Supplementary Methods

Sanger sequencing

Genomic DNA was used as input for PCR amplification with MyTaq HS Red (Bioline). Amplicons were then treated with ExoSAP-IT Express (Thermo Fisher) and submitted for sequencing (Eurofins USA). The naming convention for each primer is the sample ID, followed by the mutation that is targeted by the amplicon. We used the reverse PCR primer as sequencing primer for 1909, and the forward PCR primer for all others.

PCR Conditions

Temperature	Time	Stage
98	3 minutes	denature
94	20 seconds	amplification
60	15 seconds	(x36)
72	30 seconds	
72	1 minute	extension
4	infinity	hold

Primer list (5'-3')

1506_1916DEL_F	GTCAGACAGCGAGCAGAGCTTT
1506_1916DEL_R	AAGTGGGCTCTGAAGTTTCATGT
1511_1106FS_F	GGGCCAGTCACAGTTTTGACTA
1511_1106FS_R	CTTTACAAATTGCTGCCAGACTCA
1511_splice_F	TTTGCTCTATTTTGTGTCATTCCATTTTGT
1511_splice_R	GCAGTGTGAGAACAGACTCAACAG
1644_1342FS_F	TGCAAAATATCTGCATGCAGTTAGAAAATC
1644_1342FS_R	CAAGTAAGTTGTTACAATTGCTGCCAA
1644_719FS_F	CCAAGGTACAGTGGACCAACAT
1644_719FS_R	AGGGAGATGTGAACTCTGGGAT
1870_1872ARG_F	CTTACACAAATTAAGTGATGCTAATGGTCA
1870_1872ARG_R	ACATAGTCTGGGCCATACTTTTCAC
1909_1633TER_F	ACCCTGGGCTTTTGAATCAGAAT
1909_1633TER_R	CATGAAGTGGCCATCCATCTCA
1967_1013FS_F	CTCTTACAGAAGCAAGAACAGCAGCAAAC
1967_1013FS_R	GGTGTGGCTATCAAGTTCTGCA
1967_1268TER_F	GCTGCAAGTGACCCTTGTTTTG
1967_1268TER_R	TGTAAAAGTGCACGCTGAACTCT

Reduced Representation Bisulfite Sequencing

RRBS samples were prepared using 100 nanograms of DNA extracted from each WGS NK-LGL sample and normal NK cell controls enriched by negative selection (Miltenyi Biotec). RRBS libraries were prepared from extracted DNA (AnaPrep, BioChain Institute) according to the directions of the Ovation RRBS kit (NuGEN). Libraries were quantified with a droplet digital PCR assay from Illumina on the QX200 instrument (Bio-Rad). RRBS libraries were pooled and sequenced using a single 80 base pair reads approach on a NextSeq 500 (Illumina). RRBS data was aligned using Bismark.[1] An average coverage for RRBS regions of 17-25X was achieved. After removing SNP-enriched sites, outliers, sites on sex chromosomes, and sites with low coverage, 2,646,527 sites were retained for analysis. Only CpG locations that were covered to a depth of at least ten reads in each sample were retained for analysis.

High variance CpGs were determined by implementing inter quartile range (IQR) for each cytosine (CpG) across all the samples and calculated using the “iqr” function in R(version 3.6.3). CpGs in the 90th percentile of all the IQRs are annotated as “highvariance CpGs.” Principal component analysis on the highvariance CpGs was performed using the “prcomp” function in R. The scores were determined for principal component 1 (PC1) and principal component 2 (PC2). Highvariance CpGs were annotated to the promoter regions of genes annotated in the hg19 assembly (Genocode v19) . The promoter region for a given gene was defined as transcription start site (TSS) +/- 500 bp. The % CpG methylation of CpGs in the promoter regions were visualized using the “heatmap” function in the “Complex Heatmap” package in R.

Differentially methylated cytosines between *TET2* mutant or WT NK-LGL samples and normal controls were identified using the Methylkit (v1.10.0) package.[2] The following parameters were used to run methylkit: assembly = “hg19” , context = CpG , min.per.group = 2, lo.count = 10, lo.perc = NULL, hi.count = 500, hi.perc = NULL. The other parameters were kept at default values. CpGs with an absolute methylation difference of at least 20% at a statistical significance (q-value) less than 0.05 were denoted as differentially methylated sites (DMCs).

Differentially methylated regions between *TET2* mutant or WT NK-LGL samples and normals was identified using the Edmr (v 0.6.4.1) package.[3] The input for the edmr package is the “myDiff” object generated from the methylkit tool. The following parameters were used to calculate the background regions and differentially methylated regions: Background regions: DMC.qvalue = 1, DMC.methdiff = 0, num.DMCs = 0, num.CpGs = 3, DMR.methdiff = 0, mode = 2, ACF = T, fuzzypval = 1. Differentially methylated regions (DMRs): DMC.qvalue = 0.01, DMC.methdiff = 25, num.DMCs = 3, plot = FALSE, mode = 2, ACF = TRUE. Further, differentially methylated regions were filtered for an absolute methylation difference of greater than 25 at a statistical significance (qvalue) less than 0.05 are annotated as differentially methylated regions.

Pathway Analysis of DMRs using GREAT: differentially methylated regions unique to *TET2* mutant when compared to WT were annotated as “hyper DMRs” and “hypo DMRs” based on positive or negative change in the methylation, respectively. These unique regions were used to identify enriched pathways using GREAT[4] with the following parameters: Basal plus extension, Proximal 5kb upstream, 1kb downstream plus distal up to 1000 kb. Pathways enriched at a q-value of less than 0.05 were used to understand the regulatory mechanisms associated with DNA methylation changes.

Visualization plots in Figure 4 and Supplemental Figure 6 were generated with Methylation plotter.[5]

Methylation-specific PCR

Genomic DNA was isolated using an Anaprep DNA Extraction Kit (Biochain) and bisulfite converted using an EZ DNA Methylation-Gold Kit (Zymo) according to the manufacturer's protocol. A universal methylated human DNA standard (Zymo) was used as a positive control. The methylation status was determined by PCR as previously described for TET2[6] and PTPRD.[7] The PCR mixture contained 12.5 uL of MyTaq HS Red Mix (Meridian Bioscience), 1 uL of purified bisulfite-converted DNA, 2.5 uL ddH2O, and 2 uL of each of the forward and reverse primers (5 uM) to a final reaction volume of 20 uL. The cycling parameters were an initial denaturation step of 95°C for 10 min; 39 cycles of denaturation at 95°C for 30 s, annealing for 30 s (62°C for TET2; 63°C for PTPRD), and extension at 72°C for 60 s, with a final extension step at 72°C for 7 min. PCR products were analyzed by agarose gel electrophoresis with imaging and quantification using BioRad Image Lab software. Methylated bands were scored as yes in the TET2 assay if they were >average+1.45 standard deviations of the normal NK sample methylated band. Methylated bands were scored as yes in the PTPRD assay if they were >average+2 standard deviations of the normal NK sample methylated band.

Supplemental Table 1

Patients are listed in order of ID number in panels A, B, and C, with mutation status included in each panel. Panel D presents the patients by mutation group. **A** includes demographics and CBC data. CBC parameters for each patient were retrieved as close as possible to the sequencing date, when mutations were assessed. Of the 58, n=43 had an exact date match, n=8 were <6 months from sequencing, n=4 were <12 months from sequencing, and n=3 were >12 months from sequencing. **B** provides information about treatment status, treatments attempted, diagnosis to sequencing sample, time to treatment, survival to 60 months, concomitant disorders, and other data. Treatment status for both sequencing sample and CBC sample match, regardless of the 15 patients who do not have matching CBC sample dates. **C** provides peripheral blood flow cytometry data for relevant NK cell markers and bone marrow results, if available. **D** shows data for immunosuppressive treatment and response. Patients who received treatment for LGL leukemia, not a concomitant disorder, are listed in this table. Patients are marked according to response; non-evaluable indicates the patient took treatment for LGL leukemia symptoms other than cytopenias.

Supplemental Table 1A: Patient Mutation, Demographics, and CBC Data

MPV = mean platelet volume, RBC = red blood cell count, HCT = hematocrit, HGB = hemoglobin, WBC = white blood cell, MCV = mean corpuscular volume, RDW = red blood cell distribution width,

ANC = absolute neutrophil count, ALC = absolute lymphocyte count, *= mutation validated in CD94+/CD94- Sanger, 90+ = patient > 90 years of age, # = 1870 CBC values excluded from statistics (genetic β thalassemia)

Patient ID	Mutations in STAT3, TET2, TFNAIP3, PI3KCD, PIK3AP1	Sex	Age	WBC (k/μL)	ALC (k/μL)	ANC (k/μL)	RBC (10^6/μL)	HGB (g/dL)	HCT (%)	RDW (%)	MCV (fL)	MPV (fL)	Platelets (k/μL)
1001	STAT3 D661Y (38%) TET2 G1184D (9%) TET2 Q1445L (5%)	M	76	9.5	4.8	1.5	3.4	11.0	32.1		93.3		396.0
1002		F	53	7.3	5.0	1.9	4.4	11.8	35.9	18.0	82.0	7.0	208.0
1059		M	74	10.3	4.4	4.7	4.6	14.6	43.7	13.5	94.8		207.0
1061	STAT3 S614R (13%)	M	79	6.3	3.0	2.4	3.7	12.6	37.4	14.4	101.6	7.6	257.0
1086		F	69	14.1	1.5	12.1	4.2	12.8	37.9	13.3	90.2		321.0
1092		F	46	14.6	10.1	3.2	4.3	12.8	40.1	13.1	94.4	9.5	217.0
1104	STAT3 Y640F (47%)	M	83	11.1	8.1	2.7	4.0	12.3	35.6	14.8	89.0		130.0
1133		M	75	18.5	15.3	2.4		14.9	44.7				331.0
1139		F	56	10.5	8.7	0.5	3.8	12.4	37.0	15.5	98.7	10.9	331.0
1140		F	54	16.6	13.3	3.2	4.3	13.5	39.2	13.8	91.6	6.8	329.0
1166	TET2 T1251fs (43%)	M	40	11.9	3.5	6.7	5.7	15.5	44.5		77.5		136.0
1257	STAT3 E286del (23%) TET2 G1860E (25%) PIK3CD E1021K (23%)	M	79	8.8	5.9	2.0	4.5	13.1	39.2	14.6	86.9	8.7	196.0
1289	STAT3 D661Y (42%)	M	74	6.0	4.5	1.0	2.5	9.5	28.0	21.6	113.8	10.2	181.0
1340	STAT3 I659L (4%)	F	59	2.0	0.6	1.2	4.1	12.3	37.3	16.3	91.0		9.0
1362	TNFAIP3 Y443fs (7%)	M	38	21.4	14.6	6.0	5.3	15.9	45.8	13.4	86.7	9.4	241.0
1376		M	50	15.8	9.4	4.5	5.2	15.6	46.1	16.4	88.8	8.1	444.0
1429	TET2 R1134fs (33%) TET2 R550Tter (40%)	M	80	34.1	4.1	16.4	4.0	14.2	42.2	14.1	105.8	11.6	122.0
1444	STAT3 D661I (39%) TET2 Q1523ter (41%) TET2 F1104fs (42%) TET2 Q897fs (5%) TNFAIP3 N340fs (37%)	M	77	9.0	4.1	3.1	3.9	12.7	38.2	15.7	97.4	11.2	123.0
1483	STAT3 G618R (30%)	M	63	4.3	1.9	1.8	3.7	11.4	32.9	23.4	89.6	8.9	239.0
1489	STAT3 G618R (32%)	M	48	6.8	5.5	0.8	3.5	11.7	32.8	17.4	93.2	9.1	332.0
1498		M	65	13.9	2.4	10.8	4.7	15.3	44.9	14.0	95.3	11.5	224.0
1506	TET2 L1916del (29%)* TNFAIP3 Q241fs (5%)	F	63	12.6	8.3	3.5	4.6	13.1	38.4	12.8	84.4	11.2	229.0
1507	STAT3 D661Y (32%) TET2 Q764fs (33%)	M	62	10.7	7.2	2.2	3.8	12.3	38.0	18.7	99.7	10.4	478.0
1511	STAT3 N647I (48%) TET2 E1106fs (11%)* TET2 splice (15%)*	M	77	6.2	4.4	0.8	3.6	11.4	33.8	17.5	94.7	5.3	218.0
1528		M	40	5.4	3.2	1.6		12.2	34.4				61.0
1556		F	68	4.7	1.5	2.7	3.6	12.0	34.9	13.5	98.0	9.0	171.0
1573		F	74	10.8	1.7	8.3	2.3	8.2	24.4	25.9	104.3	9.6	550.0
1586		F	77	9.4	7.5	1.3	4.7	14.5	41.2	13.6	88.0	10.2	252.0
1591	TNFAIP3 S266fs (10%)	F	34	6.5	3.3	2.4	4.6	13.2	38.4	10.2	84.4	6.7	238.0
1612	TET2 C1271fs (28%)	F	68	7.2	6.0	0.8	3.0	10.1	30.0	21.8	100.0		87.0
1644	TET2 L719fs (28%)* TET2 P1342fs (28%)*	M	66	3.5	2.1	0.70	3.3	11.2	34.0	15.5	102.0	8.9	74.0
1724		M	53	7.2	3.7	2.4	4.0	13.7	39.2	14.3	97.8	9.8	191.0
1760	STAT3 D661V (37%)	M	62	10.0	6.8	2.3	4.6	13.7	40.2	14.7	87.4	10.1	228.0
1768		M	63	6.1	2.7	2.8	5.1	15.2	44.0	13.2	85.8	9.6	180.0
1791	STAT3 K658R (43%)	F	58	24.9	19.9	3.7	2.8	10.1	30.9	18.8	109.2	9.4	681.0
1794	STAT3 D661Y (34%)	M	90+	10.5	6.4	3.7	3.5	9.3	27.8	19.7	80.6	10.0	195.0
1818	STAT3 N647I (14%)	M	75	4.4	2.2	1.6	3.9	12.8	37.0	15.6	94.6		172.0
1820	TET2 R1452ter (22%) PIK3CD E81K (13%)	M	68	9.2	3.0	5.4	4.6	13.1	38.0	12.4	84.0	11.8	141.0
1823		M	7	14.2	8.8	4.7	5.7	13.8		16.0	73.0		
1856	Global CNV	F	51	10.3	7.4	2.4	4.6	14.1	41.0	12.3	88.7	9.4	219.0
1862	TNFAIP3 Q379ter (46%) TNFAIP3 M433fs (44%)	M	62	8.1	0.4	0.6	3.6	9.7	29.9	19.7	82.6		40.0
1866	PIK3AP1 S718N (28%) Global CNV	F	72	5.4	3.7	1.1	3.6	11.8	35.1	15.3	98.3	9.5	254.0
1870#	TET2 L1872R (12%)	*M*	*47*	*3.7*	*2.3*	*1.1*	*3.2*	*8.6*	*27.6*	*16.7*	*85.7*	*8.8*	*175.0*
1882		M	63	3.5	2.8	0.6	2.6	7.2	21.8	20.7	84.2	9.0	47.0
1909	STAT3 S614R (28%) TET2 C1633ter (29%)*	M	54	4.4	2.7	1.4	2.8	7.9	23.9	26.2	84.2	10.3	413.0
1928		M	64	2.2	0.7	1.3	4.5	13.2	40.5	15.7	89.2	8.6	177.0
1967	STAT3 S614R (12%) TET2 E1268ter (43%)* TET2 P1013fs (38%)*	M	64	8.0	6.2	1.3	3.0	9.2	29.3		98.3		190.0
1978		M	34	14.6	8.7	1.5	4.3	12.3	36.8	16.1	86.0		212.0
1984		F	63	6.4	4.3	1.4	4.0	11.9	35.1	13.3	87.5		182.0
2003	STAT3 Y640F (43%)	M	21	7.2	6.0	0.7	4.7	12.7	38.9	16.2	83.3	9.7	125.0
2010	TET2 Q720ter (14%)	F	73	3.4	2.3	0.8	2.5	8.4	26.3	19.0	105.6	9.2	165.0
2011		M	25	3.9	3.2	0.3	3.6	10.7	33.3	20.3	93.0	8.9	178.0
2012	STAT3 D661Y (36%)	M	71	6.4	3.2	1.6	2.6	9.1	26.6	16.5	101.5	9.6	223.0
2069	TET2 R814fs (4%)	M	83	4.9	0.9	2.9	4.0	11.8	36.2	13.7	90.5	10.5	148.0
2079		M	65	6.3	1.1	4.3	4.5	14.5	42.0	14.6	94.4	12.0	156.0
2099		F	78	1.8	1.2	0.5	2.7	8.7	26.4	17.2	99.2	9.7	171.0
2104		F	75	4.0	1.3	2.1	4.5	13.9	42.0	13.0	94.2	9.5	258.0
2112	TNFAIP3 C200fs (8%) TNFAIP3 V209_S211 delinsA (8%)	F	69	8.0	3.4	4.0	4.9	14.5	42.1	12.8	86.4	8.8	284.0

Supplemental Table 1B: Patient Mutation, Treatment, Survival, and Misc. Data

MTX = methotrexate, Pred. = prednisone, CP = cyclophosphamide, CsA = Cyclosporine A, transf dep = transfusion dependent, EPO=erythropoeitin, Tx=treatment, Dx=diagnosis, mos=months, * = mutation validated in CD94+/CD94- Sanger

Patient ID	Sample types	Sequencing type	Mutations in STAT3, TET2, TFNAIP3, PI3KCD, PIK3AP1	Immuno Tx at sequencing?	All Tx Attempted	Diagnosis→ sequencing (mos)	Diagnosis→1st LGLL Tx (mos)	Tx needed by 60 mos post-dx?	Survival to 60 mos?	Concomitant disorders	Other
1001	PBMC	gene panel	STAT3 D661Y (38%) TET2 G1184D (9%) TET2 Q1445L (5%)	No (transf dep)	Pred.; MTX; CsA; EPO	13	0	Yes	Yes	Telangiectasia	
1002	PBMC	gene panel		No (transf dep)	CP; CsA; EPO; Alemtuzumab	9	1	Yes	Yes	Hashimoto's thyroiditis; DLBCL (in remission)	
1059	PBMC/Saliva	gene panel		No	Never	109	Never	No	Yes	Ogilvie syndrome	
1061	PBMC	gene panel	STAT3 S614R (13%)	No	Never	52	Never	No	Yes	Psoriasis; Splenectomy	
1086	PBMC	gene panel		Pred.	MTX (for rheumatoid arthritis)	105	123	No	Yes	Polymyalgia rheumatica; necrotizing vasculitis with thrombosis	
1092	PBMC/Saliva	gene panel		No	Never	47	Never	No	Yes		
1104	PBMC/Saliva	gene panel	STAT3 Y640F (47%)	No	Never	182	Never	No	Yes	Raynaud's syndrome	
1133	PBMC	gene panel		No	Rituximab (tx not related to LGLL)	18	Never	No	Yes	Marginal zone lymphoma	
1139	PBMC	gene panel		No	Unknown	4	Unknown	Unknown	Lost to follow-up	Splenectomy; Hodgkin's disease (in remission); Pulmonary fibrosis	
1140	PBMC	gene panel		No	Never	12	Never	No	Yes		
1166	PBMC	gene panel	TET2 T1251fs (43%)	Pred.	CP	0	0	Yes	Lost to follow-up	Neuropathy; Skin rash	
1257	PBMC/Saliva	gene panel	STAT3 E286del (23%) TET2 G1860E (25%) PIK3CD E1021K (23%)	No	Never	178	Never	No	Yes	Carcinoid tumor of appendix	
1289	PBMC	gene panel	STAT3 D661Y (42%)	No	MTX; Pred.	2	2	Yes	Yes	Anemia; Neutropenia	
1340	PBMC	gene panel	STAT3 I659L (4%)	Pred.	CP	2	0	Yes	No	Thrombocytopenia	
1362	PBMC/Saliva	gene panel	TNFAIP3 Y443fs (7%)	No	CP, Pred	1	3	Yes	Yes		
1376	PBMC	gene panel		No	Never (up to 42 mos follow-up)	42	Unknown	Unknown	Lost to follow-up	Neuropathy	
1429	PBMC	gene panel	TET2 R1134fs (33%) TET2 R550Tter (40%)	No (Filgrastim)	Only Filgrastim known (up to 41 mos follow-up)	41	Unknown	Unknown	Yes		
1444	Enriched NK/Saliva	whole genome, gene panel	STAT3 D661I (39%) TET2 Q1523ter (41%) TET2 F1104fs (42%) TET2 Q897fs (5%) TNFAIP3 N340fs (37%)	No	CP; Pred.	59	0	Yes	Yes	AIHA	
1483	PBMC/Saliva	gene panel	STAT3 G618R (30%)	No (transf dep)	CP; Procrit; EPO; Filgrastim	2	3	Yes	Yes	Transfusion dependent anemia secondary to hemolytic anemia; Neutropenia	
1489	PBMC/Saliva	gene panel	STAT3 G618R (32%)	No	CP; Pred.	9	1	Yes	Lost to follow-up	Type 1 Diabetes; Anemia; Neutropenia; IgA-kappa monoclonal gammopathy	
1498	PBMC/Saliva	gene panel		No	CP;	0	<6	Yes	Yes	Neuropathy	
1506	PBMC	gene panel	TET2 L1916del (29%)* TNFAIP3 Q241fs (5%)	No	Never	6	Never	No	Yes		
1507	PBMC	gene panel	STAT3 D661Y (32%) TET2 Q764fs (33%)	No	CP; Pred.	0	7	Yes	Yes	Anemia; Splenectomy	
1511	Enriched NK/Saliva	whole genome, gene panel	STAT3 N647I (48%) TET2 E1106fs (11%)* TET2 splice (15%)*	No	Never	75	Never	No	Yes	Diabetes, iron deficiency	
1528	PBMC	gene panel		No	Never (up to 18 mos follow-up)	18	Unknown	Unknown	Lost to follow-up		
1556	PBMC	gene panel		Etanercept	MTX (for rheumatoid arthritis)	0	Unknown	Unknown	Lost to follow-up	Rheumatoid arthritis; Type 2 diabetes; psoriasis	
1573	PBMC	gene panel		Pred.	MTX; CP; transf dep.	7	4	Yes	No	Transfusion dependent hemolytic anemia; Hereditary Spherocytosis; Splenectomy	
1586	PBMC	gene panel		No	Unknown	0	Unknown	Unknown	Lost to follow-up		
1591	PBMC	gene panel	TNFAIP3 S266fs (10%)	No	Never (up to 39 mos follow-up)	39	Unknown	Unknown	Yes	Psoriasis	
1612	PBMC	gene panel	TET2 C1271fs (28%)	No (transf dep)	MTX; CP; Cladribine; Alemtuzumab	82	2	Yes	Yes	Transfusion dependent hemolytic anemia; fibromyalgia	T to NK switch
1644	PBMC	gene panel	TET2 L719fs (28%)* TET2 P1342fs (28%)*	MTX; Pred.	CP; Pegfilgrastim	1	0	Yes	No	Mouth sore	
1724	PBMC/Saliva	gene panel		MTX	CP; Pred.	51	1	Yes	Yes	Neuropathy; livedo reticularis	
1760	PBMC/Saliva	gene panel	STAT3 D661V (37%)	No	MTX	87	69	No	Yes	Neuropathy; Skin rash	
1768	PBMC/Saliva	gene panel		No	Never	21	Never	No	Yes		
1791	PBMC/Saliva	whole genome, gene panel	STAT3 K658R (43%)	Pred.	only Pred. (one-time tx notrelated to LGLL)	2	Never	No	Yes	Splenectomy	
1794	PBMC	gene panel	STAT3 D661Y (34%)	No	Never	1	Never	No	No	Hairy cell leukemia (in remission)	
1818	PBMC/Saliva	gene panel	STAT3 N647I (14%)	MTX	only MTX	44	11	Yes	Yes		
1820	Enriched NK/Saliva	whole genome	TET2 R1452ter (22%) PIK3CD E81K (13%)	No	Never	42	Never	No	Yes	Pruritis	
1823	PBMC GP	gene panel		No	Never (up to 36 mos follow-up)	36	Unknown	Unknown	Yes		
1856	PBMC/Saliva	whole genome, gene panel	Global CNV	No	Pred.; MTX	2	61	No	Yes		
1862	PBMC/Saliva	whole genome, gene panel	TNFAIP3 Q379ter (46%) TNFAIP3 M433fs (44%)	Pred.	CP; CsA; MTX	11	3	Yes	No	Intention tremor; Erythematous rash; Psoriasis	
1866	Enriched NK/Saliva	whole genome	PIK3AP1 S718N (28%) Global CNV	Pred.	MTX	0	0	Yes	Yes	Mouth sores	
1870	PBMC/Saliva	gene panel	TET2 L1872R (12%)	CsA; Pred.	CP; MTX	75	49	Yes	Yes	Beta thalassemia; Pure red cell aplasia	
1882	PBMC/Saliva	gene panel		Pred. (transf dep)	MTX	23	<12	Yes	Lost to follow-up	Paranoid schizophrenia	
1909	PBMC/Saliva	gene panel	STAT3 S614R (28%) TET2 C1633ter (29%)*	Pred. (transf dep)	CP; Pred.; Rituximab	1	1	Yes	Yes	Transfusion dependent anemia secondary to coombs negative hemolysis	
1928	PBMC/Saliva	gene panel		No	Pred.; Filgrastim, CsA; MTX (for rheumatoid arthritis)	46	<26	No	Yes	Rheumatoid arthritis	
1967	PBMC/Saliva	gene panel	STAT3 S614R (12%) TET2 E1268ter (43%)* TET2 P1013fs (38%)*	Pred.	CP	0	0	Yes	Lost to follow-up		
1978	PBMC/Saliva	gene panel		No	Never (up to 9 mos follow-up)	1	Unknown	Unknown	Lost to follow-up	Hemochromatosis	
1984	PBMC/Saliva	gene panel		No	Never (up to 26 mos follow-up)	3	Unknown	Unknown	Lost to follow-up	Sjogren's disease; neuropathy	
2003	PBMC/Saliva	gene panel	STAT3 Y640F (43%)	CP	Pred.	16	0	Yes	Yes		EBV nuclear antibody positive
2010	PBMC/Saliva	gene panel	TET2 Q720ter (14%)	CP	Pred.	2	0	Yes	Not yet achieved	Insulin dependent diabetes	
2011	PBMC/Saliva	gene panel		MTX	Pred.	10	2	Yes	Yes	Periventricular leukomalacia; complex partial seizures	
2012	PBMC/Saliva	gene panel	STAT3 D661Y (36%)	No	CP	1	3	Yes	Not yet achieved		
2069	PBMC/Saliva	gene panel	TET2 R814fs (4%)	No	CP; Pred.	18	6	Yes	Not yet achieved		
2079	PBMC/Saliva	gene panel		MTX	only MTX	67	1	Yes	Yes	Arrhythmogenic right ventricular cardiomyopathy	
2099	PBMC/Saliva	gene panel		No	MTX; Pred.	4	1	Yes	Not yet achieved	Polymyalgia Rheumatica	
2104	PBMC/Saliva	gene panel		No	MTX	16	5	Yes	Yes	Sjogren's disease; asthma	
2112	PBMC/Saliva	gene panel	TNFAIP3 C200fs (8%) TNFAIP3 V209_S211 delinsA (8%)	No	Never (up to 50 mos follow-up)	6	Unknown	Unknown	Not yet achieved	Rosacea	

Supplemental Table 1C: Flow Cytometry and Bone Marrow Data

* = mutation validated in CD94+/CD94- Sanger, CD markers = peripheral blood data, MDS=myelodysplastic syndrome, NK=natural killer

Patient ID	Sample types	Sequencing type	Mutations in STAT3, TET2, TFNAIP3, PI3KCD, PIK3AP1	CD16+	CD56+	CD94+	CD3-CD16+	CD3-CD56+	CD3-CD57+	Bone marrow morphology	NK cell infiltration of marrow	Cytogenetics and/or FISH Data
1001	PBMC	gene panel	STAT3 D661Y (38%) TET2 G1184D (9%) TET2 Q1445L (5%)		4%		59%			no MDS	yes	not done
1002	PBMC	gene panel								no MDS	yes	normal cytogenetics
1059	PBMC/Saliva	gene panel								not available		
1061	PBMC	gene panel	STAT3 S614R (13%)	68%	5%	39%				not available		
1086	PBMC	gene panel		22%	33%	24%				not available		
1092	PBMC/Saliva	gene panel		79%	80%					not available		
1104	PBMC/Saliva	gene panel	STAT3 Y640F (47%)	64%	1%					no MDS	no	not done
1133	PBMC	gene panel								not available		
1139	PBMC	gene panel		65%	3%					no MDS	no	normal cytogenetics
1140	PBMC	gene panel		89%	31%					no MDS	yes	not done
1166	PBMC	gene panel	TET2 T1251fs (43%)	50%	63%					no MDS	yes	not done
1257	PBMC/Saliva	gene panel	STAT3 E286del (23%) TET2 G1860E (25%) PIK3CD E1021K (23%)	56%	0%	56%				no MDS	no	not done
1289	PBMC	gene panel	STAT3 D661Y (42%)	2%	5%				29%	no MDS	yes	not done
1340	PBMC	gene panel	STAT3 I659L (4%)	60%	66%	66%				no MDS	yes	normal cytogenetics
1362	PBMC/Saliva	gene panel	TNFAIP3 Y443fs (7%)	55%	73%	72%		73%		no MDS	yes	normal cytogenetics
1376	PBMC	gene panel		7%	1%					no MDS	no	not done
1429	PBMC	gene panel	TET2 R1134fs (33%) TET2 R550Tter (40%)		48%				23%	no MDS	yes	not done
1444	Enriched NK/Saliva	whole genome, gene panel	STAT3 D661I (39%) TET2 Q1523ter (41%) TET2 F1104fs (42%) TET2 Q897fs (5%) TNFAIP3 N340fs (37%)	15%	62%	67%		61%		no MDS	yes	not done
1483	PBMC/Saliva	gene panel	STAT3 G618R (30%)	73%	15%	4%				no MDS	yes	normal cytogenetics; FISH neg.
1489	PBMC/Saliva	gene panel	STAT3 G618R (32%)	80%	5%	79%				no MDS	yes	11:14 translocation FISH
1498	PBMC/Saliva	gene panel		51%	61%	59%				no MDS	yes	not done
1506	PBMC	gene panel	TET2 L1916del (29%)* TNFAIP3 Q241fs (5%)	NK cells incr ~70% of lymphoid cells; no values						no MDS	no	not done
1507	PBMC	gene panel	STAT3 D661Y (32%) TET2 Q764fs (33%)	76%	3%	15%				no MDS	yes	normal cytogenetics
1511	Enriched NK/Saliva	whole genome, gene panel	STAT3 N647I (48%) TET2 E1106fs (11%)* TET2 splice (15%)*	CD2+ mod CD7+ mod, CD56+ dim, CD57+ dim						no MDS	yes	normal cytogenetics
1528	PBMC	gene panel								no MDS	yes	normal cytogenetics
1556	PBMC	gene panel		32%	34%	23%	30%	32%		not available		
1573	PBMC	gene panel		35%		28%	32%	45%		no MDS	yes	normal cytogenetics; MDS FISH neg.
1586	PBMC	gene panel		71%	45%	75%		45%		no MDS	yes	normal cytogenetics; FISH neg.
1591	PBMC	gene panel	TNFAIP3 S266fs (10%)	71%	71%					no MDS	yes	not done
1612	PBMC	gene panel	TET2 C1271fs (28%)	22%	22%					no MDS	yes	normal cytogenetics
1644	PBMC	gene panel	TET2 L719fs (28%)* TET2 P1342fs (28%)*	15%	33%	10%		33%		no MDS	no	normal cytogenetics; MDS & BCR/ABL FISH neg.
1724	PBMC/Saliva	gene panel		18%	12%	46%		11%		no MDS	yes	not done
1760	PBMC/Saliva	gene panel	STAT3 D661V (37%)	48%	1%	7%	48%	1%	55%	not available		
1768	PBMC/Saliva	gene panel		2%	45%	51%		42%	28%	not available		
1791	PBMC/Saliva	whole genome, gene panel	STAT3 K658R (43%)	93%	6%	93%	93%	6%		no MDS	no	normal cytogenetics; MDS & BCR/ABL FISH neg.
1794	PBMC	gene panel	STAT3 D661Y (34%)					35%		no MDS	no	not done
1818	PBMC/Saliva	gene panel	STAT3 N647I (14%)							no MDS	yes	not done
1820	Enriched NK/Saliva	whole genome	TET2 R1452ter (22%) PIK3CD E81K (13%)	48%	26%	53%	47%	24%	44%	no MDS	yes	not done
1823	PBMC GP	gene panel		70%	70%					not available		
1856	PBMC/Saliva	whole genome, gene panel	Global CNV	78%	74%	76%	76%	75%	17%	no MDS	yes	normal cytogenetics
1862	PBMC/Saliva	whole genome, gene panel	TNFAIP3 Q379ter (46%) TNFAIP3 M433fs (44%)	29%	56%	94%	29%	56%	21%	no MDS	yes	abnormal cyto; EVI-1 on 3q26 FISH
1866	Enriched NK/Saliva	whole genome	PIK3AP1 S718N (28%) Global CNV	63%	16%	63%	63%	16%	43%	no MDS	yes	normal cytogenetics
1870	PBMC/Saliva	gene panel	TET2 L1872R (12%)	29%	0%	35%	29%	0%	0%	no MDS	yes	not done
1882	PBMC/Saliva	gene panel		0%	22%	82%	0%	21%	48%	no MDS	yes	normal cytogenetics; MDS FISH neg.
1909	PBMC/Saliva	gene panel	STAT3 S614R (28%) TET2 C1633ter (29%)*	84%	2%	83%				no MDS	no	normal cytogenetics; MDS FISH neg.
1928	PBMC/Saliva	gene panel								no MDS	yes	normal cytogenetics
1967	PBMC/Saliva	gene panel	STAT3 S614R (12%) TET2 E1268ter (43%)* TET2 P1013fs (38%)*	67%					67%	no MDS	yes	normal cytogenetics
1978	PBMC/Saliva	gene panel								no MDS	yes	normal cytogenetics
1984	PBMC/Saliva	gene panel								no MDS	no	normal cytogenetics
2003	PBMC/Saliva	gene panel	STAT3 Y640F (43%)	86%	5%	1%	86%	4%	12%	no MDS	yes	normal cytogenetics
2010	PBMC/Saliva	gene panel	TET2 Q720ter (14%)	39%	36%	46%	39%	32%	38%	no MDS	yes	normal cytogenetics
2011	PBMC/Saliva	gene panel		48%	3%	57%	48%	2%	17%	no MDS	yes	normal cytogenetics
2012	PBMC/Saliva	gene panel	STAT3 D661Y (36%)	82%	22%	84%	82%	22%	21%	no MDS	yes	normal cytogenetics; FISH neg.
2069	PBMC/Saliva	gene panel	TET2 R814fs (4%)	58%	2%	0%	58%	1%	41%	no MDS	yes	normal cytogenetics
2079	PBMC/Saliva	gene panel		12%	14%	8%	10%	9%	3%	no MDS	yes	normal cytogenetics
2099	PBMC/Saliva	gene panel		0%	31%	2%	0%	30%	36%	no MDS	no	normal cytogenetics; FISH neg.
2104	PBMC/Saliva	gene panel		23%	21%	9%	23%	19%	13%	no MDS	yes	normal cytogenetics; FISH neg.
2112	PBMC/Saliva	gene panel	TNFAIP3 C200fs (8%) TNFAIP3 V209_S211 delinsA (8%)	31%	65%	65%	31%	65%	32%	not available		

Supplemental Table 1D: Immunosuppressive Treatment Response

* = mutation validated in CD94+/CD94- Sanger, Dx=diagnosis, Tx=treatment, Pred=prednisone, MTX=methotrexate, CP=cyclophosphamide, CsA=cyclosporine A

NE=not evaluable, CR=complete response, PR=partial response, NR=no response

				MTX			CP			CsA		
	Patient ID	Mutations in STAT3, TET2, TFNAIP3, PI3KCD, PIK3AP1	1st LGLL Tx	Response	Dx→Tx (mos)	w/ Pred	Response	Dx→Tx (mos)	w/ Pred	Response	Dx→Tx (mos)	w/ Pred
WT	1002		CP				NR	1	No	NR	12	No
	1362	TNFAIP3 Y443fs (7%)	CP+Pred				NE	3	Yes			
	1498		CP				NE	<6	No			
	1573		Pred	PR	7	Yes	PR	12	No			
	1724		CP+Pred	NE	2	No	NE	1	Yes			
	1856	Global CNV	Pred	NE	63	No						
	1862	TNFAIP3 Q379ter (46%) TNFAIP3 M433fs (44%)	Pred	NR	27	Yes	CR	11	Yes	NE	31	Yes
	1866	PIK3AP1 S718N (28%) Global CNV	MTX	NE	0	No						
	1882		MTX+Pred	NR	<12	Yes						
	2011		MTX+Pred	PR	2	Yes						
	2079		MTX	CR	1	No						
	2099		MTX	NR	1	No						
	2104		MTX	NE	5	No						
STAT3	1289	STAT3 D661Y (42%)	MTX	PR	2	No						
	1340	STAT3 I659L (4%)	Pred				NE	0	yes			
	1483	STAT3 G618R (30%)	CP				CR	3	No			
	1489	STAT3 G618R (32%)	CP				PR	1	No			
	1760	STAT3 D661V (37%)	MTX	NE	69	No						
	1818	STAT3 N647I (14%)	MTX	CR	11	No						
	2003	STAT3 Y640F (43%)	Pred				PR	3	No			
	2012	STAT3 D661Y (36%)	CP				CR	3	No			
TET2	1166	TET2 T1251fs (43%)	CP+Pred				NE	0	Yes			
	1612	TET2 C1271fs (28%)	cladribine	NR	75	No	NR	82	No			
	1644	TET2 L719fs (28%)* TET2 P1342fs (28%)*	MTX+Pred	NR	0	yes	NR	9	Yes			
	1870	TET2 L1872R (12%)*	CsA+Pred	NR	70	No	NR	67	No	NR	49	Yes
	2010	TET2 Q720ter (14%)	Pred				NR	1	No			
	2069	TET2 R814fs (4%)	CP+Pred				CR	6	Yes			
Co-Mut	1001	STAT3 D661Y (38%) TET2 G1184D (9%) TET2 Q1445L (5%)	CsA	NR	4	Yes				NR	0	No
	1444	STAT3 D661I (39%) TET2 Q1523ter (41%) TET2 F1104fs (42%) TET2 Q897fs (5%) TNFAIP3 N340fs (37%)	CP+Pred				CR	0	Yes			
	1507	STAT3 D661Y (32%) TET2 Q764fs (33%)	CP+Pred				CR	7	Yes			
	1909	STAT3 S614R (28%) TET2 C1633ter (29%)*	CP+Pred				CR	1	Yes			
	1967	STAT3 S614R (12%) TET2 E1268ter (43%)* TET2 P1013fs (38%)*	CP+Pred				CR	0	Yes			

Supplemental Table 2: Mutect2 Somatic Mutation Calls from Seven WGS Samples in this Study.
Variants with the variant classifications missense, nonsense, nonstop, splice site, and transcriptional start site with the biotype protein coding are included here.

Sample ID	Hugo Symbol	HGVSp Short	Chromosome	Start	Variant Classification	Reference Allele	Tumor Allele2	HGVSc	tumor_vaf
1444	C1orf213	p.F77C	1	23696020	Missense	T	G	c.230T>G	0.12
1444	ZNF697	p.S475I	1	120165542	Missense	C	A	c.1424G>T	0.38
1444	NBPF14	p.A38T	1	148024903	Missense	C	T	c.111G>A	0.13
1444	RPTN	p.N448S	1	152128232	Missense	T	C	c.1343A>G	0.42
1444	F5	p.P1242L	1	169510603	Missense	G	A	c.3725C>T	0.07
1444	FMO1	p.M452I	1	171254440	Missense	G	C	c.1356G>C	0.49
1444	ZNF678	p.V402E	1	227843156	Missense	T	A	c.1205T>A	0.12
1444	CEP170	p.S792*	1	243328887	Nonsense	G	T	c.2375C>A	0.07
1444	RGPD4	p.G589S	2	108477228	Missense	G	A	c.1765G>A	0.13
1444	RGPD8	p.V1041I	2	113147401	Missense	C	T	c.3121G>A	0.11
1444	CCNT2	p.D711N	2	135712156	Missense	G	A	c.2131G>A	0.04
1444	DNAJB2	p.F46L	2	220145370	Missense	T	C	c.136T>C	0.04
1444	C3orf20	p.S718C	3	14799089	Missense	A	T	c.2152A>T	0.40
1444	MUC13	p.S24*	3	124646819	Nonsense	G	C	c.71C>G	0.34
1444	COL6A6	p.R327Q	3	130284156	Missense	G	A	c.980G>A	0.36
1444	ZNF141	p.F267S	4	367026	Missense	T	C	c.800T>C	0.11
1444	TET2	p.Q1523*	4	106196234	Nonsense	C	T	c.4567C>T	0.37
1444	LRP2BP	p.V250L	4	186294065	Missense	C	G	c.748G>C	0.42
1444	MUC22	p.F749S	6	30995454	Missense	T	C	c.2246T>C	0.16
1444	MUC22	p.E990A	6	30996177	Missense	A	C	c.2969A>C	0.11
1444	GSTA5	p.D101Y	6	52699052	Missense	C	A	c.301G>T	0.39
1444	FAM120B	p.C356Y	6	170627545	Missense	G	A	c.1067G>A	0.04
1444	GLI3	p.G1241E	7	42004949	Missense	C	T	c.3722G>A	0.04
1444	SPDYE1	p.G234R	7	44046934	Missense	G	A	c.700G>A	0.07
1444	AUTS2	p.X634_splice	7	70239087	Splice_Site	T	C	c.1902+2T>C	0.05
1444	ZAN	p.S916P	7	100350474	Missense	T	C	c.2746T>C	0.24
1444	MUC12	p.S4353P	7	100646901	Missense	T	C	c.13057T>C	0.07
1444	KCND2	p.P401L	7	120373043	Missense	C	T	c.1202C>T	0.44
1444	TMEM229A	p.V71L	7	123672847	Missense	C	A	c.211G>T	0.37
1444	MGAM	p.A1027S	7	141752704	Missense	G	T	c.3079G>T	0.10
1444	UNC5D	p.K637R	8	35606188	Missense	A	G	c.1910A>G	0.04
1444	TYRP1	p.Y438H	9	12708047	Missense	T	C	c.1312T>C	0.36
1444	TRPM6	p.F576L	9	77418715	Missense	A	G	c.1726T>C	0.06
1444	LRRC8A	p.S395L	9	131670627	Missense	C	T	c.1184C>T	0.36
1444	C9orf96	p.G17S	9	136243393	Missense	G	A	c.49G>A	0.42
1444	FRMD4A	p.A181V	10	13789742	Missense	G	A	c.542C>T	0.18
1444	RIC8A	p.D42V	11	209311	Missense	A	T	c.125A>T	0.41
1444	ZNF195	p.Q164R	11	3381747	Missense	T	C	c.491A>G	0.05
1444	AHNAK	p.M2007V	11	62295870	Missense	T	C	c.6019A>G	0.09
1444	ANO4	p.R78Q	12	101336195	Missense	G	A	c.233G>A	0.04
1444	UNC119B	p.T80A	12	121148515	Missense	A	G	c.238A>G	0.42
1444	CKAP2	p.Y646H	13	53049160	Missense	T	C	c.1936T>C	0.03
1444	EIF2B2	p.Q128*	14	75470351	Nonsense	C	T	c.382C>T	0.45
1444	SYNE3	p.*976Yext*7	14	95884163	Nonstop	T	G	c.2928A>C	0.06
1444	PLD4	p.A331T	14	105398157	Missense	G	A	c.991G>A	0.40
1444	FKSG62	p.E5A	15	47426211	Missense	T	G	c.14A>C	0.07
1444	AC137056.1	p.D101E	16	20499844	Missense	T	G	c.303T>G	0.20
1444	GTF3C1	p.V523A	16	27517422	Missense	A	G	c.1568T>C	0.44
1444	MMP2	p.D615N	16	55536764	Missense	G	A	c.1843G>A	0.40
1444	ARHGEF15	p.N49T	17	8215503	Missense	A	C	c.146A>C	0.20
1444	STAT3	p.D661V	17	40474419	Missense	T	A	c.1982A>T	0.41
1444	STAT3	p.D661N	17	40474420	Missense	C	T	c.1981G>A	0.41
1444	COA3	p.A66S	17	40950504	Missense	C	A	c.196G>T	0.41
1444	PPM1D	p.R552*	17	58740749	Nonsense	C	T	c.1654C>T	0.06
1444	CD209	p.L120Q	19	7810793	Missense	A	T	c.359T>A	0.08
1444	RDH8	p.I198F	19	10131474	Missense	A	T	c.592A>T	0.34
1444	ZNF844	p.F487L	19	12187394	Missense	T	C	c.1459T>C	0.11
1444	ZNF430	p.S480T	19	21240552	Missense	T	A	c.1438T>A	0.08

Sample	Hugo Symbol	HGVSp Short	Chromosome	Start	Variant Classification	Reference Allele	Tumor Allele2	HGVSc	tumor_vaf
1444	ZNF724P	p.V582I	19	23405303	Missense	C	T	c.1744G>A	0.05
1444	ZNF681	p.K405Q	19	23927139	Missense	T	G	c.1213A>C	0.13
1444	PNKP	p.S143*	19	50368454	Nonsense	G	C	c.428C>G	0.11
1444	RBM12	p.R423G	20	34241978	Missense	T	C	c.1267A>G	0.37
1444	FAM230A	p.Q507H	22	20709789	Missense	A	C	c.1521A>C	0.27
1444	TRIOBP	p.L801P	22	38120965	Missense	T	C	c.2402T>C	0.15
1444	PABPC1L2B	p.S181Y	X	72224023	Missense	C	A	c.542C>A	0.30
1444	MAGEC1	p.H661Q	X	140995173	Missense	T	G	c.1983T>G	0.15
1444	ARHGAP4	p.Q14*	X	153191617	Nonsense	G	A	c.40C>T	0.72
1511	NBPF1	p.F314S	1	16912031	Missense	A	G	c.941T>C	0.03
1511	UBXN11	p.S494R	1	26608873	Missense	T	G	c.1480A>C	0.15
1511	NBPF9	p.D636E	1	144828640	Missense	C	G	c.1907C>G	0.05
1511	NBPF10	p.K2709N	1	145353585	Missense	G	C	c.8127G>C	0.14
1511	HRNR	p.R1996H	1	152188118	Missense	C	T	c.5987G>A	0.04
1511	USH2A	p.T4839M	1	215821936	Missense	G	A	c.14516C>T	0.03
1511	ITPRIPL1	p.S277A	2	96993174	Missense	T	G	c.829T>G	0.06
1511	REV1	p.R595H	2	100038008	Missense	C	T	c.1784G>A	0.48
1511	RGPD8	p.L1095P	2	113147238	Missense	A	G	c.3284T>C	0.18
1511	TUBA3D	p.R221S	2	132237927	Missense	C	A	c.661C>A	0.08
1511	NFE2L2	p.V591L	2	178095560	Missense	C	G	c.1771G>C	0.19
1511	CACNA2D3	p.R440L	3	54798317	Missense	G	T	c.1319G>T	0.03
1511	ZDHHC23	p.V169I	3	113672890	Missense	G	A	c.505G>A	0.08
1511	ZNF721	p.T565A	4	436563	Missense	T	C	c.1693A>G	0.05
1511	GAK	p.X330_splice	4	887163	Splice_Site	A	C	c.990+2T>G	0.08
1511	CC2D2A	p.P1473H	4	15597811	Missense	C	A	c.4418C>A	0.07
1511	TET2	p.X1394_splice	4	106190905	Splice_Site	G	T	c.4182+1G>T	0.19
1511	MYO10	p.R1834Q	5	16671017	Missense	C	T	c.5501G>A	0.11
1511	MRPS27	p.X94_splice	5	71533956	Splice_Site	C	G	c.282-1G>C	0.03
1511	C1QTNF2	p.P86S	5	159781898	Missense	G	A	c.256C>T	0.05
1511	SYNCRIP	p.G449V	6	86325000	Missense	C	A	c.1346G>T	0.11
1511	ZNF92	p.D372E	7	64864143	Missense	T	A	c.1116T>A	0.10
1511	HIP1	p.D415G	7	75189167	Missense	T	C	c.1244A>G	0.03
1511	CSMD1	p.A2374T	8	2954389	Missense	C	T	c.7120G>A	0.08
1511	PSD3	p.P16L	8	18941993	Missense	G	A	c.47C>T	0.08
1511	ZFHX4	p.R2926Q	8	77767934	Missense	G	A	c.8777G>A	0.03
1511	C8orf33	p.I210V	8	146279481	Missense	A	G	c.628A>G	0.03
1511	FRMPD1	p.G137R	9	37719066	Missense	G	C	c.409G>C	0.52
1511	ANKRD20A4	p.L524H	9	69423275	Missense	T	A	c.1571T>A	0.02
1511	TUBB8	p.F85L	10	94579	Missense	A	G	c.253T>C	0.04
1511	RSU1	p.X200_splice	10	16737156	Splice_Site	T	G	c.599-2A>C	0.08
1511	SFTPA1	p.V34A	10	81371637	Missense	T	C	c.101T>C	0.04
1511	LRIT1	p.L256P	10	85993957	Missense	A	G	c.767T>C	0.04
1511	MUC5B	p.I3478T	11	1268543	Missense	T	C	c.10433T>C	0.05
1511	OR8U1	p.M206I	11	56143717	Missense	G	A	c.618G>A	0.10
1511	AHNAK	p.T2181A	11	62295348	Missense	T	C	c.6541A>G	0.09
1511	APAF1	p.L1164F	12	99120986	Missense	G	T	c.3492G>T	0.45
1511	TDG	p.X322_splice	12	104378700	Splice_Site	T	C	c.964+2T>C	0.04
1511	IRS2	p.P780A	13	110436063	Missense	G	C	c.2338C>G	0.46
1511	AHNAK2	p.V4126M	14	105409412	Missense	C	T	c.12376G>A	0.04
1511	GOLGA6B	p.D676N	15	72958627	Missense	G	A	c.2026G>A	0.11
1511	ISLR2		15	74422893	Splice_Site	A	G	c.-186-2A>G	0.15
1511	NPIPB6	p.V236A	16	28354499	Missense	A	G	c.707T>C	0.10
1511	KRTAP4-11	p.R103S	17	39274259	Missense	T	G	c.309A>C	0.14
1511	STAT3	p.N647I	17	40474461	Missense	T	A	c.1940A>T	0.51
1511	ZNF257	p.V249I	19	22271297	Missense	G	A	c.745G>A	0.08
1511	ZNF283	p.K572E	19	44352467	Missense	A	G	c.1714A>G	0.04
1511	INSM1	p.A418G	20	20350164	Missense	C	G	c.1253C>G	0.49
1511	ZNF831	p.E1061*	20	57769255	Nonsense	G	T	c.3181G>T	0.02
1511	RUNX1	p.M25I	21	36265244	Missense	C	A	c.75G>T	0.04
1511	BRD1	p.R267W	22	50217167	Missense	G	A	c.799C>T	0.13
1511	MT-ND4L	p.M9T	MT	10495	Missense	T	C	c.26T>C	0.00
1791	F5	p.N1257T	1	169510558	Missense	T	G	c.3770A>C	0.15
1791	CEP170	p.S792*	1	243328887	Nonsense	G	T	c.2375C>A	0.04

Sample	Hugo Symbol	HGVSp Short	Chromosome	Start	Variant Classification	Reference Allele	Tumor Allele2	HGVSc	tumor_vaf
1791	RMND5A	p.V302A	2	86997196	Missense	T	C	c.905T>C	0.40
1791	POTEE	p.V644I	2	132020958	Missense	G	A	c.1930G>A	0.08
1791	TTN	p.A13230V	2	179515498	Missense	G	A	c.39689C>T	0.36
1791	FANCD2	p.K871N	3	10114944	Missense	A	C	c.2613A>C	0.07
1791	DNAH12	p.E386G	3	57488136	Missense	T	C	c.1157A>G	0.03
1791	TCTEX1D2	p.D13A	3	196044986	Missense	T	G	c.38A>C	0.13
1791	CRIPAK	p.M48V	4	1388441	Missense	A	G	c.142A>G	0.11
1791	MTHFD2L	p.V219I	4	75067030	Missense	G	A	c.655G>A	0.13
1791	WNT8A	p.A9T	5	137419803	Missense	G	A	c.25G>A	0.52
1791	RSPH10B	p.T148M	7	6000452	Missense	G	A	c.443C>T	0.18
1791	MUC17	p.N1390T	7	100678866	Missense	A	C	c.4169A>C	0.14
1791	VPS13A	p.R2786T	9	79981674	Missense	G	C	c.8357G>C	0.36
1791	NSMCE4A	p.Q88*	10	123734419	Nonsense	G	A	c.262C>T	0.40
1791	OR52L1	p.Q42P	11	6008036	Missense	T	G	c.125A>C	0.04
1791	LRFN4	p.R367G	11	66626314	Missense	C	G	c.1099C>G	0.47
1791	GOLGA8K	p.X401_splice	15	32686943	Splice_Site	T	G	c.1201-2A>C	0.35
1791	IGF1R	p.R753Q	15	99465433	Missense	G	A	c.2258G>A	0.05
1791	NPIPB6	p.V236A	16	28354499	Missense	A	G	c.707T>C	0.11
1791	IL17C	p.G26V	16	88705459	Missense	G	T	c.77G>T	0.43
1791	STAT3	p.K658R	17	40474428	Missense	T	C	c.1973A>G	0.48
1791	SPOP	p.M255I	17	47684684	Missense	C	T	c.765G>A	0.42
1791	KDM4B	p.V408G	19	5119771	Missense	T	G	c.1223T>G	0.05
1791	RGAG1	p.E779*	X	109696180	Nonsense	G	T	c.2335G>T	0.05
1820	PIK3CD	p.E81K	1	9775698	Missense	G	A	c.241G>A	0.14
1820	CROCC	p.A440S	1	17264922	Missense	G	T	c.1318G>T	0.03
1820	HSPG2	p.R2408Q	1	22176927	Missense	C	T	c.7223G>A	0.08
1820	C1orf87	p.Q75*	1	60520995	Nonsense	G	A	c.223C>T	0.03
1820	C1orf51	p.T108S	1	150256000	Missense	C	G	c.323C>G	0.39
1820	HRNR	p.G1210R	1	152190477	Missense	C	T	c.3628G>A	0.29
1820	FLG	p.H3034Y	1	152278262	Missense	G	A	c.9100C>T	0.44
1820	LRRC52	p.G222R	1	165532783	Missense	G	A	c.664G>A	0.03
1820	DNAH6	p.G2465C	2	84921473	Missense	G	T	c.7393G>T	0.09
1820	TUBA3D	p.R221S	2	132237927	Missense	C	A	c.661C>A	0.11
1820	TTLL4	p.G238D	2	219603112	Missense	G	A	c.713G>A	0.05
1820	CCDC108	p.X181_splice	2	219897295	Splice_Site	C	T	c.543-1G>A	0.56
1820	SLITRK3	p.L506V	3	164907103	Missense	A	C	c.1516T>G	0.18
1820	MUC4	p.V3726A	3	195507274	Missense	A	G	c.11177T>C	0.20
1820	MUC4	p.S1591T	3	195513680	Missense	A	T	c.4771T>A	0.16
1820	SOD3	p.R232W	4	24801837	Missense	C	T	c.694C>T	0.48
1820	HPSE	p.G349R	4	84230044	Missense	C	T	c.1045G>A	0.39
1820	TET2	p.R1452*	4	106193892	Nonsense	C	T	c.4354C>T	0.49
1820	SLC6A19	p.A167T	5	1212435	Missense	G	A	c.499G>A	0.05
1820	SLCO4C1	p.Y266C	5	101606333	Missense	T	C	c.797A>G	0.52
1820	PCDHA10	p.T437M	5	140236943	Missense	C	T	c.1310C>T	0.03
1820	ADAM19	p.E698D	5	156918624	Missense	C	G	c.2094G>C	0.48
1820	MDC1	p.M1316R	6	30673013	Missense	A	C	c.3947T>G	0.10
1820	DPCR1	p.S420P	6	30917499	Missense	T	C	c.1258T>C	0.12
1820	DPCR1	p.L874P	6	30918862	Missense	T	C	c.2621T>C	0.16
1820	TNXB	p.A1860T	6	32037339	Missense	C	T	c.5578G>A	0.17
1820	DNAH8	p.P505A	6	38749054	Missense	C	G	c.1513C>G	0.38
1820	POM121	p.K391N	7	72412500	Missense	A	C	c.1173A>C	0.20
1820	POM121	p.T486S	7	72412783	Missense	A	T	c.1456A>T	0.08
1820	RSBN1L	p.H136R	7	77326193	Missense	A	G	c.407A>G	0.17
1820	MUC17	p.R2742P	7	100682922	Missense	G	C	c.8225G>C	0.07
1820	PTPRZ1	p.S487N	7	121650560	Missense	G	A	c.1460G>A	0.05
1820	RP1L1	p.L2209S	8	10464982	Missense	A	G	c.6626T>C	0.09
1820	HMCN2	p.P183S	9	133300198	Missense	C	T	c.547C>T	0.51
1820	FGFR2	p.K570N	10	123256202	Missense	T	G	c.1710A>C	0.10
1820	OTOG	p.R2062H	11	17633734	Missense	G	A	c.6185C>A	0.04
1820	OR5D18	p.N37S	11	55587215	Missense	A	G	c.110A>G	0.04
1820	ARCN1	p.G418S	11	118468432	Missense	G	A	c.1252G>A	0.07
1820	FAM186A	p.S1626P	12	50745739	Missense	A	G	c.4876T>C	0.23
1820	HCFC2	p.Y164C	12	104473240	Missense	A	G	c.491A>G	0.48

Sample	Hugo Symbol	HGVSp Short	Chromosome	Start	Variant Classification	Reference Allele	Tumor Allele2	HGVSc	tumor_vaf
1820	MMP17	p.E345*	12	132329727	Nonsense	G	T	c.1033G>T	0.18
1820	AHNAK2	p.L3217P	14	105412138	Missense	A	G	c.9650T>C	0.11
1820	SPG21	p.M238V	15	65257759	Missense	T	C	c.712A>G	0.24
1820	SCAMP5	p.A225T	15	75311289	Missense	G	A	c.673G>A	0.11
1820	ADAMTSL3	p.Q788H	15	84611708	Missense	G	C	c.2364G>C	0.22
1820	MSLNL	p.C161R	16	830520	Missense	A	G	c.481T>C	0.10
1820	CCDC135	p.D164A	16	57734169	Missense	A	C	c.491A>C	0.05
1820	EVPLL		17	18291604	Splice_Site	T	C	c.*40+2T>C	0.04
1820	CNTNAP1	p.L1111H	17	40847878	Missense	T	A	c.3332T>A	0.21
1820	AC012123.1	p.D175A	18	30352227	Missense	A	C	c.524A>C	0.05
1820	LOXHD1	p.F85L	18	44125313	Missense	A	G	c.253T>C	0.20
1820	DNASE2	p.A14T	19	12992150	Missense	C	T	c.40G>A	0.51
1820	ZNF729	p.D502A	19	22497724	Missense	A	C	c.1505A>C	0.06
1820	ZNF91	p.T308A	19	23544859	Missense	T	C	c.922A>G	0.04
1820	CEACAM7	p.G70R	19	42191009	Missense	C	T	c.208G>A	0.04
1820	ZNF835	p.T307A	19	57175648	Missense	T	C	c.919A>G	0.08
1820	DLGAP4	p.V164I	20	35060610	Missense	G	A	c.490G>A	0.04
1820	KRTAP10-6	p.P45R	21	46012232	Missense	G	C	c.134C>G	0.16
1820	KRTAP10-6	p.P45T	21	46012233	Missense	G	T	c.133C>A	0.14
1820	USP27X	p.T99M	X	49645206	Missense	C	T	c.296C>T	0.48
1820	ACRC	p.N172S	X	70823642	Missense	A	G	c.515A>G	0.21
1820	AFF2	p.P132L	X	147743643	Missense	C	T	c.395C>T	0.94
1856	ROR1	p.R117Q	1	64515549	Missense	G	A	c.350G>A	0.04
1856	MSH4	p.K435M	1	76333272	Missense	A	T	c.1304A>T	0.03
1856	IFI44L	p.R157*	1	79094069	Nonsense	C	T	c.469C>T	0.36
1856	TCHH	p.E501V	1	152084191	Missense	T	A	c.1502A>T	0.08
1856	TCHH	p.E501Q	1	152084192	Missense	C	G	c.1501G>C	0.08
1856	FLG	p.S3662T	1	152276377	Missense	C	G	c.10985G>C	0.06
1856	FLG2	p.S650G	1	152328314	Missense	T	C	c.1948A>G	0.09
1856	ASTN1	p.E418G	1	176993736	Missense	T	C	c.1253A>G	0.04
1856	BRINP3	p.A369V	1	190129876	Missense	G	A	c.1106C>T	0.40
1856	IGFN1	p.K1563E	1	201178708	Missense	A	G	c.4687A>G	0.11
1856	ANKRD36	p.T1018S	2	97869991	Missense	A	T	c.3052A>T	0.02
1856	BAZ2B	p.K1057T	2	160245902	Missense	T	G	c.3170A>C	0.03
1856	ANO7	p.E880D	2	242163142	Missense	G	T	c.2640G>T	0.04
1856	SETMAR	p.N504T	3	4358386	Missense	A	C	c.1511A>C	0.32
1856	ZSWIM6	p.P946S	5	60839332	Missense	C	T	c.2836C>T	0.39
1856	BDP1	p.Q1115E	5	70806262	Missense	C	G	c.3343C>G	0.08
1856	KCNMB1	p.V146I	5	169805848	Missense	C	T	c.436G>A	0.39
1856	PXDNL	p.S585C	8	52336176	Missense	G	C	c.1754C>G	0.44
1856	CD274	p.G245R	9	5465549	Missense	G	A	c.733G>A	0.03
1856	SGMS1	p.G250R	10	52071169	Missense	C	T	c.748G>A	0.25
1856	SFTPA1	p.V34A	10	81371637	Missense	T	C	c.101T>C	0.06
1856	HELLS	p.L645V	10	96352233	Missense	C	G	c.1933C>G	0.35
1856	API5	p.S199C	11	43345032	Missense	C	G	c.596C>G	0.28
1856	ALX4	p.V241M	11	44296954	Missense	C	T	c.721G>A	0.05
1856	MS4A6A	p.E56K	11	59949119	Missense	C	T	c.166G>A	0.03
1856	AHNAK	p.L2567F	11	62294188	Missense	T	G	c.7701A>C	0.08
1856	TENM4	p.M1673V	11	78412641	Missense	T	C	c.5017A>G	0.22
1856	SLCO1B1	p.G394R	12	21355469	Missense	G	A	c.1180G>A	0.27
1856	MUC19	p.N3605D	12	40879268	Missense	A	G	c.10813A>G	0.09
1856	FAM186A	p.K1258Q	12	50746843	Missense	T	G	c.3772A>C	0.13
1856	KRT75	p.I214T	12	52826894	Missense	A	G	c.641T>C	0.16
1856	LHX5	p.P183L	12	113906059	Missense	G	A	c.548C>T	0.29
1856	PPP1R3E		14	23770505	Splice_Site	A	C	c.*138+2T>G	0.16
1856	ZFHX2	p.A276T	14	24003709	Missense	C	T	c.826G>A	0.22
1856	ZWILCH	p.W546R	15	66832497	Missense	T	C	c.1636T>C	0.30
1856	CCL22	p.L45Q	16	57394409	Missense	T	A	c.134T>A	0.31
1856	ZNF207	p.T337A	17	30694878	Missense	A	G	c.1009A>G	0.24
1856	KRT31	p.S15N	17	39553748	Missense	C	T	c.44G>A	0.05
1856	DNM2	p.V234M	19	10893647	Missense	G	A	c.700G>A	0.28
1856	ZNF676	p.I525R	19	22362945	Missense	A	C	c.1574T>G	0.07
1856	GPATCH1	p.D904H	19	33617584	Missense	G	C	c.2710G>C	0.25

Sample	Hugo Symbol	HGVSp Short	Chromosome	Start	Variant Classification	Reference Allele	Tumor Allele2	HGVSc	tumor_vaf
1856	FCGBP	p.R2925W	19	40386541	Missense	G	A	c.8773C>T	0.09
1856	ZNF845	p.L522P	19	53855493	Missense	T	C	c.1565T>C	0.06
1856	ZNF71	p.A423S	19	57133922	Missense	G	T	c.1267G>T	0.05
1856	ZNF586	p.I181S	19	58290497	Missense	T	G	c.542T>G	0.10
1856	ZNF814	p.D404E	19	58385546	Missense	G	T	c.1212C>A	0.11
1856	PIGU	p.P214A	20	33176399	Missense	G	C	c.640C>G	0.03
1856	SLC7A4	p.L597M	22	21383463	Missense	G	T	c.1789C>A	0.21
1856	TBL1X	p.K455N	X	9677726	Missense	A	C	c.1365A>C	0.05
1856	RBMXL3	p.N405D	X	114425217	Missense	A	G	c.1213A>G	0.03
1862	NBPF1	p.H567R	1	16905789	Missense	T	C	c.1700A>G	0.03
1862	NBPF1	p.F314S	1	16912031	Missense	A	G	c.941T>C	0.05
1862	COL24A1	p.G774E	1	86453327	Missense	C	T	c.2321G>A	0.48
1862	COL11A1	p.G1522S	1	103354177	Missense	C	T	c.4564G>A	0.03
1862	RAP1A	p.C48G	1	112240078	Missense	T	G	c.142T>G	0.42
1862	NBPF10	p.P26S	1	145293481	Missense	C	T	c.76C>T	0.18
1862	PRUNE	p.Q423*	1	151006615	Nonsense	C	T	c.1267C>T	0.40
1862	OBSCN	p.R5973Q	1	228509589	Missense	G	A	c.17918G>A	0.44
1862	PCNXL2	p.Q1398K	1	233190173	Missense	G	T	c.4192C>A	0.49
1862	CEP170	p.T684K	1	243329211	Missense	G	T	c.2051C>A	0.04
1862	OR2T12	p.E230*	1	248458193	Nonsense	C	A	c.688G>T	0.51
1862	PLB1	p.S290A	2	28764667	Missense	T	G	c.868T>G	0.07
1862	NLRC4	p.S742N	2	32474708	Missense	C	T	c.2225G>A	0.37
1862	PLEKHH2	p.V315A	2	43927041	Missense	T	C	c.944G>C	0.48
1862	NOTO	p.F175S	2	73435669	Missense	T	C	c.524T>C	0.04
1862	TUBA3D	p.R221S	2	132237927	Missense	C	A	c.661C>A	0.05
1862	NCKAP5	p.P909H	2	133541658	Missense	G	T	c.2726C>A	0.34
1862	ITGAV	p.T978N	2	187541544	Missense	C	A	c.2933C>A	0.09
1862	FN1	p.S708R	2	216274461	Missense	G	T	c.2124C>A	0.45
1862	ECEL1	p.A31D	2	233351272	Missense	G	T	c.92C>A	0.39
1862	GRM7	p.P569L	3	7620299	Missense	C	T	c.1706C>T	0.85
1862	LHFPL4	p.S4L	3	9594353	Missense	G	A	c.11C>T	0.10
1862	STAB1	p.F1362L	3	52550194	Missense	T	C	c.4084T>C	0.38
1862	ADCY5	p.P22L	3	123167328	Missense	G	A	c.65C>T	0.45
1862	EIF4A2	p.T219S	3	186504319	Missense	C	G	c.656C>G	0.66
1862	MUC4	p.H3490P	3	195507982	Missense	T	G	c.10469A>C	0.15
1862	ZNF732	p.S382R	4	265500	Missense	A	T	c.1146T>A	0.09
1862	PTTG2	p.I148F	4	37962497	Missense	A	T	c.442A>T	0.49
1862	ATOH1	p.R96W	4	94750363	Missense	C	T	c.286C>T	0.30
1862	BBS12	p.Q75K	4	123663270	Missense	C	A	c.223C>A	0.07
1862	DCHS2	p.E2262Q	4	155157655	Missense	C	G	c.6784G>C	0.53
1862	CAST	p.P134L	5	96065404	Missense	C	T	c.401C>T	0.51
1862	AFAP1L1	p.G355S	5	148695426	Missense	G	A	c.1063G>A	0.35
1862	DPCR1	p.L318P	6	30917194	Missense	T	C	c.953T>C	0.14
1862	MUC22	p.I361T	6	30994290	Missense	T	C	c.1082T>C	0.09
1862	MUC22	p.I610T	6	30995037	Missense	T	C	c.1829T>C	0.09
1862	PRRC2A	p.N21S	6	31590628	Missense	A	G	c.62A>G	0.03
1862	CYP21A2	p.A435V	6	32008727	Missense	C	T	c.1304C>T	0.09
1862	MDGA1	p.E807K	6	37611702	Missense	C	T	c.2419G>A	0.53
1862	BAI3	p.R588*	6	69703687	Nonsense	C	T	c.1762C>T	0.50
1862	CTAGE9	p.K379N	6	132031021	Missense	C	A	c.1137G>T	0.44
1862	FGL2	p.P40L	7	76828992	Missense	G	A	c.119C>T	0.51
1862	MUC12	p.R363S	7	100634933	Missense	G	C	c.1089G>C	0.09
1862	MUC17	p.N2194T	7	100681278	Missense	A	C	c.6581A>C	0.09
1862	RASA4B	p.H677R	7	102125543	Missense	T	C	c.2030A>G	0.10
1862	SMO	p.V240I	7	128845224	Missense	G	A	c.718G>A	0.46
1862	CTAGE8	p.R655G	7	143964381	Missense	T	C	c.1963A>G	0.08
1862	ZFHX4	p.T2041P	8	77765278	Missense	A	C	c.6121A>C	0.16
1862	HHLA1	p.R445T	8	133088736	Missense	C	G	c.1334G>C	0.41
1862	RLN2	p.S75F	9	5300432	Missense	G	A	c.224C>T	0.43
1862	ZNF658	p.V815A	9	40772831	Missense	A	G	c.2444T>C	0.04
1862	FAM171A1	p.G28C	10	15412970	Missense	C	A	c.82G>T	0.50
1862	SFTPA1	p.V34A	10	81371637	Missense	T	C	c.101T>C	0.06
1862	ANO3	p.A638T	11	26655789	Missense	G	A	c.1912C>A	0.21

Sample	Hugo Symbol	HGVSp Short	Chromosome	Start	Variant Classification	Reference Allele	Tumor Allele2	HGVSc	tumor_vaf
1862	GLYATL1	p.N7Y	11	58710790	Missense	A	T	c.19A>T	0.05
1862	AHNAK	p.L2567F	11	62294188	Missense	T	G	c.7701A>C	0.11
1862	OTUB1	p.K201R	11	63764700	Missense	A	G	c.602A>G	0.04
1862	PDE2A	p.D580N	11	72293601	Missense	C	T	c.1738G>A	0.42
1862	RAB6A	p.R169C	11	73390756	Missense	G	A	c.505C>T	0.08
1862	FAT3	p.R2731K	11	92534371	Missense	G	A	c.8192G>A	0.43
1862	KIAA1377	p.C1113Y	11	101868358	Missense	G	A	c.3338G>A	0.47
1862	PHC1	p.A418D	12	9085306	Missense	C	A	c.1253C>A	0.16
1862	PKP2	p.G175R	12	33031291	Missense	C	T	c.523G>A	0.45
1862	KRT75	p.V104F	12	52827779	Missense	C	A	c.310G>T	0.45
1862	PSPC1	p.M437V	13	20279879	Missense	T	C	c.1309A>G	0.06
1862	PCDH17	p.P46S	13	58206816	Missense	C	T	c.136C>T	0.47
1862	FOXA1	p.G315R	14	38061046	Missense	C	T	c.943G>A	0.43
1862	ACTN1	p.S348R	14	69358812	Missense	G	C	c.1044C>G	0.45
1862	TRIP11	p.K343N	14	92480716	Missense	C	A	c.1029G>T	0.42
1862	DDX24	p.K527R	14	94526777	Missense	T	C	c.1580A>G	0.54
1862	RTL1	p.E477D	14	101349695	Missense	C	A	c.1431G>T	0.43
1862	C14orf144	p.G9S	14	104710642	Missense	G	A	c.25G>A	0.39
1862	AHNAK2	p.V3209L	14	105412163	Missense	C	G	c.9625G>C	0.10
1862	AHNAK2	p.M2119V	14	105415433	Missense	T	C	c.6355A>G	0.13
1862	AHNAK2	p.T720A	14	105419630	Missense	T	C	c.2158A>G	0.06
1862	BTBD6	p.P47S	14	105715346	Missense	C	T	c.139C>T	0.36
1862	CHD2	p.E287K	15	93486105	Missense	G	A	c.859G>A	0.51
1862	NOMO1	p.X557_splice	16	14959013	Splice_Site	G	A	c.1669+1G>A	0.06
1862	NQO1	p.D245N	16	69744971	Missense	C	T	c.733G>A	0.54
1862	RTN4RL1	p.E103Q	17	1840809	Missense	C	G	c.307G>C	0.51
1862	CDRT1	p.I23N	17	15522759	Missense	A	T	c.68T>A	0.05
1862	KRTAP9-9	p.L67V	17	39411836	Missense	C	G	c.199C>G	0.06
1862	ADAM11	p.R63Q	17	42837216	Missense	G	A	c.188G>A	0.49
1862	MPO	p.R511H	17	56350864	Missense	C	T	c.1532G>A	0.45
1862	SDK2	p.V1391A	17	71386446	Missense	A	G	c.4172G>C	0.16
1862	TXNDC2	p.L299I	18	9887371	Missense	C	A	c.895C>A	0.11
1862	ZBTB7A	p.Q165*	19	4054738	Nonsense	G	A	c.493C>T	0.38
1862	PLIN4	p.G329S	19	4512945	Missense	C	T	c.985G>A	0.09
1862	ZNF100	p.D460E	19	21909734	Missense	G	T	c.1380C>A	0.04
1862	ZNF43	p.S694T	19	21990759	Missense	A	T	c.2080T>A	0.07
1862	ZNF730	p.N356T	19	23328913	Missense	A	C	c.1067A>C	0.09
1862	RHPN2	p.Q384R	19	33490566	Missense	T	C	c.1151A>G	0.06
1862	ZNF234	p.K412R	19	44661404	Missense	A	G	c.1235A>G	0.45
1862	FCAR	p.A51D	19	55396728	Missense	C	A	c.152C>A	0.53
1862	C20orf194	p.A261T	20	3329180	Missense	C	T	c.781G>A	0.48
1862	JPH2	p.M292T	20	42788552	Missense	A	G	c.875T>C	0.13
1862	IL10RB	p.S77P	21	34648956	Missense	T	C	c.229T>C	0.03
1862	TRPM2	p.T1298M	21	45846913	Missense	C	T	c.3893C>T	0.49
1862	KRTAP10-4	p.L97P	21	45993925	Missense	T	C	c.290T>C	0.12
1862	ARVCF	p.R609W	22	19964983	Missense	G	A	c.1825C>T	0.21
1862	CCDC157	p.V116A	22	30765519	Missense	T	C	c.347T>C	0.09
1866	AGRN	p.H625P	1	979278	Missense	A	C	c.1874A>C	0.14
1866	FMO5	p.M1?	1	146696621	Trans_Start_	T	C	c.1A>G	0.04
1866	LCE3C	p.R86H	1	152573464	Missense	G	A	c.257G>A	0.20
1866	PRG4	p.G809E	1	186277277	Missense	G	A	c.2426G>A	0.07
1866	LMOD1	p.S194R	1	201869559	Missense	A	C	c.582T>G	0.12
1866	TGOLN2	p.S95P	2	85554572	Missense	A	G	c.283T>C	0.10
1866	AC017081.1	p.L90P	2	207220731	Missense	T	C	c.269T>C	0.08
1866	COL6A5	p.V1867G	3	130150660	Missense	T	G	c.5600T>G	0.08
1866	MUC4	p.L4057S	3	195506281	Missense	A	G	c.12170T>C	0.20
1866	MUC4	p.L4057V	3	195506282	Missense	A	C	c.12169T>G	0.31
1866	TTC37	p.*1565Qext*6	5	94800313	Nonstop	A	G	c.4693T>C	0.03
1866	MDC1	p.N1274S	6	30673139	Missense	T	C	c.3821A>G	0.10
1866	MDGA1	p.E188D	6	37623491	Missense	C	A	c.564G>T	0.42
1866	PTPRK	p.A345T	6	128505706	Missense	C	T	c.1033G>A	0.11
1866	TXLNB	p.Q616P	6	139563871	Missense	T	G	c.1847A>C	0.18
1866	SP8	p.Y143S	7	20825008	Missense	T	G	c.428A>C	0.13

Sample	Hugo Symbol	HGVSp Short	Chromosome	Start	Variant Classification	Reference Allele	Tumor Allele2	HGVSc	tumor_vaf
1866	ABCA13	p.P1484R	7	48313714	Missense	C	G	c.4451C>G	0.08
1866	MUC17	p.R2742P	7	100682922	Missense	G	C	c.8225G>C	0.06
1866	MUC17	p.V3416A	7	100684944	Missense	T	C	c.10247T>C	0.11
1866	GATA4	p.R259C	8	11606586	Missense	C	T	c.775C>T	0.43
1866	SPATC1	p.T327P	8	145095681	Missense	A	C	c.979A>C	0.26
1866	CNTRL	p.W2012G	9	123930563	Missense	T	G	c.6034T>G	0.05
1866	ENG	p.A367S	9	130586618	Missense	C	A	c.1099G>T	0.07
1866	HKDC1	p.A839T	10	71025483	Missense	G	A	c.2515G>A	0.25
1866	ADAMTS14	p.C152G	10	72434683	Missense	T	G	c.454T>G	0.06
1866	PIK3AP1	p.S718N	10	98369486	Missense	C	T	c.2153G>A	0.39
1866	FOXM1	p.V217G	12	2981266	Missense	A	C	c.650T>G	0.04
1866	NAV3	p.T1197A	12	78513565	Missense	A	G	c.3589A>G	0.35
1866	DYNC1H1	p.P1104L	14	102461164	Missense	C	T	c.3311C>T	0.07
1866	MYO5C	p.M603V	15	52539729	Missense	T	C	c.1807A>G	0.31
1866	INO80E	p.R160Q	16	30012817	Missense	G	A	c.479G>A	0.37
1866	MYO15A	p.R1835C	17	18044429	Missense	C	T	c.5503C>T	0.39
1866	UBBP4	p.L149R	17	21731144	Missense	T	G	c.446T>G	0.10
1866	KRTAP4-7	p.S57P	17	39240627	Missense	T	C	c.169T>C	0.08
1866	USH1G	p.G65D	17	72916737	Missense	C	T	c.194G>A	0.38
1866	MED16	p.H449Q	19	879943	Missense	G	C	c.1347C>G	0.06
1866	WDR18	p.K341E	19	992044	Missense	A	G	c.1021A>G	0.05
1866	ZNF626	p.I495T	19	20807199	Missense	A	G	c.1484T>C	0.14
1866	ZNF257	p.T222I	19	22271217	Missense	C	T	c.665C>T	0.06
1866	NPHS1	p.F973V	19	36330408	Missense	A	C	c.2917T>G	0.06
1866	RYR1	p.F4076C	19	39039005	Missense	T	G	c.12227T>G	0.04
1866	FAM155B	p.H402P	X	68749585	Missense	A	C	c.1205A>C	0.10
1866	CAPN6	p.T472A	X	110491867	Missense	T	C	c.1414A>G	0.05
1866	TENM1	p.C784S	X	123695604	Missense	C	G	c.2351G>C	0.33
1866	GPC4	p.A23V	X	132548926	Missense	G	A	c.68C>T	0.41
1866	SPANXN2	p.P156S	X	142795212	Missense	G	A	c.466C>T	0.07

ABL1	DOK3	NCSTN	SOCS1	SF3B1
BAD	EIF2B2	PIK3AP1	SOD3	ASXL1
BRD1	FOXA1	PIK3CD	STAT3	
CCDC108	GATA4	PKP2	TENM1	
CCND1	HPSE	PNKP	TET2	
COL24A1	IFI44L	PTPRK	TNFAIP3	
COL6A6	IRS2	RBMXL3	TYRP1	
CSMD1	MDC1	RUNX1	ZFHX3	
DNASE2	MPO	SGMS1	ZWILCH	
DNM2	NCKAP5	SMO	STAT5B	

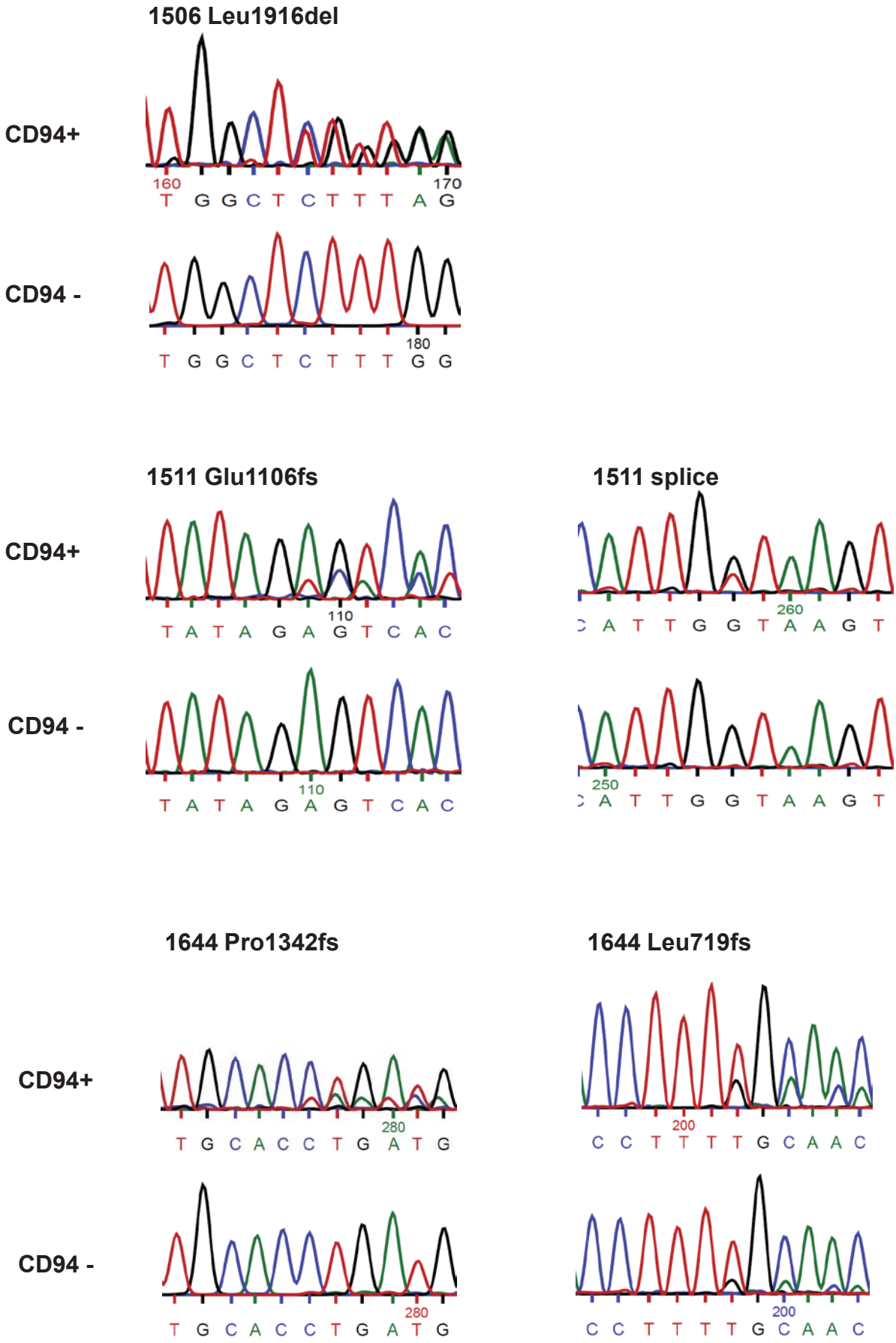
Supplemental Table 3. A limited resequencing panel of genes found to be mutated in the WGS samples. We first generated a list of somatic calls like those from Mutect2 in Supplemental Table 2 and other iterations of Mutect and Strelka from all WGS samples. We prioritized these genes based on their known role in other hematological disorders and leukemia. This analysis revealed 39 genes with functions consistent with a plausible role in the etiology of the disease. We added three genes of interest, underlined above, that had not been found to be mutated in the discovery cohort. Signal transducer and activator of transcription 5B (*STAT5B*) mutations, particularly N642H, have been shown to occur in aggressive NK-LGL leukemia.[4] *ASXL1* and *SF3B1* have been shown to be frequently mutated in myelodysplastic syndromes.[5,6] We included these genes as indicators that these other conditions may be present, but none of the samples used in this study showed mutations in these three genes. All exons plus a 5 basepair pad to include splice sites were targeted in the resequencing panel.

Supplemental Table 4: Assessment of TET2 Mutation Pathogenicity

Each line in the table represents a TET2 mutation in a patient; some patients harbored more than one TET2 mutation. The ACMG/ASH RefSeq transcript NM_001127208.3 was used for this analysis. The ACMG assessment of pathogeneticity for each mutation is listed in the last column.
Abbreviations: ACMG=American College of Medical Genetics , del=deletion, delins=deletion-insertion, VAF=variant allele frequency, VUS=variant of unknown significance

Patient ID	VAF	gDNA	cDNA	protein	ACMG assessment of pathogenicity
1001	5%	chr4:g.106193872A>T	c.4334A>T	p.Q1445L	VUS
1001	9%	chr4:g.106164041G>A	c.3551G>A	p.G1184D	Likely Pathogenic
1166	43%	chr4:g.106164882_106164883dup	c.3750_3751dup	p.T1251Rfs*3	Pathogenic
1257	25%	chr4:g.106197246G>A	c.5579G>A	p.G1860E	VUS
1429	33%	chr4:g.106158500_106158501del	c.3401_3402del	p.R1134Mfs*7	Likely Pathogenic
1429	40%	chr4:g.106156747C>T	c.1648C>T	p.R550*	Pathogenic
1444	41%	chr4:g.106196234C>T	c.4567C>T	p.Q1523*	Pathogenic
1444	42%	chr4:g.106158411_106158415del	c.3312_3316del	p.F1104Lfs*24	Pathogenic
1444	5%	chr4:g.106157788del	c.2689del	p.Q897Rfs*24	Pathogenic
1506	29%	chr4:g.106197413_106197415del	c.5746_5748del	p.L1916delL	VUS
1507	33%	chr4:g.106157389del	c.2290del	p.Q764Kfs*49	Pathogenic
1511	11%	chr4:g.106158416_106158417del	c.3317_3318del	p.E1106Vfs*23	Pathogenic
1511	15%	chr4:g.106190905G>T	c.4182+1G>T	.	Pathogenic
1612	28%	chr4:g.106180784dup	c.3812dup	p.C1271Wfs*29	Pathogenic
1644	28%	chr4:g.106157255del	c.2156del	p.L719Cfs*32	Likely Pathogenic
1644	28%	chr4:g.106182986_106182998del	c.4025_4037del	p.P1342Lfs*17	Pathogenic
1820	22%	chr4:g.106193892C>T	c.4354C>T	p.R1452*	Pathogenic
1870	12%	chr4:g.106197282T>G	c.5615T>G	p.L1872R	VUS
1909	29%	chr4:g.106196565_106196566delinsAA	c.4898_4899delinsAA	p.C1633*	Pathogenic
1967	38%	chr4:g.106158137del	c.3038del	p.P1013Lfs*20	Pathogenic
1967	43%	chr4:g.106164934G>T	c.3802G>T	p.E1268*	Pathogenic
2010	14%	chr4:g.106157257C>T	c.2158C>T	p.Q720*	Pathogenic
2069	4%	chr4:g.106157540_106157541del	c.2441_2442del	p.R814Qfs*6	Likely Pathogenic

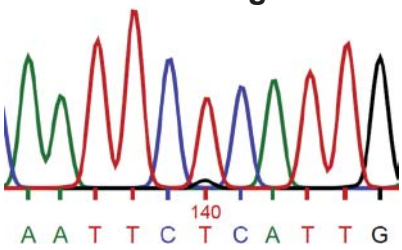
Supplemental Figure 1: (1/2) Sanger Sequencing of TET2 after CD94 isolation.
Patient PBMCS were separated into CD94+ and CD94- fractions. DNA was then extracted and samples were prepared for sequencing as described in the Supplementary Methods. Mutation labels indicate sample ID followed by the mutation being measured.



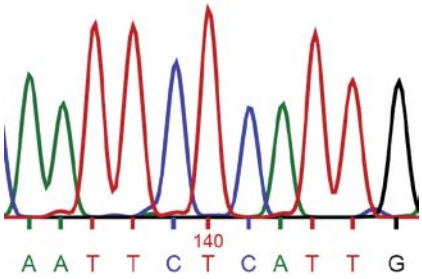
Supplemental Figure 1: (2/2) Sanger Sequencing of TET2 after CD94 isolation.
Patient PBMCS were separated into CD94+ and CD94- fractions. DNA was then extracted and samples were prepared for sequencing as described in the Supplementary Methods. Mutation labels indicate sample ID followed by the mutation being measured.

1870 Leu1872Arg

CD94+

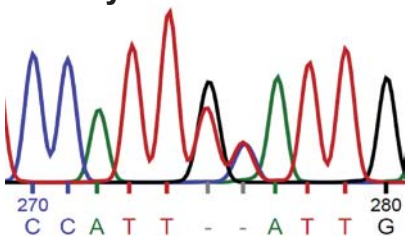


CD94 -

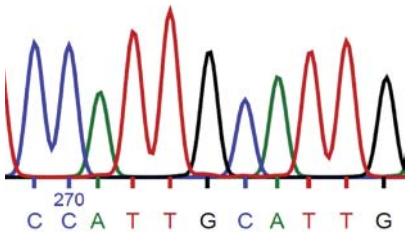


1909 Cys1633Ter

CD94+

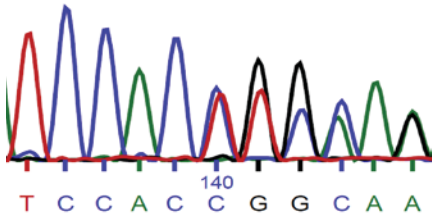


CD94 -

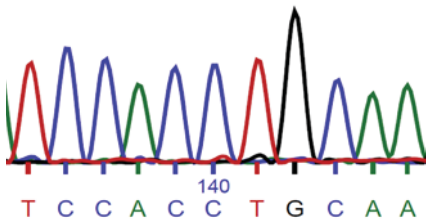


1967 Pro1013fs

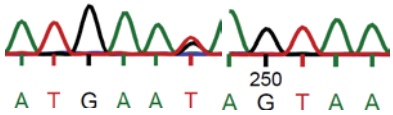
CD94+

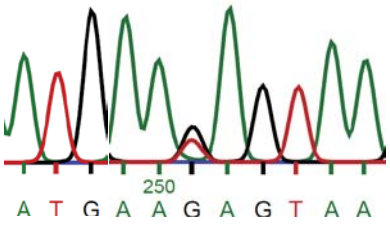


CD94 -



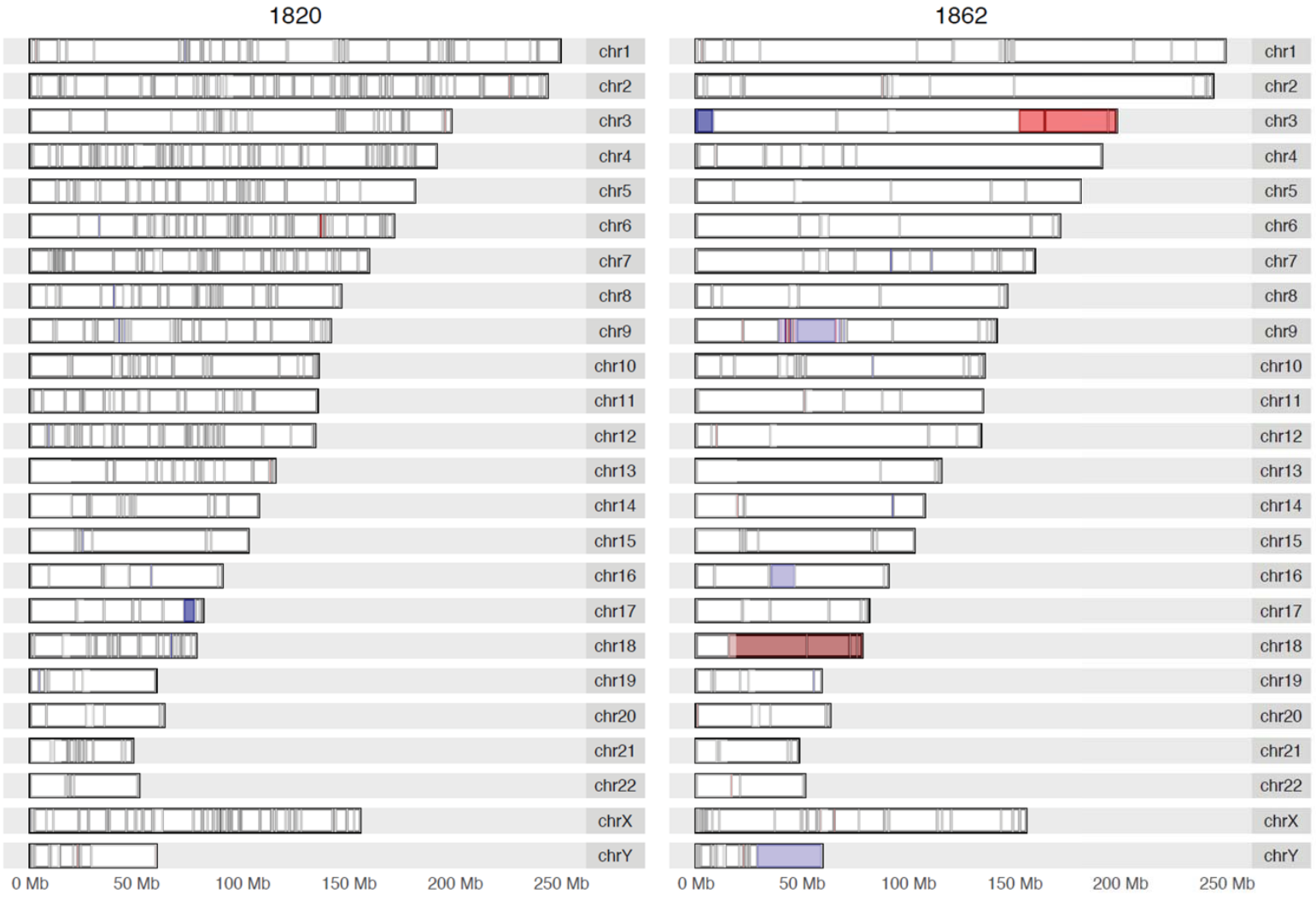
1967 Glu1268Ter

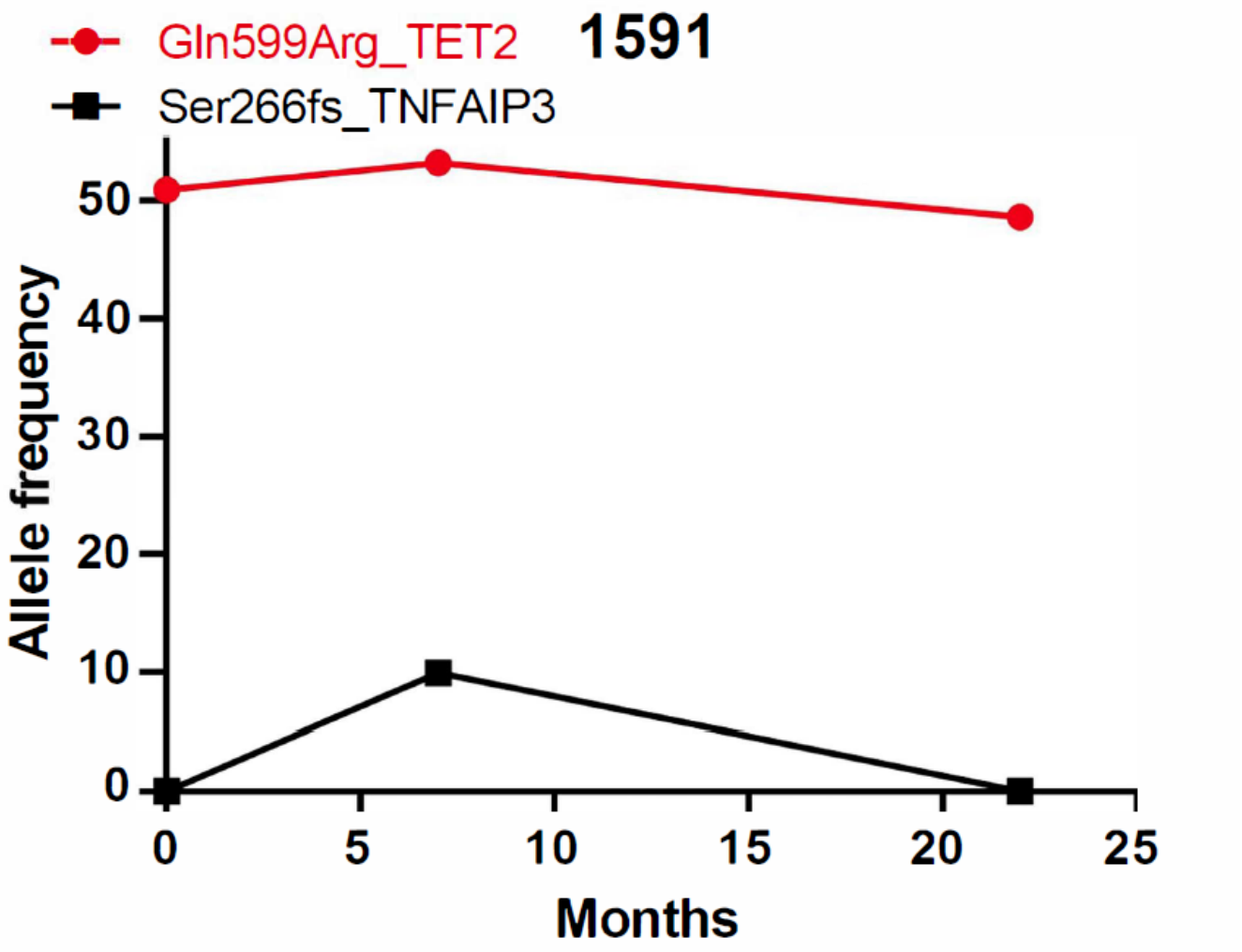




Supplemental Figure 2: Copy Number Variation

Two WGS samples that displayed copy number variation are shown with chromosome number indicated. Regions shown in red and dark red represent amplification event with 4 copies and high level amplification with > 4 copies, respectively. Regions shown in blue and dark blue represent heterozygous and homozygous deletion, respectively.

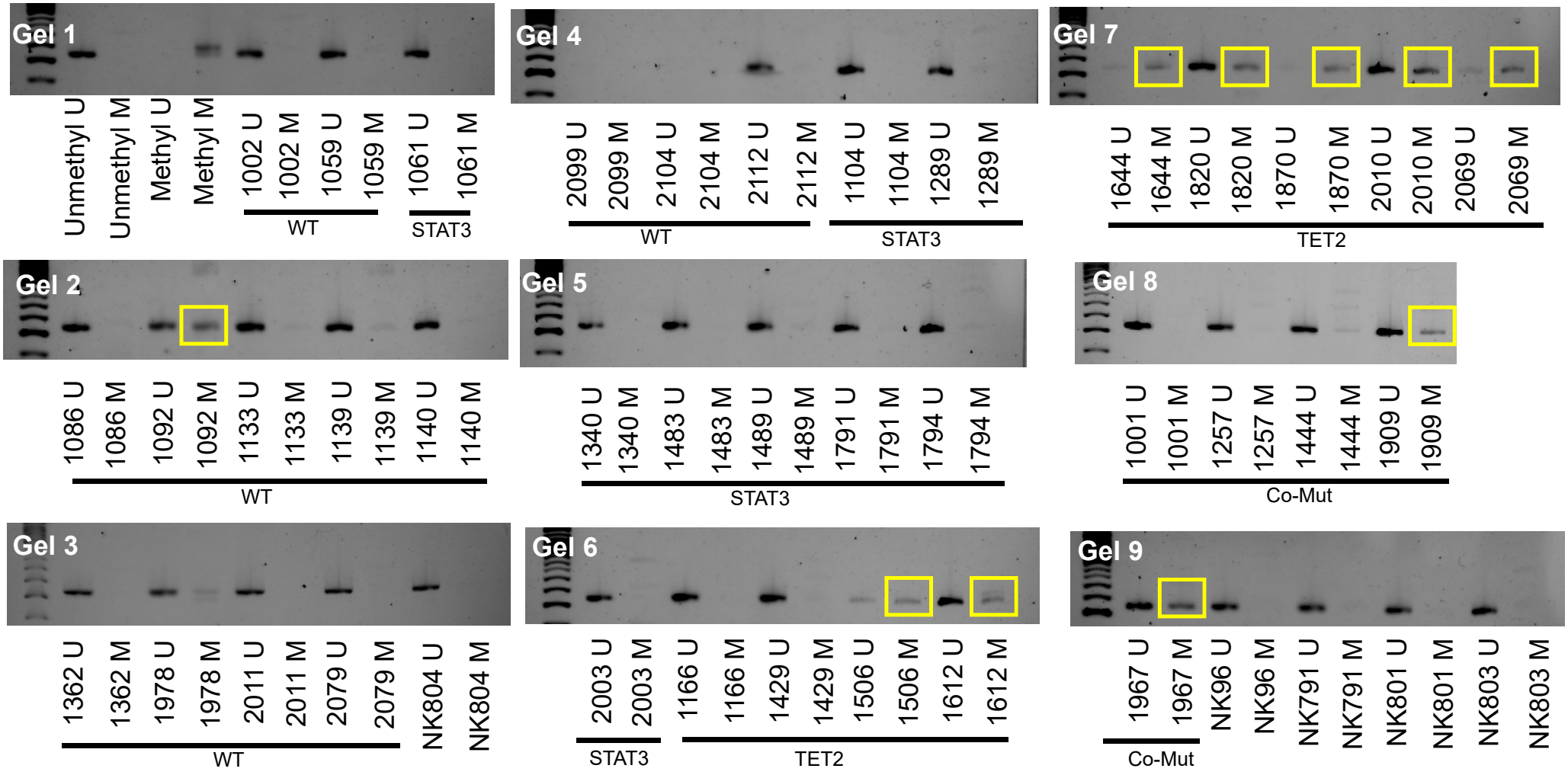




Supplemental Figure 3: Suspected Non-Somatic SNP in *TET2*.

Patient 1591 saw no change in mutation frequency for *TET2*Gln599Arg in a 22- month monitoring period. This mutation has been previously associated with myeloproliferative neoplasms[7], but was suspiciously stable at an allele frequency near 50%. The Exome Aggregation Consortium (ExAC)[8] notes this allele to be present in 0.006 of persons of East Asian descent, which is the self-reported ethnicity of this patient. For this reason we did not include this variant in our list of *TET2* somatic mutations and note the earlier study[7] was in a Korean population. The somatic nature of this variant in myeloid neoplasms may be doubtful as opposed to the others listed there.

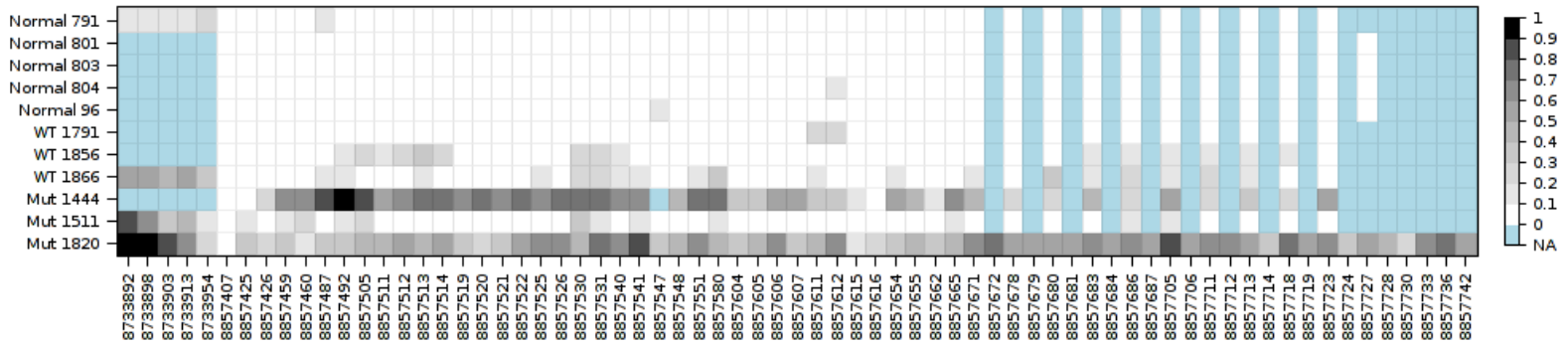
Supplemental Figure 4. TET2 promoter methylation specific assay. All available DNA samples from each mutation group was assayed for methylation of the TET2 promoter. U and M are primer sets to amplify unmethylated (U) and methylated (M) TET2 promoter region. Samples with NK nomenclature are normal donors; mutant groups are marked. Two failed samples in Gel 4 (2099 and 2104) were omitted.



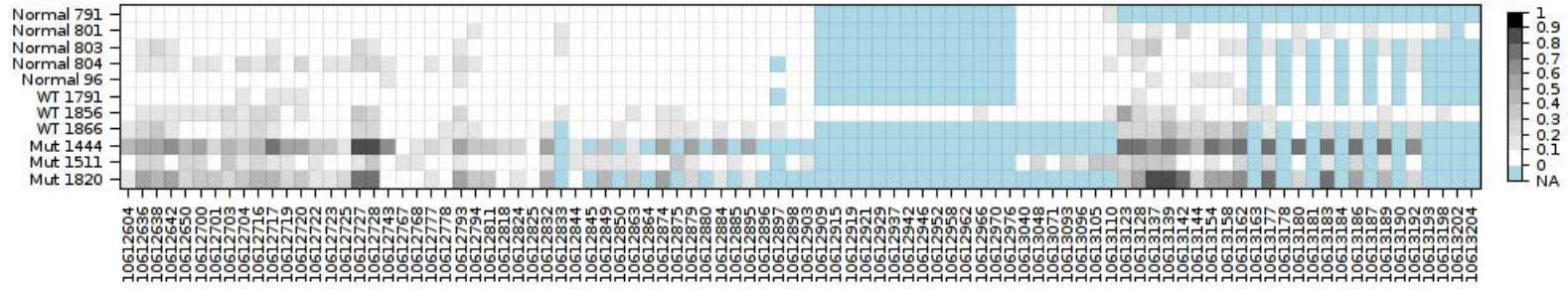
Supplemental Figure 5. Promoter methylation of STAT3 negative regulators.

Fractional methylation at individual CpGs in promoters, where 1=100%methylation. NA=insufficient coverage to call in that sample: PTPRD promoter 1 **(A)**, PTPRD promoter 2 **(B)**, PTPRN promoter **(C)**.

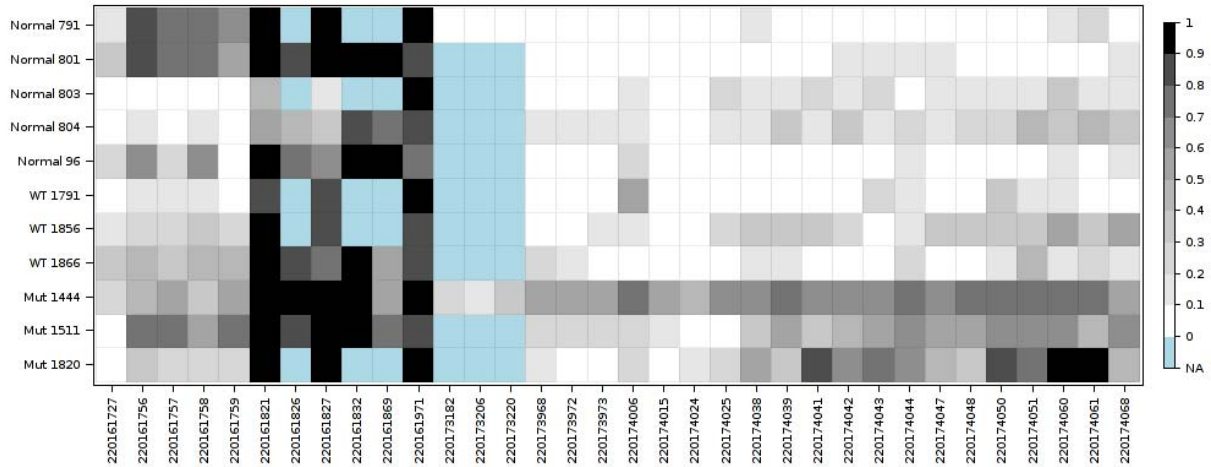
A



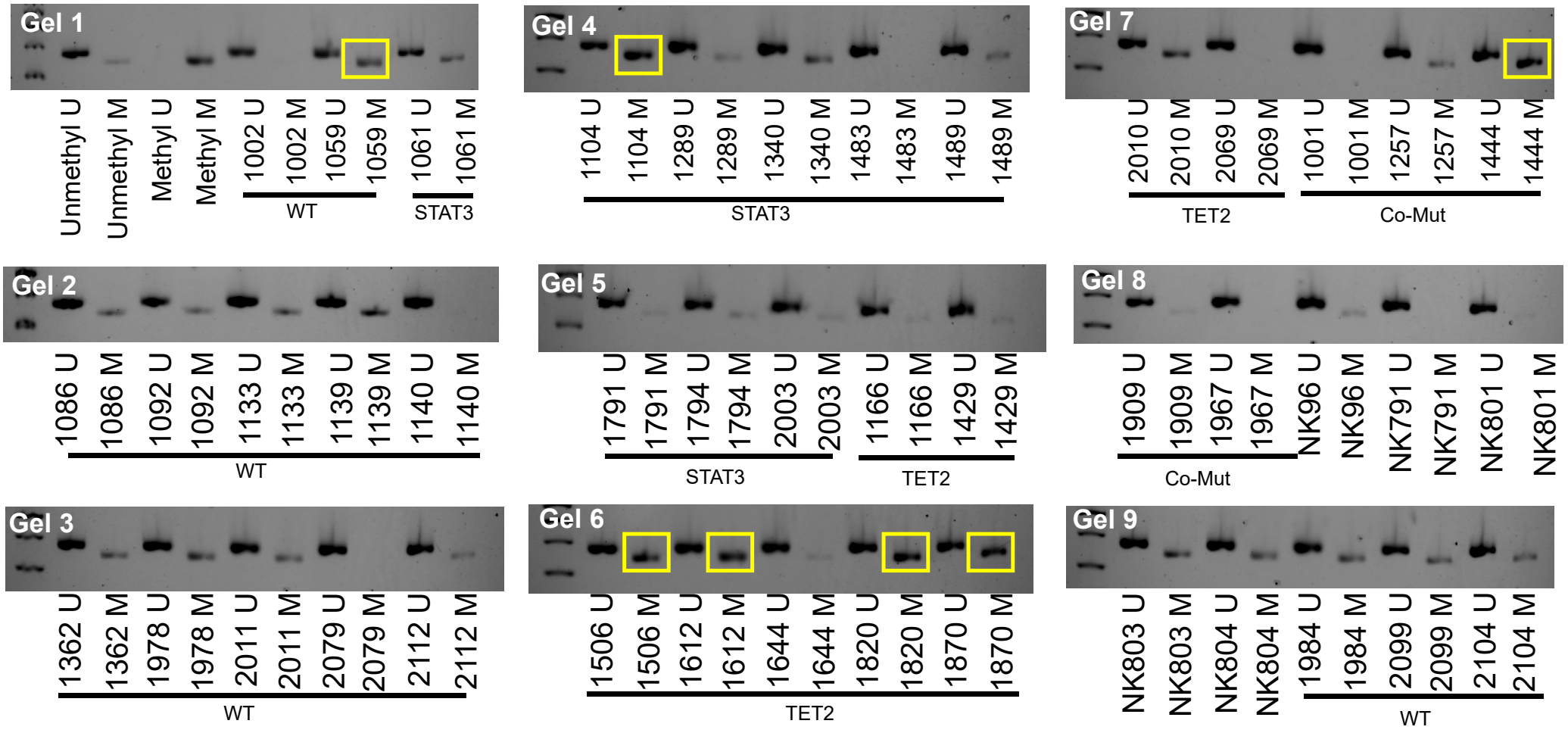
B



C



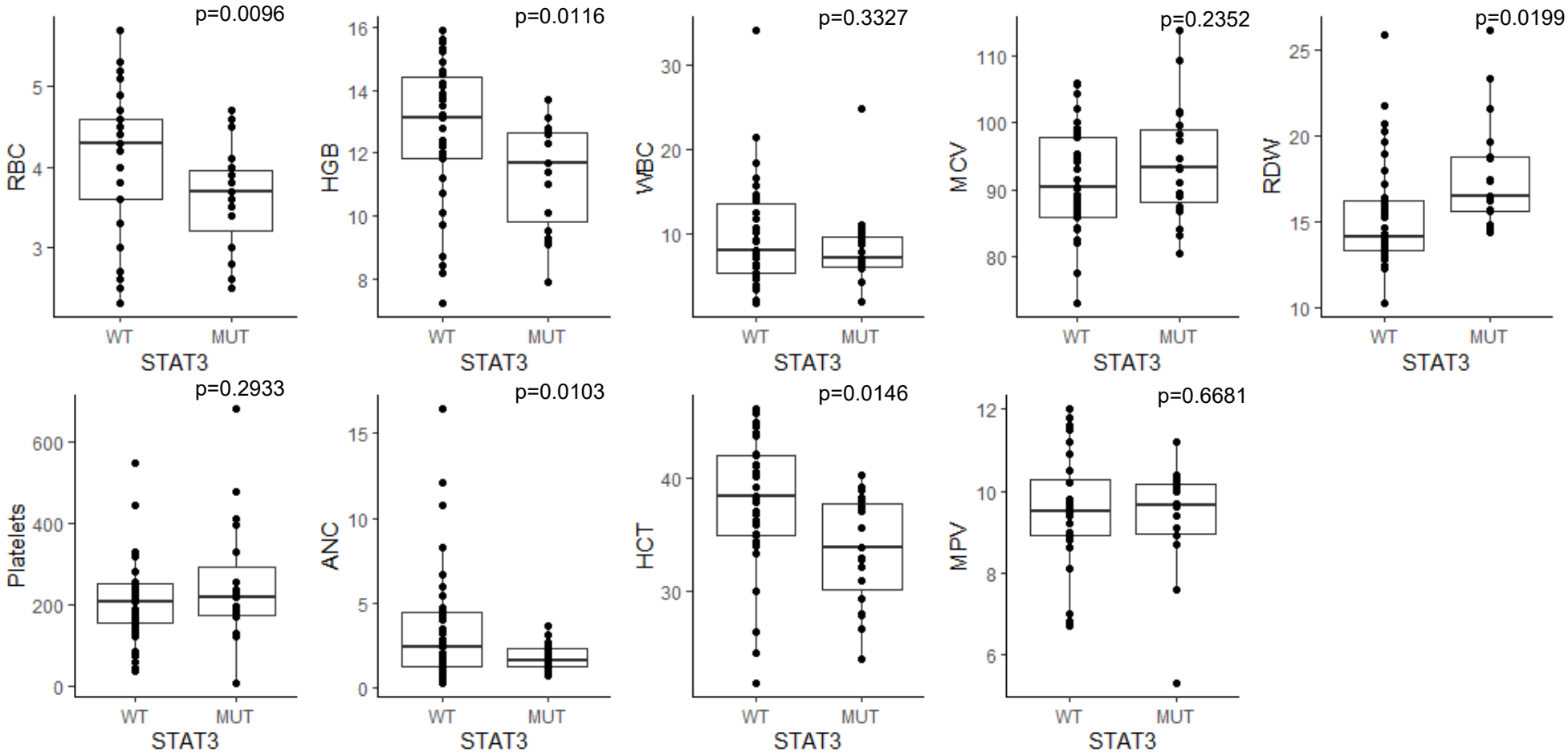
Supplemental Figure 6. PTPRD promoter methylation specific assay. All available DNA samples from each mutation group was assayed for methylation of the PTPRD promoter. U and M are primer sets to amplify unmethylated (U) and methylated (M) PTPRD promoter region. Samples with NK nomenclature are normal donors; mutant groups are marked. Samples 1444 and 1820, clear positives, are the same as those in the RRBS data in Supplemental Figure 5.



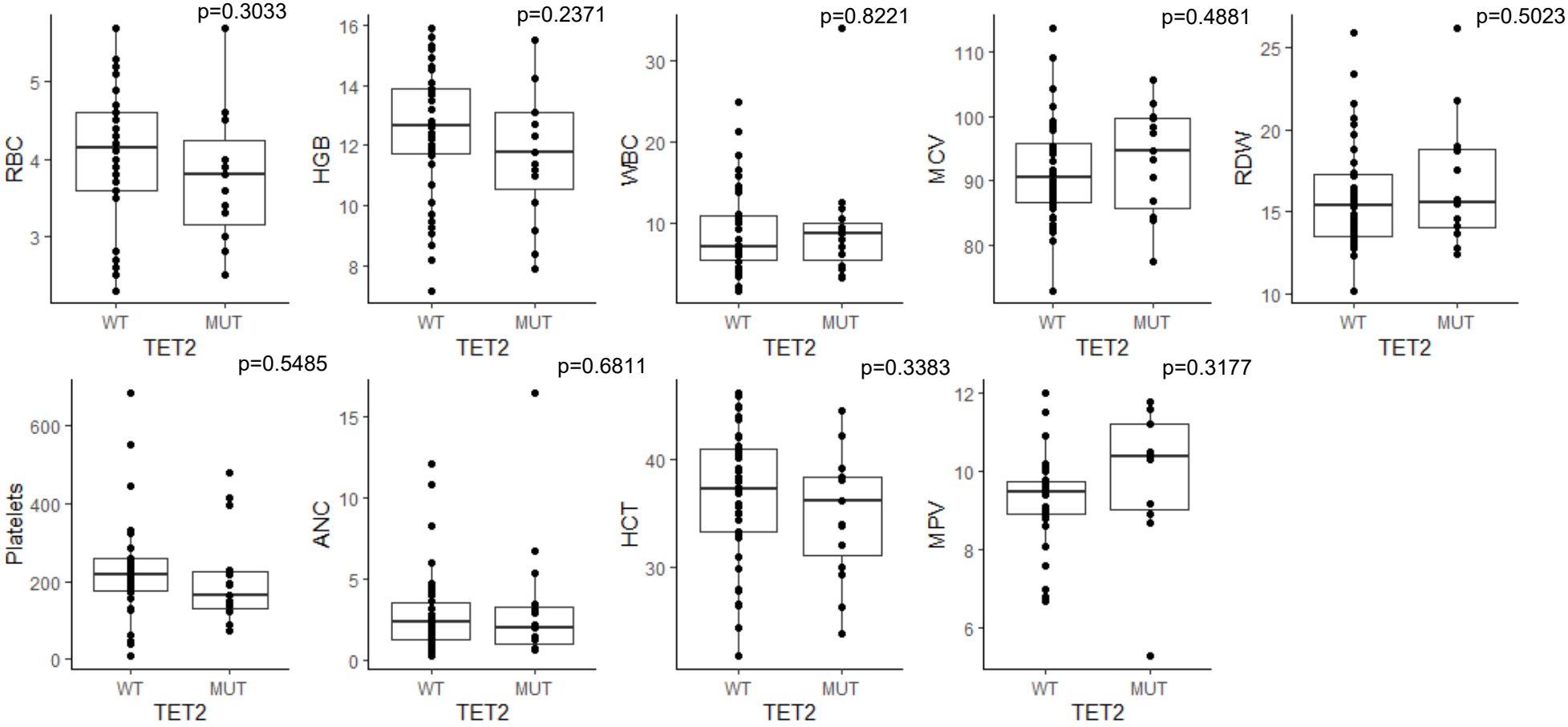
Supplemental Figure 7: CBC Parameters Stratified by STAT3 or TET2-only mutation.

CBC parameters were plotted, showing median and 25% and 75% quartiles. **A.** Samples were analyzed as WT vs. STAT3, where WT includes the TET2-only mutation group. Welch's T-test showed RBC, HGB, HCT, RDW, and ANC were significantly different in the WT group compared to STAT3 mutant. These significant parameters are presented in Figure 6 of the main text; they are also presented here to contrast with the non-significant comparisons. **B.** Samples were analyzed as WT vs. TET2, where WT includes the STAT3-only mutation group. Welch's T-test did not show any statistically significant comparisons.

A. STAT3-only mutation stratification

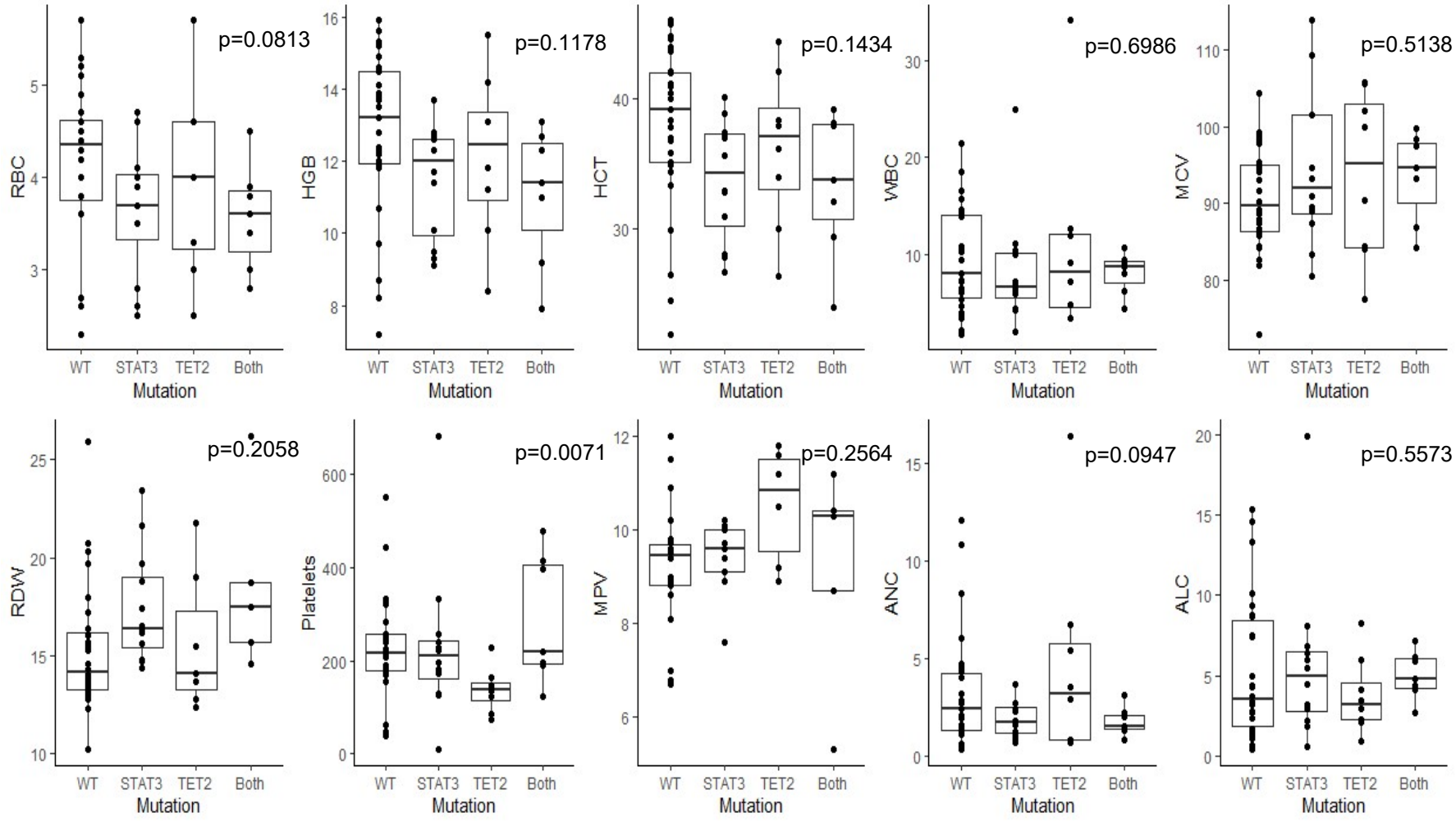


B. TET2-only mutation stratification



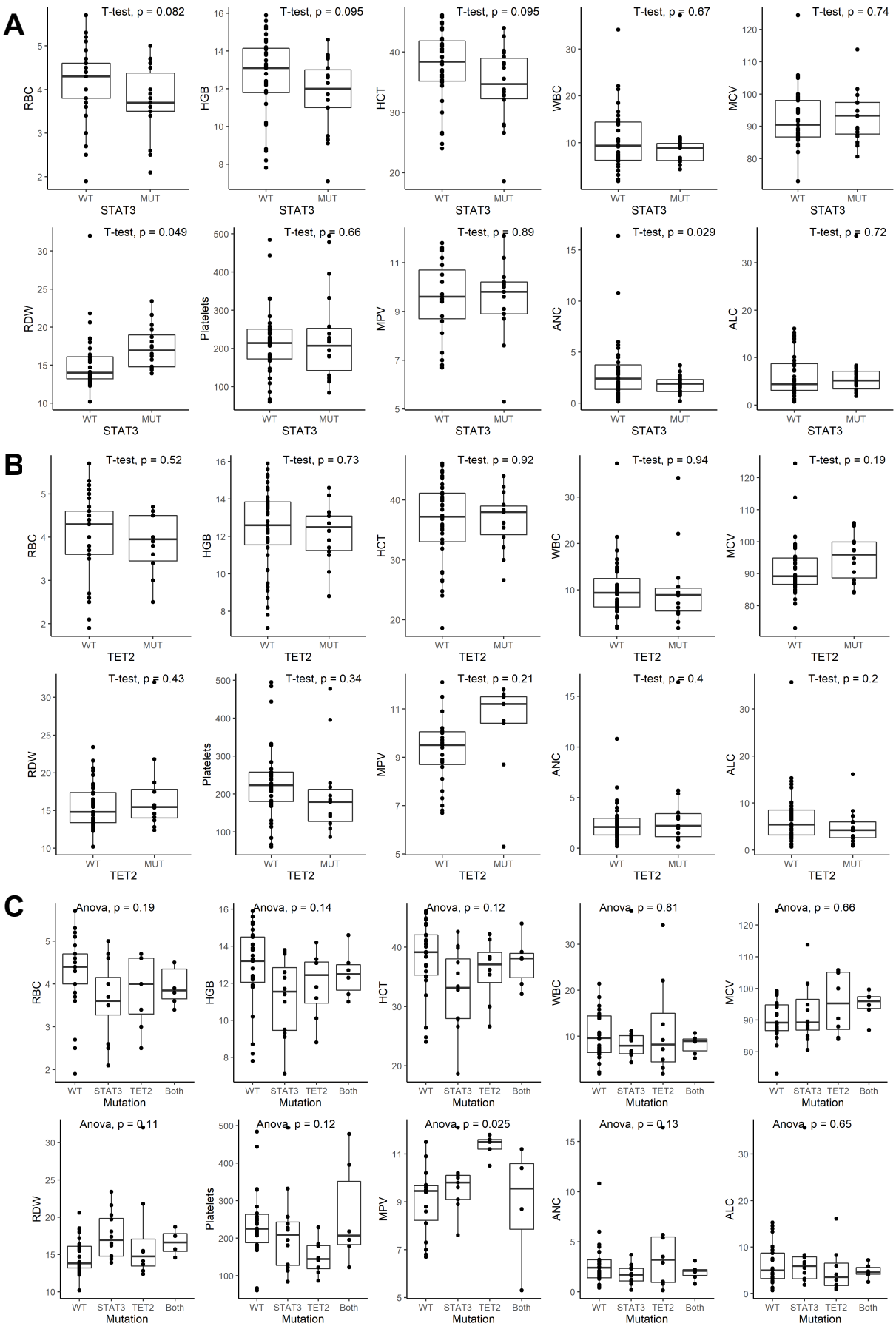
Supplemental Figure 8. CBC Parameters Stratified by Mutation Status.

CBC parameters were plotted, showing median and 25% and 75% quartiles. Data are represented as four mutation groups: WT (no STAT3 or TET2 mutation), STAT3-only, TET2-only, or co-mutation (STAT3+TET2). Welch's ANOVA showed a significant difference in platelets (global p=0.0071) with Games-Howell post-hoc pairwise comparison significance between WT and TET2-only mutation group (p=0.0074). This significant parameter is presented in Figure 7A of the main text; it is also presented here to contrast with the non-significant comparisons.



Supplemental Figure 9: Parameters from no treatment-only CBCs stratified by mutation groups.

CBC parameters were plotted, showing median and 25% and 75% quartiles. All data plotted here are derived from a no-treatment CBC. Although grouped by mutation, sequencing for some may not have been near CBC data collection, thus we cannot ensure mutations were present for those samples. **A.** Samples were analyzed as WT vs. STAT3, where WT includes the TET2-only mutation group. Welch's t-test showed ANC and RDW were significantly different in the WT group. **B.** Samples were analyzed as WT vs. TET2, where WT includes the STAT3-only mutation group. Welch's t-test showed no significant difference with the WT group. **C.** The data were grouped as WT, STAT3 only, TET2 only, or co-mutation (STAT3 and TET2). Welch's ANOVA showed MPV was statistically significant.



Supplemental Tables 5, 6, and 7 are a separate Excel file (*DMR supplemental tables*) and contain DMR, hypermethylation pathway, and hypomethylation pathway data.

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