.C4190T	p.T1397I	nonsynonymous SNV	838	26	0.0301
4	1.06E+08	106155938	-	T	TET2	c.840dupT	p.S280fs	frameshift insertion	775	148	0.1591
17	7578524	7578524	G	A	TP53	c.C406T	p.Q136X	stopgain	505	112	0.1815
17	7577539	7577539	G	A	TP53	c.C742T	p.R248W	nonsynonymous SNV	226	568	0.7154
17	7578268	7578268	A	C	TP53	c.T581G	p.L194R	nonsynonymous SNV	704	57	0.0749
X	1.19E+08	119388018	C	A	ZBTB33	c.C748A	p.P250T	nonsynonymous SNV	264	7	0.0258

Supplemental Table 3. Additional Clinical Information for Cohort.

	All (N=80)	CH (N=21)	No CH (N=59)
Malignancy	35	12	23
Hematologic Malignancy	35	12	23
T-Cell	11	4	7
B-Cell	24	8	16
Plasma Cell	1	1	0
Solid Organ Malignancy	3	1	2
Autoimmune Disease			
Immune Thrombocytopenia Purpura	2	1	1
Juvenile Idiopathic Arthritis	2	0	2
Systemic Lupus Erythematosus	2	0	2
Adult-Onset Still's Disease	2	0	2
Autoimmune Hemolytic Anemia	1	0	1
Autoimmune Lymphoproliferative Syndrome	1	1	0
Autoimmune Thyroiditis	1	0	1
Crohn's	1	1	0
Juvenile Rheumatoid Arthritis	1	1	0
Mixed Connective Tissue Disease	1	0	1
Rheumatoid Arthritis	1	0	1
Infection			
EBV	16	4	12
CMV	5	1	4
Babesia	1	0	1
HBV	1	0	1
HIV	1	0	1
VZV	1	0	1