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Supplementary Table 1. Cases with and without mutations identified during database query.

	AML	MDS	MDS/MPN	MPN	Total
No mutations*	41 (1.8%)	690 (22%)	16 (4.2%)	358 (25%)	1,105 (15%)
1+ mutation	2,214 (98%)	2,413 (78%)	363 (96%)	1,053 (75%)	6,043 (85%)

* Patients without mutations were excluded from further analysis.

Supplementary Table 2: Gene panel

Genes with complete exonic coverage:

ABL1	*ACTB*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1*	*APC*
APH1A	*AR*	*ARAF*	*ARFRP1*	*ARHGAP26*	*ARID1A*	*ARID2*	*ASMTL*
ASXL1	*ATM*	*ATRX*	*AURKA*	*AURKB*	*AXIN1*	*AXL*	*B2M*
BAP1	*BARD1*	*BCL10*	*BCL11B*	*BCL2*	*BCL2L2*	*BCL6*	*BCL7A*
BCOR	*BCORL1*	*BIRC3*	*BLM*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*
BRIP1	*BRSK1*	*BTG2*	*BTK*	*BTLA*	*C11orf30*	*CAD*	*CALR*
CARD11	*CBFB*	*CBL*	*CCND1*	*CCND2*	*CCND3*	*CCNE1*	*CCNE1*
CCT6B	*CD22*	*CD274*	*CD36*	*CD58*	*CD70*	*CD79A*	*CD79B*
CDC73	*CDH1*	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1B*	*CDKN2A*
CDKN2B	*CDKN2C*	*CEBPA*	*CHD2*	*CHEK1*	*CHEK2*	*CIC*	*CIITA*
CKS1B	*CPS1*	*CREBBP*	*CRKL*	*CRLF2*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUX1*	*CXCR4*	*DAXX*	*DDR2*	*DDX3X*	*DNM2*
DNMT3A	*DOT1L*	*DTX1*	*DUSP2*	*DUSP9*	*EBF1*	*ECT2L*	*EED*
EGFR	*ELP2*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*
ERBB3	*ERBB4*	*ERG*	*ESR1*	*ETS1*	*ETV6*	*EXOSC6*	*EZH2*
FAF1	*FAM46C*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*	*FANCF*	*FANCG*
FANCL	*FAS*	*FBXO11*	*FBXO31*	*FBXW7*	*FGF10*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FHIT	*FLCN*	*FLT1*	*FLT3*	*FLT4*	*FLYWCH1*	*FOXL2*	*FOXO1*
FOXO3	*FOXP1*	*FRS2*	*GADD45B*	*GATA1*	*GATA2*	*GATA3*	*GID4*
GNA11	*GNA12*	*GNA13*	*GNAQ*	*GNAS*	*GPR124*	*GRIN2A*	*GSK3B*
GTSE1	*HDAC1*	*HDAC4*	*HDAC7*	*HGF*	*HIST1H1C*	*HIST1H1D*	*HIST1H1E*
HIST1H2AC	*HIST1H2AG*	*HIST1H2AL*	*HIST1H2AM*	*HIST1H2BC*	*HIST1H2BJ*	*HIST1H2BK*	*HIST1H2BO*
HIST1H3B	*HNF1A*	*HRAS*	*HSP90AA1*	*ICK*	*ID3*	*IDH1*	*IDH2*
IGF1R	*IKBKE*	*IKZF1*	*IKZF2*	*IKZF3*	*IL7R*	*INHBA*	*INPP4B*
INPP5D	*IRF1*	*IRF4*	*IRF8*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JARID2	*JUN*	*KAT6A*	*KDM2B*	*KDM4C*	*KDM5A*	*KDM5C*	*KDM6A*
KDR	*KEAP1*	*KIT*	*KLHL6*	*KMT2A*	*KMT2C*	*KMT2D*	*KRAS*
LEF1	*LRP1B*	*LRRK2*	*MAF*	*MAFB*	*MAGED1*	*MALT1*	*MAP2K1*
MAP2K2	*MAP2K4*	*MAP3K1*	*MAP3K14*	*MAP3K6*	*MAP3K7*	*MAPK1*	*MCL1*
MDM2	*MDM4*	*MED12*	*MEF2B*	*MEF2C*	*MEN1*	*MET*	*MIB1*
MITF	*MKI67*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*	*MSH6*
MTOR	*MUTYH*	*MYC*	*MYCL*	*MYCN*	*MYD88*	*MYO18A*	*NCOR2*
NCSTN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOD1*	*NOTCH1*
NOTCH2	*NPM1*	*NRAS*	*NSD1*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
NUP93	*NUP98*	*P2RY8*	*PAG1*	*PAK3*	*PALB2*	*PASK*	*PAX5*
PBRM1	*PC*	*PCBP1*	*PCLO*	*PDCD1*	*PDCD11*	*PDCD1LG2*	*PDGFRA*
PDGFRB	*PDK1*	*PHF6*	*PIK3CA*	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PIM1*
PLCG2	*POT1*	*PPP2R1A*	*PRDM1*	*PRKAR1A*	*PRKDC*	*PRSS8*	*PTCH1*
PTEN	*PTPN11*	*PTPN2*	*PTPN6*	*PTPRO*	*RAD21*	*RAD50*	*RAD51*
RAF1	*RARA*	*RASGEF1A*	*RB1*	*RELN*	*RET*	*RHOA*	*RICTOR*
RNF43	*ROS1*	*RPTOR*	*RUNX1*	*S1PR2*	*SDHA*	*SDHB*	*SDHC*
SDHD	*SERP2*	*SETBP1*	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*
SMARCA1	*SMARCA4*	*SMARCB1*	*SMC1A*	*SMC3*	*SMO*	*SOCS1*	*SOCS2*
SOCS3	*SOX10*	*SOX2*	*SPEN*	*SPOP*	*SRC*	*SRSF2*	*STAG2*
STAT3	*STAT4*	*STAT5A*	*STAT5B*	*STAT6*	*STK11*	*SUFU*	*SUZ12*
TAF1	*TBL1XR1*	*TCF3*	*TCL1A*	*TET2*	*TGFBR2*	*TLL2*	*TMEM30A*
TMSB4XP8	*TNFAIP3*	*TNFRSF11A*	*TNFRSF14*	*TNFRSF17*	*TOP1*	*TP53*	*TP63*
TRAF2	*TRAF3*	*TRAF5*	*TSC1*	*TSC2*	*TSHR*	*TUSC3*	*TYK2*
U2AF1	*U2AF2*	*VHL*	*WDR90*	*WHSC1*	*WISP3*	*WT1*	*XBP1*
XPO1	*YY1AP1*	*ZMYM3*	*ZNF217*	*ZNF24*	*ZNF703*	*ZRSR2*	

Genes with select intronic coverage:

ALK	*BCL2*	*BCL6*	*BCR*	*BRAF*	*CCND1*	*CRLF2*	*EGFR*
EPOR	*ETV1*	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*FGFR2*	*IGH*
IGK	*IGL*	*JAK1*	*JAK2*	*KMT2A*	*MYC*	*NTRK1*	*PDGFRA*
PDGFRB	*RAF1*	*RARA*	*RET*	*ROS1*	*TMPRSS2*	*TRG*	

Genes with RNA sequencing coverage

ABl1	*ABL1*	*ABL2*	*ACSL6*	*AFF1*	*AFF4*	*ALK*	*ARHGAP26*
ARHGEF12	*ARID1A*	*ARNT*	*ASXL1*	*ATF1*	*ATG5*	*ATIC*	*BCL10*
BCL11A	*BCL11B*	*BCL2*	*BCL3*	*BCL6*	*BCL7A*	*BCL9*	*BCOR*
BCR	*BIRC3*	*BRAF*	*BTG1*	*CAMTA1*	*CARS*	*CBFA2T3*	*CBFB*
CBL	*CCND1*	*CCND2*	*CCND3*	*CD274*	*CDK6*	*CDX2*	*CHIC2*
CHN1	*CIC*	*CIITA*	*CLP1*	*CLTC*	*CLTCL1*	*CNTRL*	*COL1A1*
CREB3L1	*CREB3L2*	*CREBBP*	*CRLF2*	*CSF1*	*CTNNB1*	*DDIT3*	*DDX10*
DDX6	*DEK*	*DUSP22*	*EGFR*	*EIF4A2*	*ELF4*	*ELL*	*ELN*
EML4	*EP300*	*EPOR*	*EPS15*	*ERBB2*	*ERG*	*ETS1*	*ETV1*
ETV4	*ETV5*	*ETV6*	*EWSR1*	*FCGR2B*	*FCRL4*	*FEV*	*FGFR1*
FGFR1OP	*FGFR2*	*FGFR3*	*FLI1*	*FNBP1*	*FOXO1*	*FOXO3*	*FOXO4*
FOXP1	*FSTL3*	*FUS*	*GAS7*	*GLI1*	*GMPS*	*GPHN*	*HERPUD1*
HEY1	*HIP1*	*HIST1H4I*	*HLF*	*HMGA1*	*HMGA2*	*HOXA11*	*HOXA13*
HOXA3	*HOXA9*	*HOXC11*	*HOXC13*	*HOXD11*	*HOXD13*	*HSP90AA1*	*HSP90AB1*
IGH	*IGK*	*IGL*	*IKZF1*	*IL21R*	*IL3*	*IRF4*	*ITK*
JAK1	*JAK2*	*JAK3*	*JAZF1*	*KAT6A*	*KDSR*	*KIF5B*	*KMT2A*
LASP1	*LCP1*	*LMO1*	*LMO2*	*LPP*	*LYL1*	*MAF*	*MAFB*
MALT1	*MDS2*	*MECOM*	*MKL1*	*MLF1*	*MLLT1*	*MLLT10*	*MLLT3*
MLLT4	*MLLT6*	*MN1*	*MNX1*	*MSI2*	*MSN*	*MUC1*	*MYB*
MYC	*MYH11*	*MYH9*	*NACA*	*NBEAP1*	*NCOA2*	*NDRG1*	*NF1*
NF2	*NFKB2*	*NIN*	*NOTCH1*	*NPM1*	*NR4A3*	*NSD1*	*NTRK1*
NTRK2	*NTRK3*	*NUMA1*	*NUP214*	*NUP98*	*NUTM2A*	*OMD*	*P2RY8*
PAFAH1B2	*PAX3*	*PAX5*	*PAX7*	*PBX1*	*PCM1*	*PCSK7*	*PDCD1LG2*
PDE4DIP	*PDGFB*	*PDGFRA*	*PDGFRB*	*PER1*	*PHF1*	*PICALM*	*PIM1*
PLAG1	*PML*	*POU2AF1*	*PPP1CB*	*PRDM1*	*PRDM16*	*PRRX1*	*PSIP1*
PTCH1	*PTK7*	*RABEP1*	*RAF1*	*RALGDS*	*RAP1GDS1*	*RARA*	*RBM15*
RET	*RHOH*	*RNF213*	*ROS1*	*RPL22*	*RPN1*	*RUNX1*	*RUNX1T1*
RUNX2	*SEC31A*	*SEPT5*	*SEPT6*	*SEPT9*	*SET*	*SH3GL1*	*SLC1A2*
SNX29	*SRSF3*	*SS18*	*SSX1*	*SSX2*	*SSX4*	*STAT6*	*STL*
SYK	*TAF15*	*TAL1*	*TAL2*	*TBL1XR1*	*TCF3*	*TCL1A*	*TEC*
TET1	*TFE3*	*TFG*	*TFPT*	*TFRC*	*TLX1*	*TLX3*	*TMPRSS2*
TNFRSF11A	*TOP1*	*TP63*	*TPM3*	*TPM4*	*TRIM24*	*TRIP11*	*TTL*
TYK2	*USP6*	*WHSC1*	*WHSC1L1*	*YPEL5*	*ZBTB16*	*ZMYM2*	*ZNF384*
ZNF521							

Supplementary Table 3. Overall mutation rate of included myeloid neoplasms (n = 6,043).

Gene	No. of mutated cases	Frequency (included if >1%)
ASXL1	1,414	0.23399
TET2	1,233	0.204038
SRSF2	965	0.159689
TP53	909	0.150422
DNMT3A	866	0.143306
RUNX1	836	0.138342
NRAS	645	0.106735
JAK2	630	0.104253
SF3B1	555	0.091842
FLT3	515	0.085223
U2AF1	492	0.081417
IDH2	453	0.074963
NPM1	414	0.068509
KMT2A	379	0.062717
STAG2	379	0.062717
KRAS	346	0.057256
PTPN11	297	0.049148
BCOR	296	0.048982
IDH1	271	0.044845
EZH2	248	0.041039
WT1	244	0.040377
SETBP1	243	0.040212
NF1	232	0.038392
ZRSR2	223	0.036902
CBL	190	0.031441
CEBPA	182	0.030117
CUX1	176	0.029125
CHEK2	165	0.027304
ETV6	165	0.027304
PHF6	153	0.025319
CALR	136	0.022505
MLL3	128	0.021182
MPL	124	0.02052
MUTYH	122	0.020189
GATA2	119	0.019692
ATM	116	0.019196
KIT	103	0.017045
CCT6B	102	0.016879
CD36	100	0.016548
CSF3R	96	0.015886
PASK	93	0.01539
BCORL1	88	0.014562
ABL1	66	0.010922
GNAS	65	0.010756
MAP3K6	65	0.010756
MLL2	64	0.010591
ARID2	61	0.010094
SH2B3	61	0.010094

Supplementary Table 4. Patient demographics: *ASXL1*$^{c.1934dupG}$ vs. *ASXL1*^{other}

	AML			**MDS**			**MPN**		
	c.1934dupG	Others	Total	c.1934dupG	Others	Total	c.1934dupG	Others	Total
Number of patients	160	248	408	172	358	530	106	177	283
Age									
Minimum	18	18		41	18		34	20	
25% Percentile	63.25	61		67	65.75		66.75	64	
Median	70.5	70		75	74		73	70	
75% Percentile	78	76		80	79		77.25	78	
Maximum	92	95		91	95		95	93	
Range	74	77		50	77		61	73	
p (Mann-Whitney U)	0.136			0.3055			0.1932		
Sex									
Male	113	167	280	125	247	372	70	121	191
Female	47	81	128	47	111	158	36	56	92
M:F	2.40	2.06	2.19	2.66	2.23	2.35	1.94	2.16	2.08
P (Fisher's)	0.5133			0.4180			0.6960		
Ancestry signature									
European	130	190	320	140	300	440	88	139	227
Non-European	30	58	88	32	58	90	18	38	56
Eur:non-Eur	4.33	3.28	3.64	4.38	5.17	4.89	4.89	3.66	4.05
P (Fisher's)	0.3240			0.5370			0.4412		
	MDS/MPN			**All myeloid neoplasms**					
	c.1934dupG	Others	Total	c.1934dupG	Others	Total			
Number of patients	82	111	193	520	894	1414			
Age									
Minimum	56	44		18	18				
25% Percentile	65.75	64		66	64				
Median	71	71		72	72				
75% Percentile	77	78		78	78				
Maximum	90	92		95	95				
Range	34	48		77	77				
p (Mann-Whitney U)	0.8305			0.0921					
Sex									
Male	54	74	128	362	609	971			
Female	28	37	65	158	285	443			
M:F	1.93	2.00	1.97	2.29	2.14	2.19			
P (Fisher's)	1.0000			0.5927					
Ancestry signature									
European	70	91	161	420	720	1140			
Non-European	12	20	32	100	174	274			
Eur:non-Eur	5.83	4.55	5.03	4.20	4.14	4.16			
P (Fisher's)	0.5634			0.9444					

Supplementary Table 5. Co-mutation frequencies: *ASXL1*$^{c.1934dupG}$ vs. *ASXL1*^{other}

All MNs	c.1934dupG	Others	P		c.1934dupG	Others	P
SRSF2	0.3788	0.3409	0.1707	***ZRSR2***	0.0596	0.0668	0.6419
TET2	0.2846	0.2794	0.8492	***NF1***	0.0673	0.0561	0.4734
RUNX1	0.2904	0.2687	0.4077	***CUX1***	0.0692	0.0535	0.2791
NRAS	0.1865	0.1818	0.8255	***BCOR***	0.0635	0.0575	0.7185
STAG2	0.2135	0.1604	**0.0179**	***IDH1***	0.0635	0.0468	0.2065
EZH2	0.1596	0.1283	0.1199	***TP53***	0.0404	0.0628	0.0989
U2AF1	0.1173	0.1537	0.0694	***FLT3***	0.0615	0.0455	0.2472
SETBP1	0.1038	0.1524	**0.0144**	***PHF6***	0.0538	0.0508	0.7989
IDH2	0.1365	0.1083	0.1355	***DNMT3A***	0.0481	0.0548	0.7001
JAK2	0.0942	0.1190	0.1703	***ETV6***	0.0538	0.0495	0.7959
KRAS	0.1000	0.0922	0.6977	***KMT2A***	0.0635	0.0348	**0.0208**
CBL	0.0596	0.0749	0.3111	***SF3B1***	0.0404	0.0508	0.4185
PTPN11	0.0712	0.0655	0.7338				

AML	c.1934dupG	Others	P		c.1934dupG	Others	P
SRSF2	0.3688	0.4020	0.5879	***PTPN11***	0.0750	0.1029	0.4624
RUNX1	0.3938	0.3578	0.5133	***PHF6***	0.0875	0.0931	1.0000
STAG2	0.2813	0.2451	0.4715	***TP53***	0.0313	0.1127	**0.0047**
TET2	0.2375	0.2304	0.9011	***DNMT3A***	0.0938	0.0539	0.1558
NRAS	0.1938	0.2206	0.6037	***JAK2***	0.0625	0.0784	0.6828
IDH2	0.2438	0.1667	0.0861	***NF1***	0.0625	0.0784	0.6828
U2AF1	0.1000	0.1225	0.6168	***ETV6***	0.0938	0.0490	0.0999
EZH2	0.1188	0.1078	0.7419	***CEBPA***	0.0625	0.0539	0.8220
IDH1	0.1313	0.0931	0.3111	***CSF3R***	0.0688	0.0441	0.3575
KRAS	0.1188	0.1029	0.7360	***CBL***	0.0438	0.0490	1.0000
SETBP1	0.0688	0.1373	**0.0407**	***CUX1***	0.0250	0.0490	0.2820
BCOR	0.1125	0.1029	0.8647	***ZRSR2***	0.0500	0.0245	0.2568
FLT3	0.0938	0.0980	1.0000	***SF3B1***	0.0438	0.0147	0.1128
KMT2A	0.1188	0.0686	0.1402				

MDS	c.1934dupG	Others	P		c.1934dupG	Others	P
SRSF2	0.3721	0.2915	0.0951	***KRAS***	0.0581	0.0627	1.0000
RUNX1	0.3140	0.3137	1.0000	***CUX1***	0.0930	0.0332	**0.0106**
TET2	0.2965	0.2952	1.0000	***JAK2***	0.0523	0.0590	0.8353
STAG2	0.2500	0.2140	0.4165	***TP53***	0.0523	0.0590	0.8353
U2AF1	0.1802	0.2177	0.3966	***PTPN11***	0.0756	0.0406	0.1329
EZH2	0.1453	0.1439	1.0000	***DNMT3A***	0.0291	0.0590	0.1738
NRAS	0.1337	0.1181	0.6587	***PHF6***	0.0407	0.0480	0.8172
IDH2	0.1221	0.1033	0.5384	***NF1***	0.0465	0.0406	0.8121
ZRSR2	0.0930	0.1144	0.5291	***CEBPA***	0.0465	0.0369	0.6287
SETBP1	0.0814	0.1181	0.2639	***IDH1***	0.0407	0.0295	0.5937
SF3B1	0.0698	0.1033	0.3074	***GATA2***	0.0349	0.0258	0.5774
BCOR	0.0698	0.0590	0.6910	***ETV6***	0.0291	0.0295	1.0000
CBL	0.0581	0.0627	1.0000				

Supplementary Table 5 continued.

MDS/MPN	c.1934dupG	Others	P		c.1934dupG	Others	P
SRSF2	0.4634	0.4706	1.0000	***IDH2***	0.0610	0.0882	0.5826
TET2	0.4268	0.3725	0.5444	***U2AF1***	0.0732	0.0784	1.0000
NRAS	0.2805	0.3039	0.7475	***PTPN11***	0.0732	0.0686	1.0000
RUNX1	0.2683	0.2647	1.0000	***KMT2A***	0.0976	0.0196	**0.0248**
SETBP1	0.1585	0.2549	0.1464	***JAK2***	0.0244	0.0784	0.1889
KRAS	0.1707	0.1863	0.8482	***ZRSR2***	0.0488	0.0490	1.0000
CBL	0.1098	0.1961	0.1536	***KIT***	0.0366	0.0490	0.7338
EZH2	0.1707	0.1275	0.5301	***BCOR***	0.0244	0.0490	0.4639
NF1	0.1341	0.0882	0.3487	***CEBPA***	0.0244	0.0392	0.6937
CUX1	0.0854	0.1078	0.8036	***DNMT3A***	0.0244	0.0294	1.0000
STAG2	0.1220	0.0686	0.3058	***PHF6***	0.0244	0.0294	1.0000
ETV6	0.0732	0.1078	0.4555	***CSF3R***	0.0000	0.0392	0.1298
FLT3	0.0976	0.0784	0.7935	***SF3B1***	0.0000	0.0392	0.1298

MPN	c.1934dupG	Others	P		c.1934dupG	Others	P
SRSF2	0.3396	0.2733	0.2707	***GATA2***	0.0849	0.0533	0.3226
JAK2	0.2642	0.3133	0.4071	***STAG2***	0.1226	0.0133	**0.0005**
TET2	0.2264	0.2667	0.5580	***PTPN11***	0.0566	0.0600	1.0000
NRAS	0.1887	0.1800	0.8711	***CBL***	0.0472	0.0600	0.7838
EZH2	0.2358	0.1400	0.0683	***IDH2***	0.0566	0.0533	1.0000
SETBP1	0.1509	0.1867	0.5041	***DNMT3A***	0.0283	0.0600	0.3692
U2AF1	0.0755	0.1400	0.1601	***NF1***	0.0566	0.0400	0.5607
CALR	0.0943	0.0867	0.8283	***IDH1***	0.0472	0.0467	1.0000
RUNX1	0.1132	0.0667	0.2574	***TP53***	0.0566	0.0267	0.3268
MPL	0.0377	0.1000	0.0884	***ZRSR2***	0.0283	0.0467	0.5303
CSF3R	0.0472	0.0933	0.2269	***CCND2***	0.0377	0.0400	1.0000
CUX1	0.0849	0.0667	0.6328	***ETV6***	0.0189	0.0467	0.3134
KRAS	0.0849	0.0667	0.6328				

Supplementary Table 6. Cohesin gene mutations in the cohort.

	***ASXL1*^{wt} (n = 4,629)**	**Frequency**	***ASXL1*^{mut} (n = 1,414)**	**Frequency**	***ASXL1* CBM mutation**
RAD21	42	0.0090	9	0.0064	1
SMC1A	4	0.0008	4	0.0028	0
SMC3	1	0.0002	0	0	0
STAG2	144	0.0311	235	0.1670	6
Any cohesin	191	0.0412	244	0.1726	7

CBM: cohesin-binding motif

Supplementary Table 7. *ASXL1*/cohesin gene co-mutated cases by *ASXL1* region

Phenotype	Sex	Age	*ASXL1*	VAF	*RAD21*	VAF	*STAG2*	VAF*	Other mutations
AML	F	57	Q428fs*10	0.39			L688*	0.44	*EZH2, SETBP1*
MDS	M	64	Q491*	0.38			R953*	0.39	*BCOR, PHF6, RUNX1, SRSF2*
MDS	M	78	S503fs*3	0.42			R1012*	0.40	*RUNX1*
MPN	F	85	D505fs*4	0.42			R614*	0.03	*KIT, SETBP1*
AML	M	73	Q512*	0.41			F121fs*24	0.14	*CSF3R, RUNX1, SETBP1, U2AF1*
MDS/MPN	M	66	Q512*	0.39			L921fs*8	0.27	*BCOR, EZH2*
AML	M	86	Q546*	0.44	K406fs*4	0.17			*BCOR, CEBPA, EZH2, IDH1, PTPN11, RUNX1*
MDS	M	89	Y591*	0.37			Q269*	0.28	*EZH2, U2AF1*
AML	M	77	Y591*	0.41			R1045*	0.46	*SRSF2, TET2*
MDS	M	85	Y591fs*1	0.38			S819fs*53	0.34	*EZH2, RUNX1, ZRSR2*
AML	M	69	Y591fs*1	0.35			splice site 3460_ 3467+21del29	0.32	*IDH2, KMT2A, PTPN11, RUNX1, SRSF2, TET2*
MDS	F	79	Y591fs*1	0.42			L473fs*3	0.28	*IDH2, RUNX1*
AML	F	59	Y591fs*1	0.39			E552fs*25	0.47	*CHEK2, JAK2, NRAS, WT1*
MDS	M	79	Y591fs*1	0.44			P1134fs*1	0.42	*NRAS, RUNX1, TET2*
MDS	M	67	Q592*	0.39			R614*	0.30	*RUNX1, SRSF2*
MDS	F	81	C594*	0.43			A1050fs*4	0.26	*IDH1, KRAS, NRAS, PTPN11, RUNX1, SRSF2, TET2*

Cohesin-binding motif: red

7 codons just beyond the cohesin-binding motif: blue

* To compare variant allele fractions (VAF) more easily, the *STAG2* VAFs in males shown in the table are halved from the true VAF identified by sequencing, since *STAG2* is located on the X chromosome.

CBM: cohesin-binding motif; VAF: variant allele fraction

Supplementary Table 8: Distribution of cohesin gene mutations by *ASXL1* region.

CBM	Frequency	7 codons beyond CBM	Frequency	Remainder of *ASXL1* gene	Frequency
7	0.082353	9	0.145161	228	0.179953

CBM: cohesin-binding motif

Supplementary Table 9. Co-mutation frequencies with *ASXL1* cohesin-binding motif (CBM) mutations and non-CBM mutations.

	CBM mutation	Frequency	Non-CBM mutation	Frequency	P
SRSF2	22	0.26506	458	0.344102	0.152713
EZH2	19	0.228916	166	0.124718	**0.010865**
RUNX1	18	0.216867	347	0.260706	0.4386
SETBP1	17	0.204819	161	0.120962	**0.038499**
TET2	16	0.192771	373	0.28024	0.099018
JAK2	14	0.168675	140	0.105184	0.098754
NRAS	13	0.156627	223	0.167543	0.880299
CUX1	10	0.120482	71	0.053343	**0.023349**
U2AF1	9	0.108434	188	0.141247	0.513177
PTPN11	8	0.096386	81	0.060856	0.237426
BCOR	7	0.084337	75	0.056349	0.326304
IDH2	7	0.084337	158	0.118708	0.479271
KRAS	7	0.084337	121	0.090909	1
STAG2	6	0.072289	229	0.172051	**0.014732**
CSF3R	5	0.060241	49	0.036814	0.242043
ETV6	5	0.060241	63	0.047333	0.592468
IDH1	5	0.060241	69	0.051841	0.617282
MPL	4	0.048193	32	0.024042	0.156258
KMT2A-r	4	0.048193	58	0.043576	0.780972
ZRSR2	4	0.048193	86	0.064613	0.815369
FLT3	4	0.048193	67	0.050338	1
NF1	4	0.048193	75	0.056349	1
PHF6	4	0.048193	64	0.048084	1
TP53	4	0.048193	74	0.055597	1
SF3B1	3	0.036145	80	0.060105	0.475954
CBL	2	0.024096	91	0.06837	0.165978
CEBPA	2	0.024096	49	0.036814	0.764808
RAD21	1	0.012048	8	0.006011	0.420751
SMC1A	0	0	4	0.003005	1
SMC3	0	0	0	0	1

CBM: cohesin-binding motif

Supplementary Table 10: *ASXL1*-mutated cases with multiple spliceosome mutations

Phenotype	Sex	Age	Non-*ASXL1* mutations	*ASXL1*	*SF3B1*	*SRSF2*	*U2AF1*	*ZRSR2*
AML	M	70	4	G646fs*12	R625C	P95H		
AML	M	64	10	G646fs*12		P95L	S34C	
AML	M	95	6	E635fs*15		P95R	Q157P	
AML	M	72	5	E705*			Q157P	R290*
AML	M	68	4	E635fs*15			S34T	R290*
MDS	M	74	6	G645fs*12	E592K			R126*
MDS	F	65	3	R693*	H662Q		S34F	
MDS	M	74	3	E477*	K666E		Q157P	
MDS	F	78	7	G646fs*12	K666N	P95L		
MDS	M	80	5	G646fs*12	K666R	P95A		
MDS	M	88	2	G646fs*12	K666T	P95H		
MDS	M	72	5	W898*	K666T	P95H		
MDS	F	72	2	Q778*	K666W		Q157R	
MDS	M	70	5	Q588*	K700E			K92fs*16
MDS	M	87	3	G646fs*12	N626D		Q157R	
MDS	F	83	6	E635fs*15	R625H	P95L		
MDS	F	80	5	K410fs*26		P95H	Q157P	
MDS	M	62	3	E635fs*15		P95H		R448_R449insSR
MDS	M	68	5	G646fs*12		P95H		splice site 938-2A>G
MDS	M	77	3	E635fs*15		P95L		Q281*
MDS	M	72	7	G646fs*12		P95L		splice site 312+1G>A
MDS	M	66	4	G646fs*12		P95L		splice site 827+1G>A
MDS	M	77	3	Y591fs*1		P95R		E131*
MDS	M	82	3	G646fs*12		P95L	Q157R	
MDS	M	65	3	G646fs*12			Q157P	deletion
MDS	M	71	4	R693*			Q157P	E277*
MDS	M	69	5	E705*			Q157P	R290*
MDS	M	72	7	D855fs*11			Q157P	splice site 827+1G>A
MDS	M	59	4	G646fs*12			Q157P	V160fs*5
MDS	M	75	5	G646fs*12			Q157P	W153*
MDS	M	60	6	R404*			Q157R	Q44*
MDS	M	71	2	E635fs*15			Q157R	W340*
MDS	M	76	3	E635fs*15			S34F	R126*
MDS/MPN	F	92	5	A772fs*2		P95R		S445_R448del
MDS/MPN	M	92	6	S895fs*11	K666R	P95A		
MDS/MPN	M	79	8	G646fs*12		P95H		K117*
MPN	M	78	4	R693*	K666N	P95H		
MPN	M	65	3	Q757*	R625C			E226*
MPN	F	82	4	S1028*		P95H	Q157P	
MPN	M	77	4	P783fs*35		P95T	Q157R	
MPN	F	78	4	E635fs*15			Q157R	R449_R451>S
MPN	M	72	4	Y591*			Q157R	splice site 122-1G>C

Supplementary Table 11: Mutational mutual exclusivity analysis for *ASXL1/SRSF2* co-mutated myeloid neoplasms

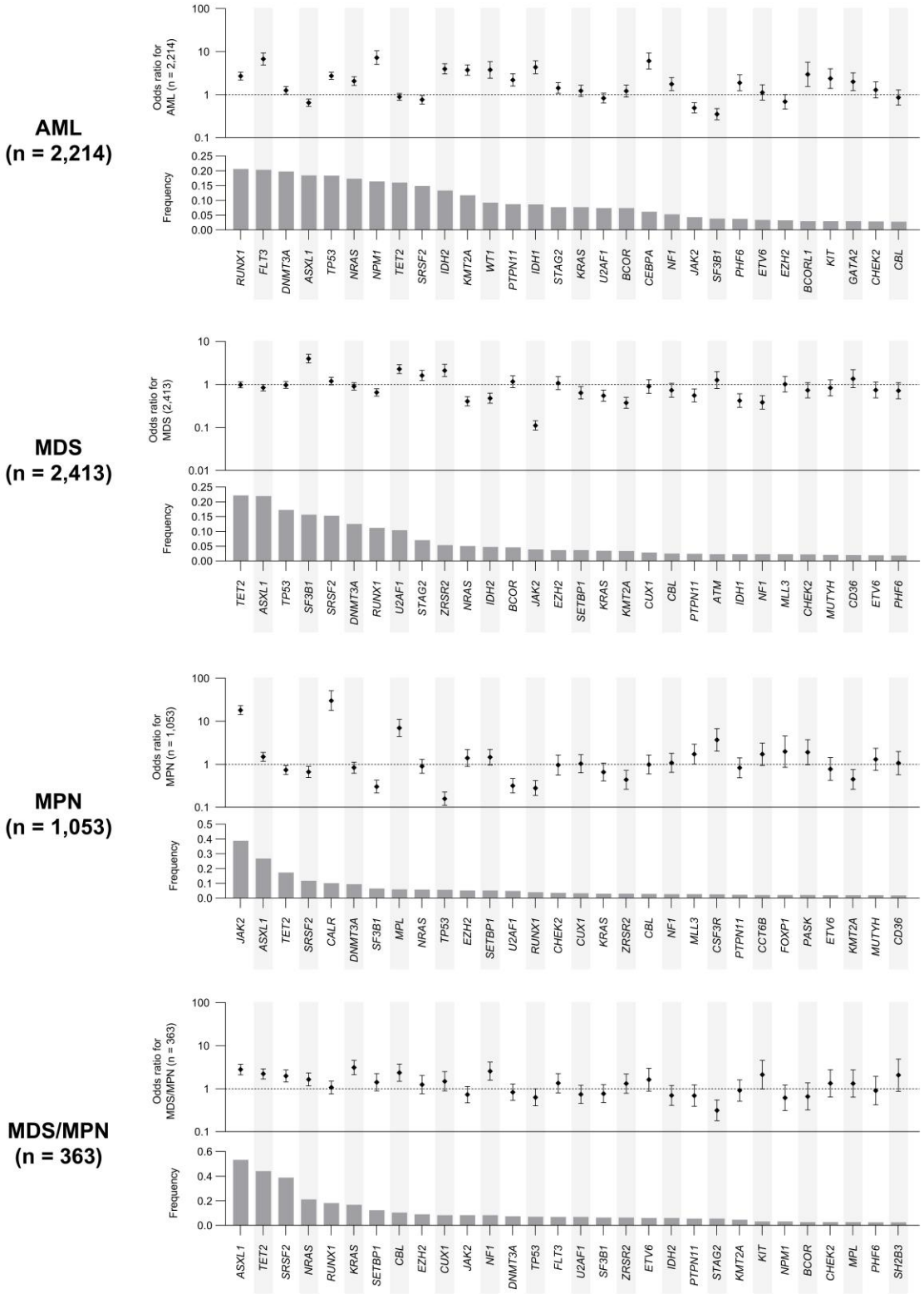
	gene1	gene2	p-value	q-value
1	*TET2*	*IDH2*	<0.000001	0.0000001
2	*RUNX1*	*CUX1*	0.0000025	0.0000211
3	*STAG2*	*SETBP1*	0.0000037	0.0000254
4	*SETBP1*	*RUNX1*	0.0000327	0.0001845
5	*SETBP1*	*IDH2*	0.0001428	0.0010848

Includes the DISCOVER output of mutually exclusive gene pairs with q < 0.01 shown.

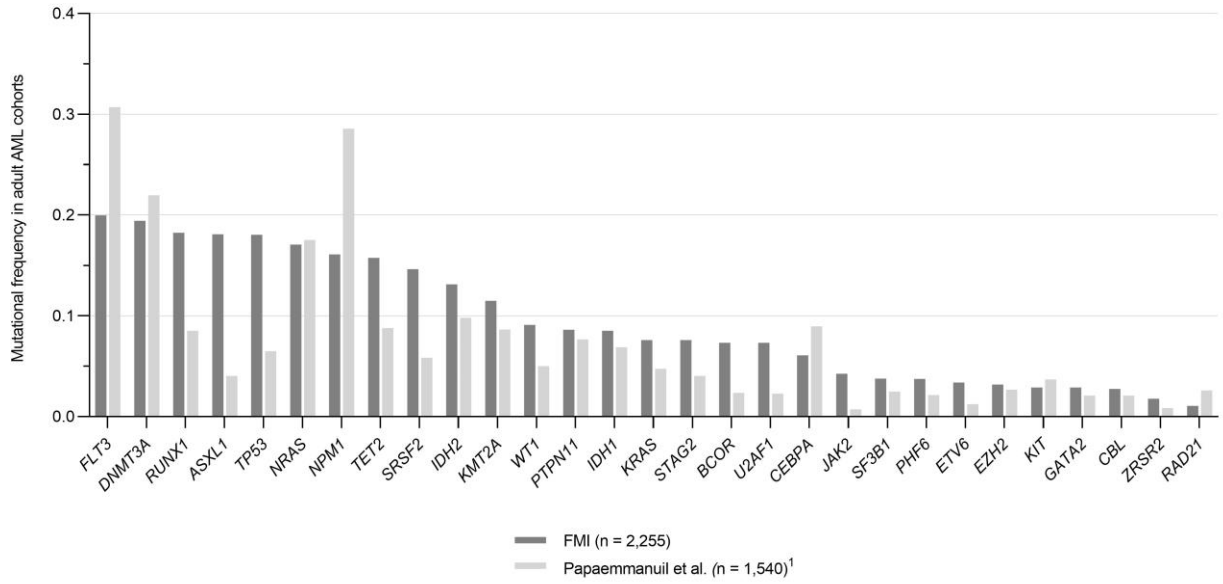
Supplementary Table 12: Unadjusted results for genotype-phenotype analysis of *ASXL1*^{mut} cohort

Phenotype	Mutation*	OR [95% CI]	P
AML	*FLT3*	3.2 [2.0-5.2]	2.08e-6
	IDH1	3.7 [2.3-6.0]	7.47e-8
	IDH2	3.0 [2.1-4.1]	1.2e-10
	NPM1	9.2 [2.6-33.4]	6.65e-4
	RUNX1	2.1 [1.6-2.7]	6.76e-9
	STAG2	2.0 [1.5-2.7]	2.56e-6
MDS	*SF3B1*	4.0 [2.5-6.4]	1.43e-8
	U2AF1	2.1 [1.6-2.9]	1.11e-6
	ZRSR2	2.4 [1.6-3.7]	6.24e-5
Chronic proliferative†	*CALR*	5.3 [2.6-10.7]	4.04e-6
	JAK2	4.2 [3.0-6.0]	9.4e-16
	KIT	4.3 [1.8-10.1]	7.37e-4
	MPL	3.6 [1.8-7.2]	2.61e-4
	NRAS	1.6 [1.2-2.2]	0.00122
	SETBP1	1.9 [1.4-2.6]	5.42e-5

Supplementary Figure 1. Overall mutation rate and multivariate phenotype-genotype analysis.

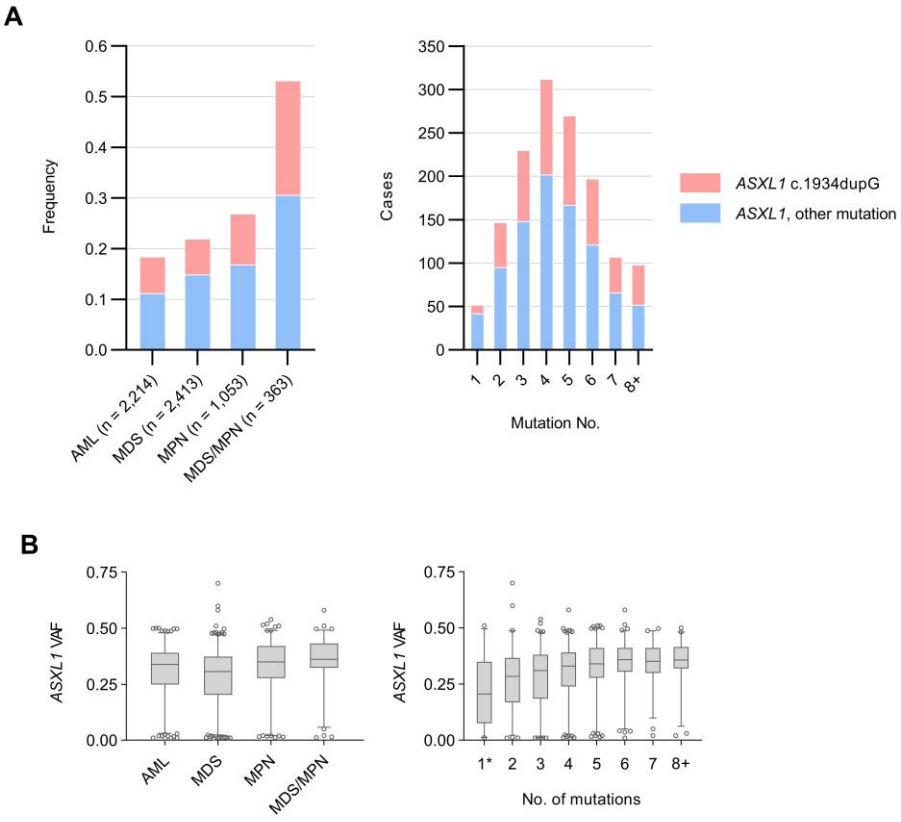


Supplementary Figure 2: Comparison of mutation frequencies in the study AML cohort at Foundation Medicine, Inc. (FMI) and a large, published AML cohort.



The gene panel in our study was significantly larger than that from the comparison cohort;[1] Two notable genes excluded in the comparison cohort that were present in our panel were *BCORL1* (2.9% mutated) and *SETBP1* (2.4% mutated). In addition, the comparison cohort excluded c.1934dupG (p.G646Xfs*12) variants from analysis. This at least partially accounts for the higher frequency of *ASXL1* mutations in the study cohort, though gene coverage also varied between AML cohorts.[1]

Supplementary Figure 3. *ASXL1* c.1934dupG mutation frequencies and VAFs by phenotype and mutation number.



* Patient's sole mutation was in *ASXL1.*

Supplementary Figure 4: *ASXL1* mutations in AML by *TP53* and *SETBP1* mutation status.

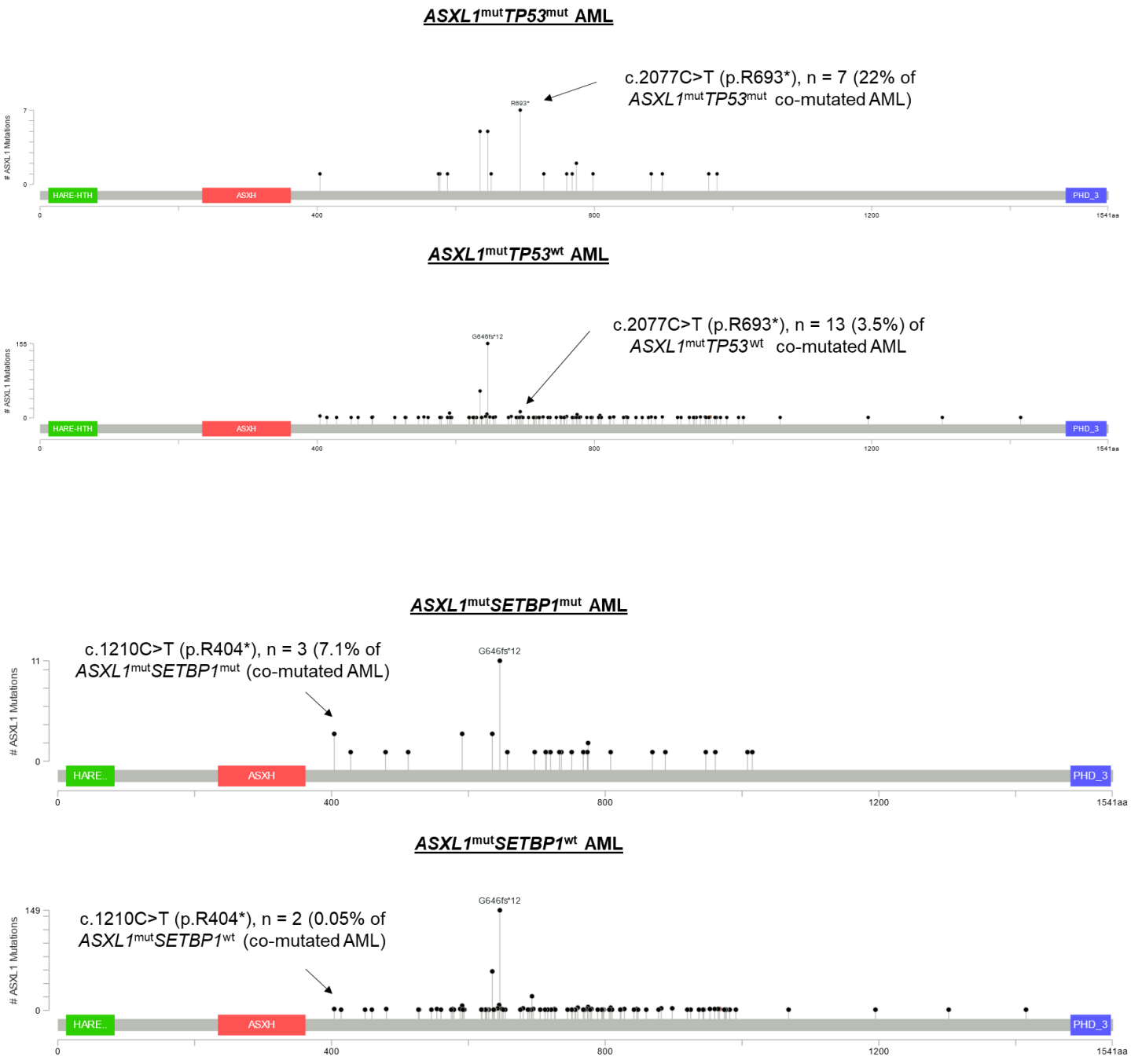
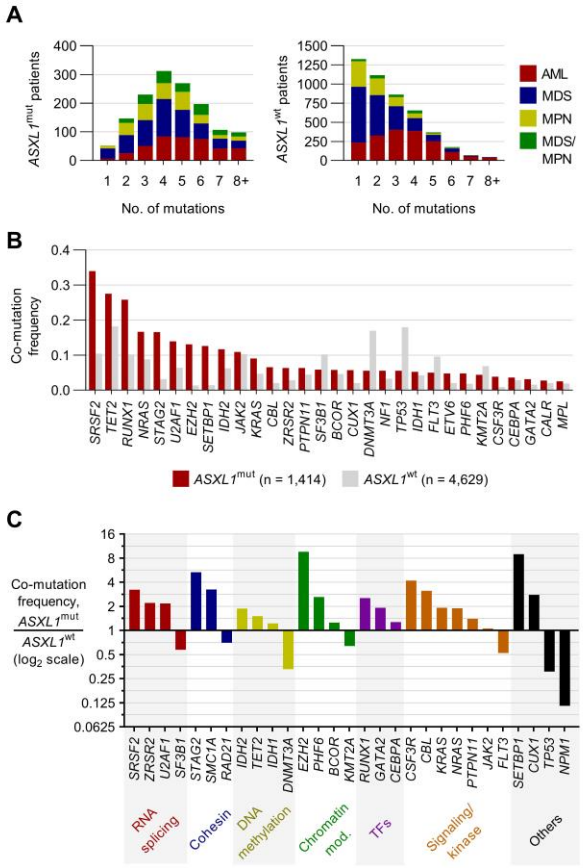


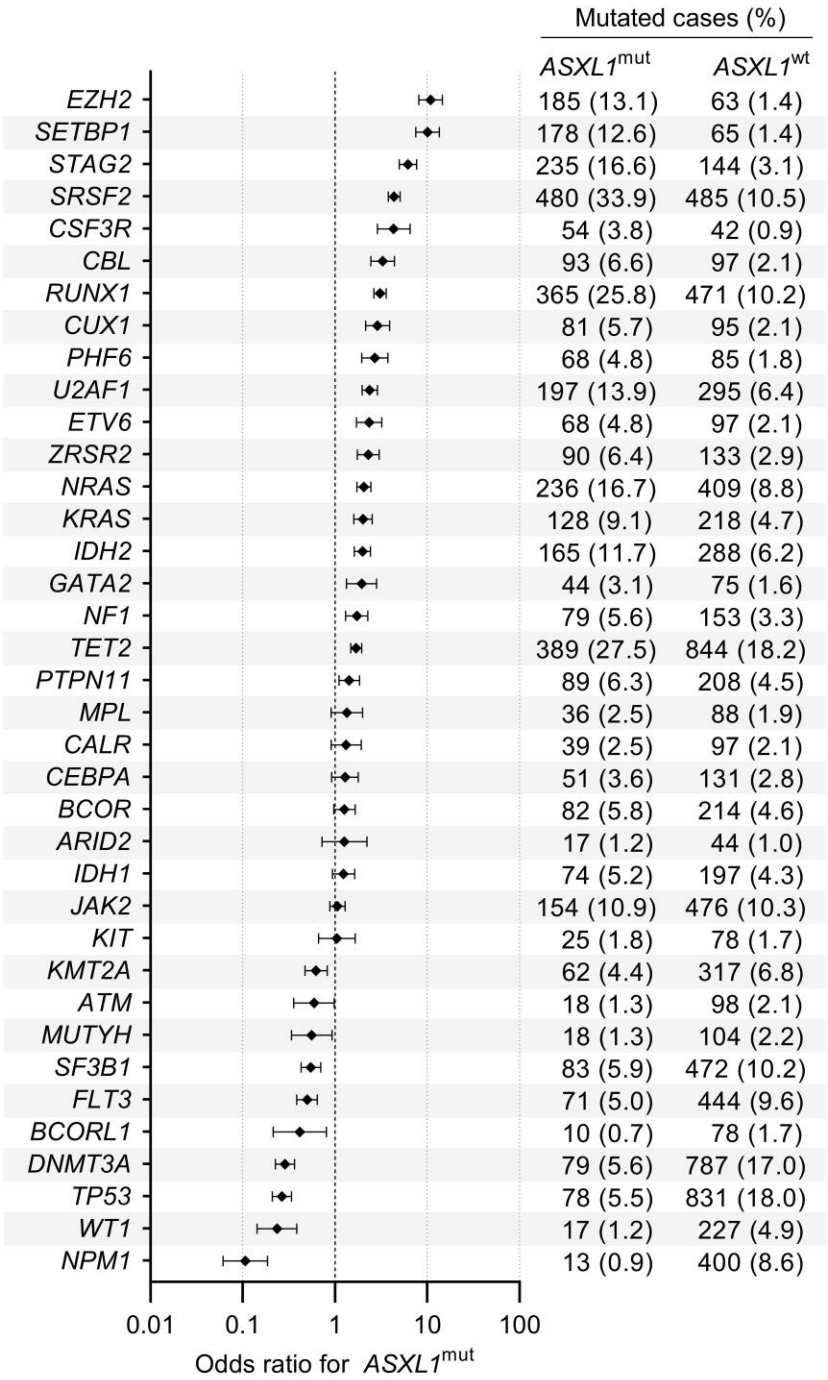
Figure generated using the mutation mapper feature in cBioPortal.[2,3]

Supplementary Figure 5: Co-mutations in *ASXL1*^{mut} and *ASXL1*^{wt} patients

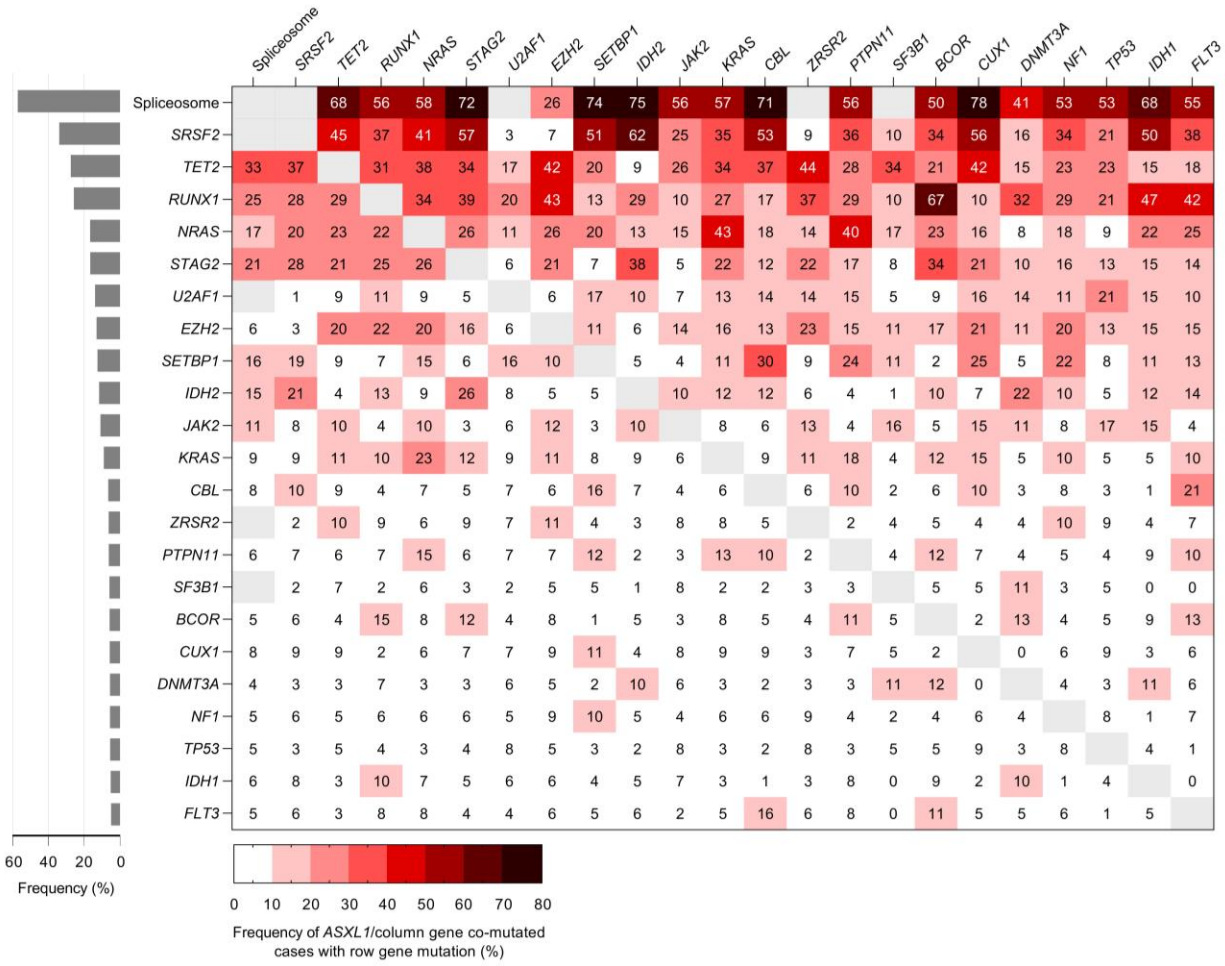


A) Mutational burden in *ASXL1*^{mut} and *ASXL1*^{wt} patients; patients with 1 mutation in the *ASXL1*^{mut} cohort represent those with *ASXL1* as the sole mutation. B) Mutation rates in the 30 most frequently mutated genes in *ASXL1*^{mut} patients. C) Fold-difference in mutational frequencies of individual genes based on *ASXL1* mutational status, displayed by gene class.

Supplementary Figure 6: Odds ratios for genetic co-mutation in *ASXL1*^{mut} myeloid neoplasms.

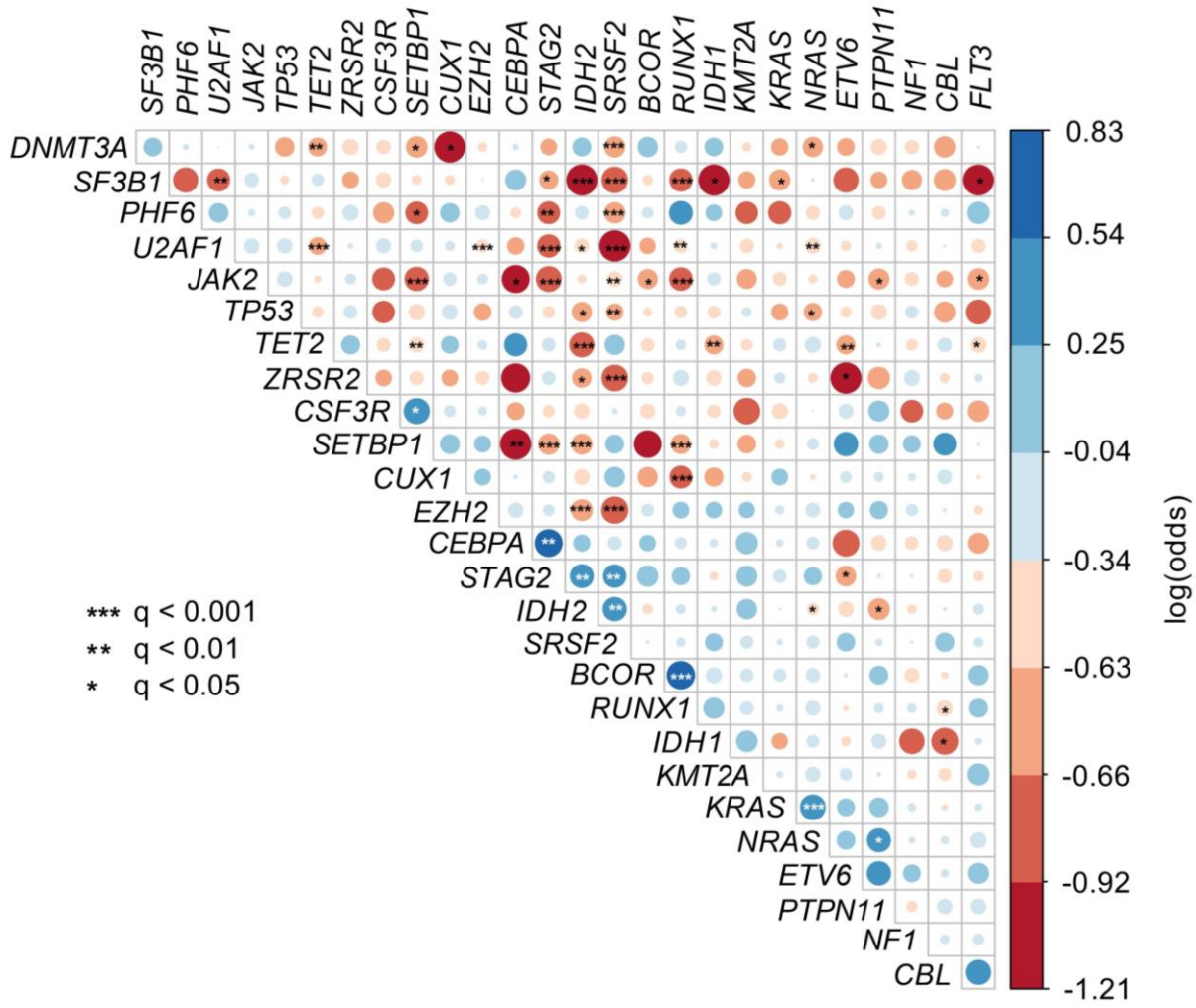


Supplementary Figure 7: Pairwise co-mutation frequencies of *ASXL1*^{mut} myeloid neoplasms.



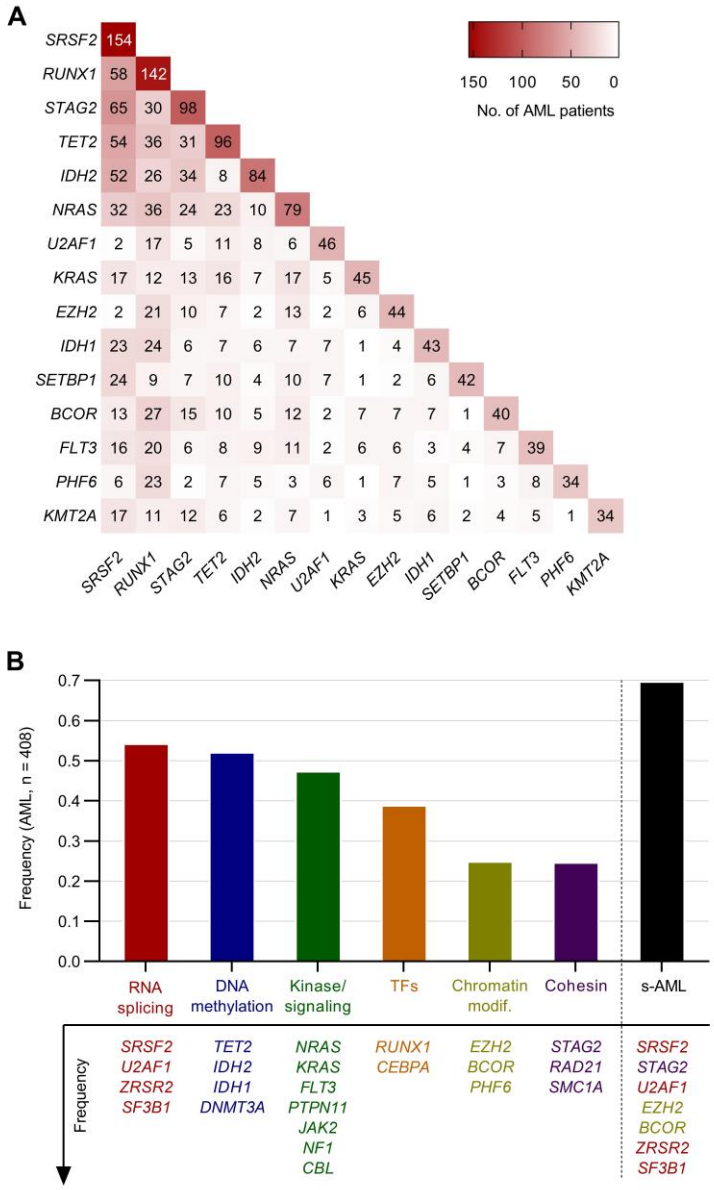
The left bar plot shows total co-mutation frequency in all *ASXL1* mutated myeloid neoplasms. The heatmap illustrates tri-mutant genotype frequencies, with each column representing all cases with co-mutation in *ASXL1* and the column gene. The number in each cell corresponds to the percentage of *ASXL1*/column gene co-mutated cases that also have an additional mutation in the row gene. For example, the cell corresponding to the 2nd column and the 3rd row denotes that 37% of *ASXL1*/*SRSF2* co-mutated myeloid neoplasms also have a *TET2* mutation.

Supplementary Figure 8: Mutation co-occurrence and mutual exclusivity in the *ASXL1*^{mut} cohort



The colored dot matrix depicts mutational co-occurrence and mutual exclusivity in gene pairs within the entire *ASXL1*^{mut} cohort. The figure was generated by first calculating odds ratios of frequencies of column gene co-mutations in *ASXL1*^{mut}/row gene^{mut} myeloid neoplasms and *ASXL1*^{mut}/row gene^{wt} myeloid neoplasms. Dot sizes and colors were assigned according to log(odds ratios), where blue and red color series represent co-occurrence and mutual exclusivity, respectively. Statistical significance by DISCOVER analysis is indicated by asterisks.

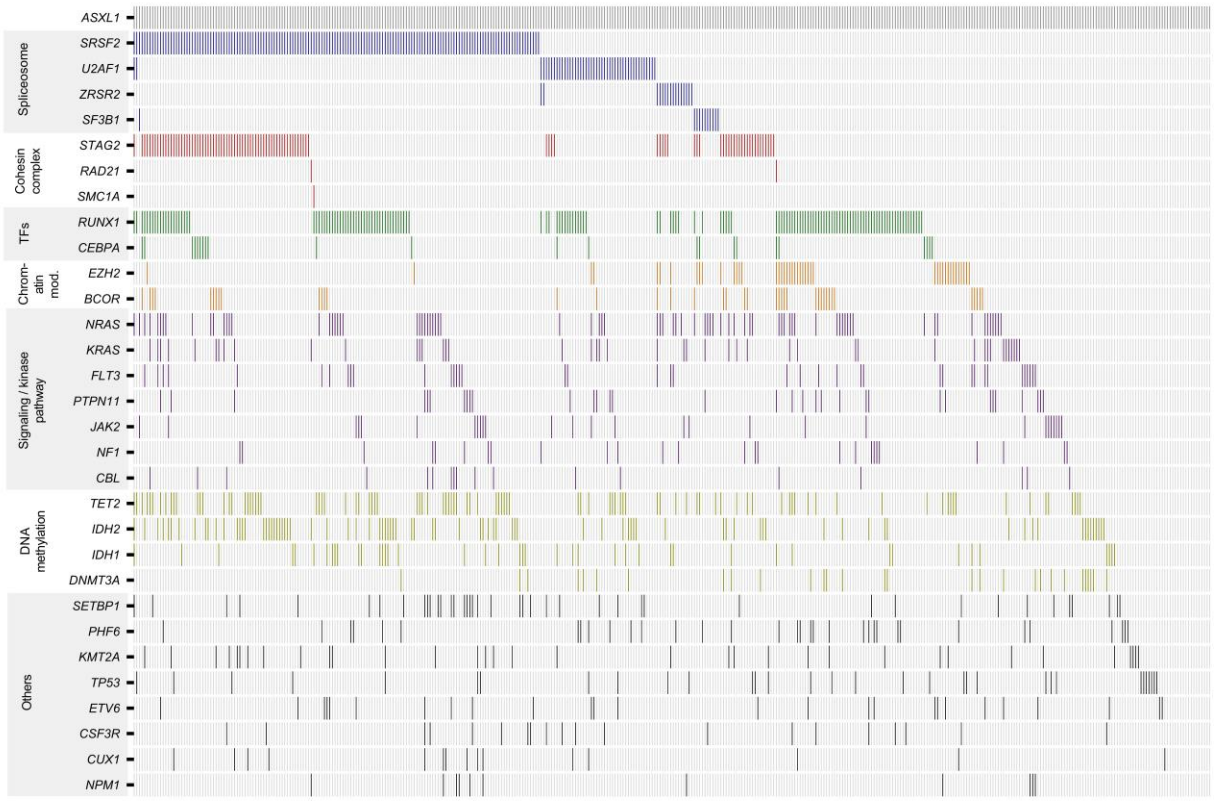
Supplementary Figure 9: Overview of co-mutations *ASXL1*^{mut} AML



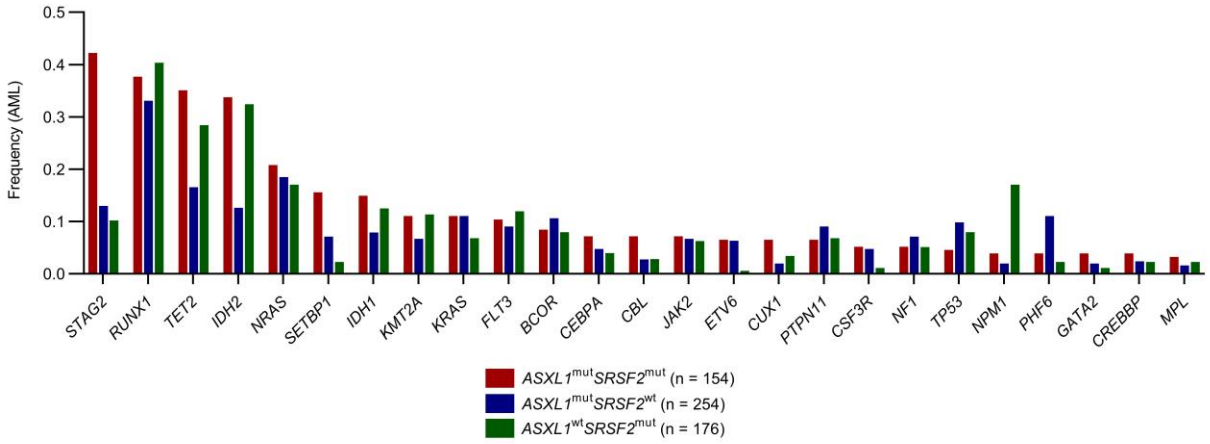
Co-mutation heatmap of individual cases (A) and collective mutation rates by gene class (B).

s-AML: secondary-AML associated genes

Supplementary Figure 10: Mutational tile plot of individual *ASXL1*^{mut} AML patients (n = 408).

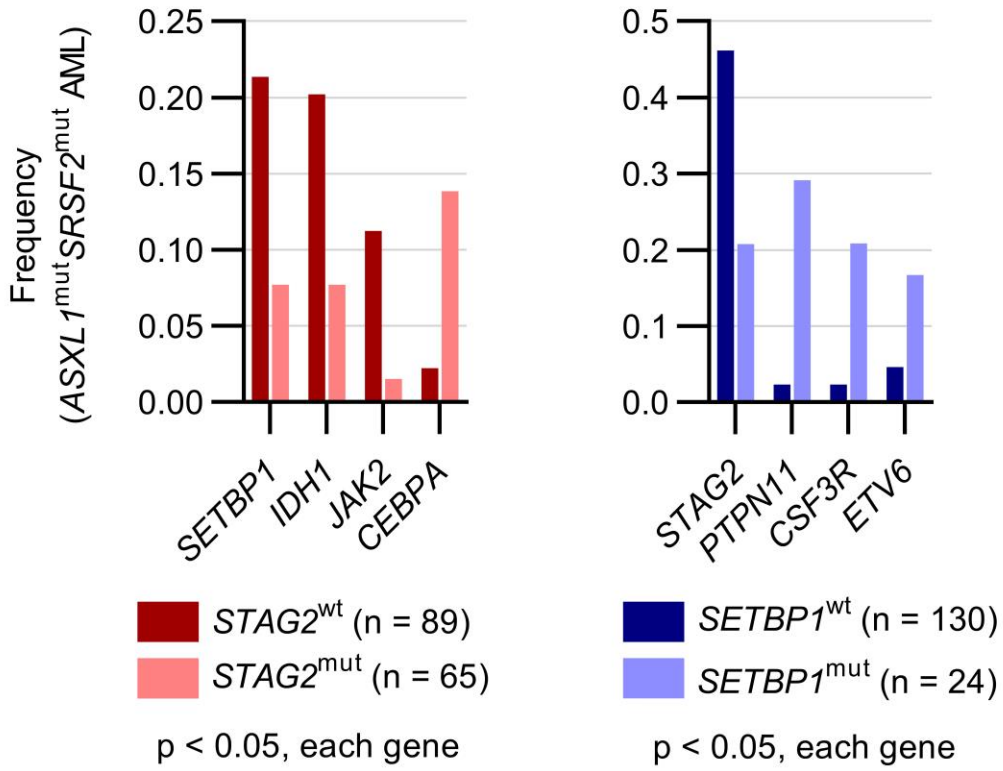


Supplementary Figure 11: Co-mutation frequencies: *ASXL1/SRSF2* co-mutated AML

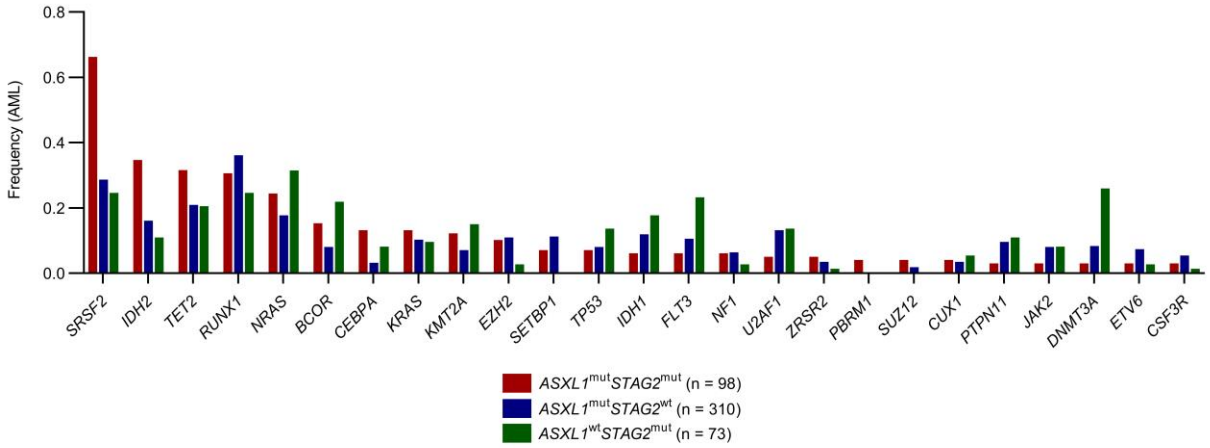


	Frequency *ASXL1*^{mut}/ *SRSF2*^{mut}	Frequency *ASXL1*^{mut}/ *SRSF2*^{wt}	P	Frequency *ASXL1*^{wt}/ *SRSF2*^{mut}	P
STAG2	0.422078	0.129921	**4.39E-11**	0.102273	**2.58E-11**
RUNX1	0.376623	0.330709	0.391197	0.403409	0.651942
TET2	0.350649	0.165354	**3.57E-05**	0.284091	0.234941
IDH2	0.337662	0.125984	**5.63E-07**	0.323864	0.815211
NRAS	0.207792	0.185039	0.606111	0.170455	0.400135
SETBP1	0.155844	0.070866	**0.007321**	0.022727	**1.34E-05**
IDH1	0.149351	0.07874	**0.030275**	0.125	0.525418
KMT2A	0.11039	0.066929	0.140662	0.113636	1
KRAS	0.11039	0.110236	1	0.068182	0.241946
FLT3	0.103896	0.090551	0.728898	0.119318	0.728029
BCOR	0.084416	0.106299	0.498348	0.079545	1
CEBPA	0.071429	0.047244	**0.046431**	0.039773	0.077577
CBL	0.071429	0.027559	0.376293	0.028409	0.231682
JAK2	0.071429	0.066929	0.842941	0.0625	0.826449
ETV6	0.064935	0.062992	**0.027507**	0.005682	0.209852
CUX1	0.064935	0.019685	0.454535	0.034091	1
PTPN11	0.064935	0.090551	1	0.068182	**0.003566**
CSF3R	0.051948	0.047244	0.533843	0.011364	1
NF1	0.051948	0.070866	0.817376	0.051136	**0.049624**
TP53	0.045455	0.098425	0.058765	0.079545	0.260356
NPM1	0.038961	0.019685	**0.01513**	0.170455	0.523687
PHF6	0.038961	0.110236	0.344461	0.022727	0.152576
GATA2	0.038961	0.019685	0.344461	0.011364	**0.000136**
CREBBP	0.038961	0.023622	0.381086	0.022727	0.523687
MPL	0.032468	0.015748	0.307204	0.022727	0.738638

Supplementary Figure 12: *ASXL1/SRSF2* co-mutated AML by *STAG2* and *SETBP1* mutational status.

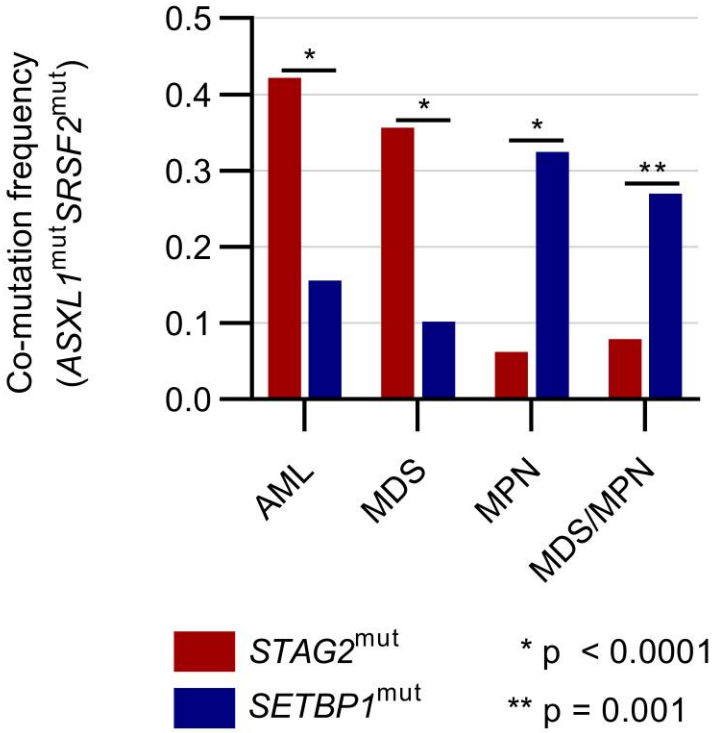


Supplementary Figure 13: Co-mutation frequencies: *ASXL1/STAG2* co-mutated AML

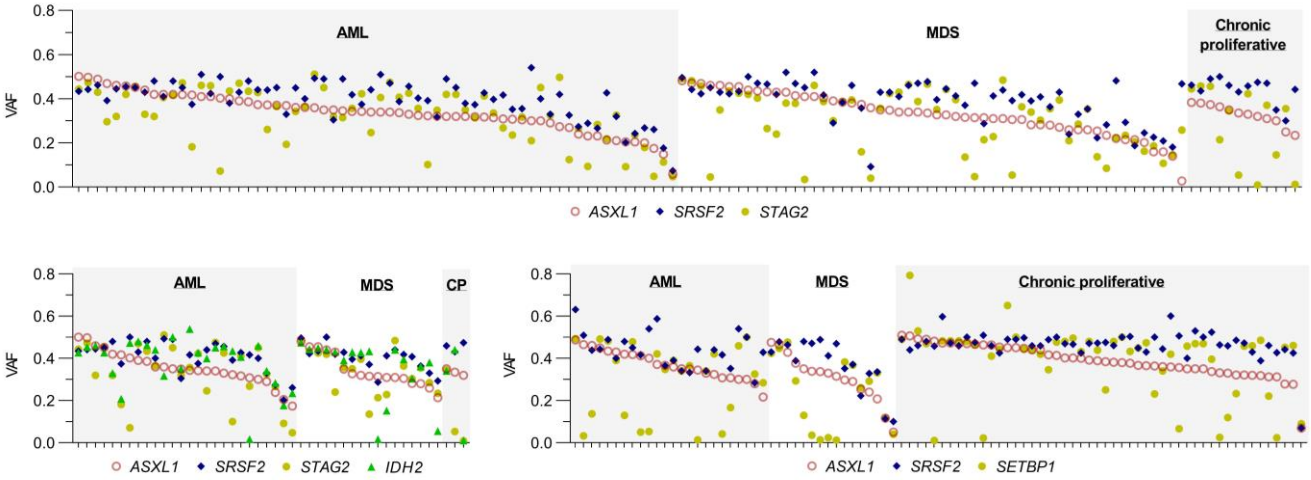


	Frequency *ASXL1*^{mut}/ *STAG2*^{mut}	Frequency *ASXL1*^{mut}/ *STAG2*^{wt}	P	Frequency *ASXL1*^{wt}/ *STAG2*^{mut}	P
SRSF2	0.663265	0.287097	**4.39E-11**	0.246575	**9.38E-08**
IDH2	0.346939	0.16129	**0.000162**	0.109589	**0.000315**
TET2	0.316327	0.209677	**0.039861**	0.205479	0.119131
RUNX1	0.306122	0.36129	0.333287	0.246575	0.491628
NRAS	0.244898	0.177419	0.144855	0.315068	0.386786
BCOR	0.153061	0.080645	**0.049611**	0.219178	0.3173
CEBPA	0.132653	0.032258	**0.00057**	0.082192	0.335829
KRAS	0.132653	0.103226	0.459449	0.09589	0.631352
KMT2A	0.122449	0.070968	0.13997	0.150685	0.653525
EZH2	0.102041	0.109677	1	0.027397	0.072659
SETBP1	0.071429	0.112903	0.339491	0	**0.020644**
TP53	0.071429	0.080645	1	0.136986	0.198343
IDH1	0.061224	0.119355	0.130522	0.178082	**0.025016**
FLT3	0.061224	0.106452	0.237618	0.232877	**0.00142**
NF1	0.061224	0.064516	1	0.027397	0.468898
U2AF1	0.05102	0.132258	**0.027437**	0.136986	0.059027
ZRSR2	0.05102	0.035484	0.550221	0.013699	0.240802
PBRM1	0.040816	0	**0.003175**	0	0.136689
SUZ12	0.040816	0.019355	0.261229	0	0.136689
CUX1	0.040816	0.035484	0.763296	0.054795	0.724939
PTPN11	0.030612	0.096774	**0.034594**	0.109589	0.056183
JAK2	0.030612	0.080645	0.108834	0.082192	0.172994
DNMT3A	0.030612	0.083871	0.111323	0.260274	**1.06E-05**
ETV6	0.030612	0.074194	0.156452	0.027397	1
CSF3R	0.030612	0.054839	0.428829	0.013699	0.636785

Supplementary Figure 14: *STAG2* and *SETBP1* co-mutation rates in *ASXL1/SRSF2* co-mutated cases



Supplementary Figure 15: Variant allele fractions (VAF) of individual cases with select multi-mutant genotypes



VAF profiles of individual patients (each represented by a single tick) with select multi-mutated genotypes. *STAG2* VAFs in males were halved given their location on the X chromosome.

CP: chronic proliferative (MPN or MDS/MPN).

References

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