

Supplementary Tables

Supplementary Table 1: Panels used for sequencing in each respective study.

Mission Bio 19-gene AML panel (Stanford and most MD Anderson)				MD Anderson 37-gene panel				Memorial Sloan Kettering 31-gene panel			
chr20	31022369	31022586	ASXL1_1	chr20	31022366	31022591	ASXL1_c1	chr1	43814923	43815097	MSK_RL_AMP1
chr20	31022899	31023110	ASXL1_2_a1	chr20	31022711	31022938	ASXL1_c2	chr1	1.15E+08	1.15E+08	MSK_RL_AMP2
chr2	25457135	25457351	DNMT3A_10	chr20	31022977	31023186	ASXL1_c3	chr1	1.15E+08	1.15E+08	MSK_RL_AMP3
chr7	1.49E+08	1.49E+08	EZH2_1	chr20	31023229	31023435	ASXL1_c4	chr2	25457136	25457350	MSK_RL_AMP4
chr7	1.49E+08	1.49E+08	EZH2_2	chr20	31023478	31023642	ASXL1_c5	chr2	25463120	25463328	MSK_RL_AMP5
chr13	28592494	28592723	FLT3_1	chr20	31023678	31023891	ASXL1_c6	chr2	25463448	25463646	MSK_RL_AMP6
chr13	28608191	28608368	FLT3_2_a3	chr20	31023938	31024136	ASXL1_c7	chr2	25464333	25464542	MSK_RL_AMP7
chr13	28602179	28602404	FLT3_3	chr20	31024173	31024389	ASXL1_c8	chr2	25466647	25466857	MSK_RL_AMP8
chr13	28609547	28609769	FLT3_4	chr20	31024623	31024835	ASXL1_c9	chr2	25467048	25467265	MSK_RL_AMP9
chr13	28608018	28608153	FLT3_5_4	chr20	31024877	31025085	ASXL1_c10	chr2	25467956	25468169	MSK_RL_AMP10
chr3	1.28E+08	1.28E+08	GATA2_1	chrX	39911549	39911774	BCOR_c1	chr2	25468813	25469023	MSK_RL_AMP11
chr2	2.09E+08	2.09E+08	IDH1_1	chrX	39913124	39913348	BCOR_c2	chr2	25469068	25469275	MSK_RL_AMP12
chr15	90631759	90631985	IDH2_1_4	chrX	39913467	39913689	BCOR_c3	chr2	25469564	25469721	MSK_RL_AMP13
chr9	5073563	5073785	JAK2_1	chrX	39914558	39914779	BCOR_c4	chr2	25469954	25470165	MSK_RL_AMP14
chr4	55599231	55599448	KIT_1	chrX	39916401	39916625	BCOR_c5	chr2	25470459	25470643	MSK_RL_AMP15
chr4	55589607	55589829	KIT_2	chrX	39921398	39921629	BCOR_c6	chr2	1.98E+08	1.98E+08	MSK_RL_AMP16
chr12	25398183	25398405	KRAS_1	chrX	39921922	39922151	BCOR_c7	chr2	1.98E+08	1.98E+08	MSK_RL_AMP17
chr12	25380259	25380466	KRAS_2	chrX	39922192	39922422	BCOR_c8	chr3	1.28E+08	1.28E+08	MSK_RL_AMP18
chr5	1.71E+08	1.71E+08	NPM1_1_2	chrX	39922873	39923088	BCOR_c9	chr4	55589610	55589817	MSK_RL_AMP19
chr1	1.15E+08	1.15E+08	NRAS_1	chrX	39923132	39923334	BCOR_c10	chr4	55599238	55599448	MSK_RL_AMP20
chr1	1.15E+08	1.15E+08	NRAS_2	chrX	39923596	39923765	BCOR_c11	chr4	1.06E+08	1.06E+08	MSK_RL_AMP21
chr12	1.13E+08	1.13E+08	PTPN11_1_1	chrX	39930808	39931024	BCOR_c12	chr4	1.06E+08	1.06E+08	MSK_RL_AMP22
chr12	1.13E+08	1.13E+08	PTPN11_2	chrX	39931479	39931704	BCOR_c13	chr4	1.06E+08	1.06E+08	MSK_RL_AMP23
chr21	36171482	36171710	RUNX1_2	chrX	39931741	39931954	BCOR_c14	chr4	1.06E+08	1.06E+08	MSK_RL_AMP24
chr21	36206705	36206884	RUNX1_3	chrX	39931996	39932212	BCOR_c15	chr4	1.06E+08	1.06E+08	MSK_RL_AMP25
chr21	36231604	36231834	RUNX1_4	chrX	39932294	39932521	BCOR_c16	chr4	1.06E+08	1.06E+08	MSK_RL_AMP26
chr21	36164785	36164997	RUNX1_5	chrX	39932582	39932807	BCOR_c17	chr4	1.06E+08	1.06E+08	MSK_RL_AMP27
chr21	36252811	36253007	RUNX1_7	chrX	39932871	39933101	BCOR_c18	chr4	1.06E+08	1.06E+08	MSK_RL_AMP28
chr2	1.98E+08	1.98E+08	SF3B1_1	chrX	39933297	39933459	BCOR_c19	chr4	1.06E+08	1.06E+08	MSK_RL_AMP29
chr2	1.98E+08	1.98E+08	SF3B1_2	chrX	39933500	39933666	BCOR_c20	chr4	1.06E+08	1.06E+08	MSK_RL_AMP30

chr17	74732882	74733050	SRSF2_2_2	chrX	39933706	39933912	BCOR_c21	chr6	40116164	40116368	MSK_RL_AMP31
chr17	7578086	7578296	TP53_1	chrX	39934221	39934450	BCOR_c22	chr6	62094189	62094395	MSK_RL_AMP32
chr17	7577397	7577615	TP53_2	chr19	13054545	13054677	CALR_c1	chr7	1.4E+08	1.4E+08	MSK_RL_AMP33
chr17	7578384	7578605	TP53_3	chr11	1.19E+08	1.19E+08	CBL_c1	chr7	1.49E+08	1.49E+08	MSK_RL_AMP34
chr17	7576953	7577180	TP53_4	chr11	1.19E+08	1.19E+08	CBL_c2	chr7	1.49E+08	1.49E+08	MSK_RL_AMP35
chr21	44514700	44514922	U2AF1_1	chr11	1.19E+08	1.19E+08	CBL_c3	chr8	1.18E+08	1.18E+08	MSK_RL_AMP36
chr21	44524279	44524505	U2AF1_2	chr1	36932055	36932276	CSF3R_c1	chr9	5073573	5073780	MSK_RL_AMP37
chr11	32414193	32414411	WT1_1_a2	chr1	36932338	36932566	CSF3R_c2	chr10	5554195	5554404	MSK_RL_AMP38
chr11	32413415	32413641	WT1_2	chr1	36933077	36933279	CSF3R_c3	chr10	77210082	77210276	MSK_RL_AMP39
chr11	32417765	32417992	WT1_3	chr1	36933363	36933585	CSF3R_c4	chr10	1.07E+08	1.07E+08	MSK_RL_AMP40
chr10	1.07E+08	1.07E+08	chr10_106721610	chr2	25536706	25536929	DNMT3A_c1	chr11	32413414	32413629	MSK_RL_AMP41
chr10	5554192	5554401	chr10_5554293	chr2	25457136	25457345	DNMT3A_c2	chr11	32414202	32414410	MSK_RL_AMP42
chr10	77210083	77210294	chr10_77210191	chr2	25458540	25458742	DNMT3A_c3	chr11	32417789	32417997	MSK_RL_AMP43
chr14	56968905	56969106	chr14_56969005	chr2	25459801	25460021	DNMT3A_c4	chr11	1.08E+08	1.08E+08	MSK_RL_AMP44
chr16	55770529	55770735	chr16_55770629	chr2	25461902	25462117	DNMT3A_c5	chr11	1.08E+08	1.08E+08	MSK_RL_AMP45
chr16	8569720	8569926	chr16_8569820	chr2	25463127	25463325	DNMT3A_c6	chr11	1.08E+08	1.08E+08	MSK_RL_AMP46
chr18	9750561	9750767	chr18_9750662	chr2	25463469	25463686	DNMT3A_c7	chr11	1.19E+08	1.19E+08	MSK_RL_AMP47
chr6	17076739	17076941	chr6_17076840	chr2	25464369	25464585	DNMT3A_c8	chr11	1.19E+08	1.19E+08	MSK_RL_AMP48
chr6	40116164	40116366	chr6_40116264	chr2	25466642	25466860	DNMT3A_c9	chr11	1.19E+08	1.19E+08	MSK_RL_AMP49
chr6	62094187	62094388	chr6_62094287	chr2	25467027	25467223	DNMT3A_c10	chr12	25380259	25380467	MSK_RL_AMP50
				chr2	25467391	25467609	DNMT3A_c11	chr12	25398178	25398390	MSK_RL_AMP51
				chr2	25468071	25468288	DNMT3A_c12	chr12	1.13E+08	1.13E+08	MSK_RL_AMP52
				chr2	25468833	25469006	DNMT3A_c13	chr12	1.13E+08	1.13E+08	MSK_RL_AMP53
				chr2	25469045	25469218	DNMT3A_c14	chr13	28592494	28592706	MSK_RL_AMP54
				chr2	25469484	25469694	DNMT3A_c15	chr13	28602179	28602380	MSK_RL_AMP55
				chr2	25469867	25470051	DNMT3A_c16	chr13	28608004	28608168	MSK_RL_AMP56
				chr2	25470456	25470643	DNMT3A_c17	chr13	28608218	28608392	MSK_RL_AMP57
				chr2	25470905	25471115	DNMT3A_c18	chr13	28609557	28609768	MSK_RL_AMP58
				chr2	25472512	25472704	DNMT3A_c19	chr14	56968905	56969108	MSK_RL_AMP59
				chr2	25497757	25497963	DNMT3A_c20	chr15	90631760	90631969	MSK_RL_AMP60
				chr2	25498343	25498539	DNMT3A_c21	chr16	8569723	8569894	MSK_RL_AMP61
				chr2	25505317	25505541	DNMT3A_c22	chr16	55770516	55770722	MSK_RL_AMP62
				chr12	11803053	11803202	ETV6_c1	chr17	7576969	7577174	MSK_RL_AMP63
				chr12	11905334	11905529	ETV6_c2	chr17	7577397	7577611	MSK_RL_AMP64
				chr12	11992060	11992271	ETV6_c3	chr17	7578089	7578296	MSK_RL_AMP65
				chr12	12006341	12006526	ETV6_c4	chr17	7578383	7578590	MSK_RL_AMP66

chr12	12022349	12022442	ETV6_c5	chr17	58740251	58740465	MSK_RL_AMP67
chr12	12022478	12022711	ETV6_c6	chr17	58740607	58740815	MSK_RL_AMP68
chr12	12022764	12022892	ETV6_c7	chr18	9750564	9750768	MSK_RL_AMP69
chr12	12037342	12037535	ETV6_c8	chr18	42531783	42531986	MSK_RL_AMP70
chr12	12038827	12038985	ETV6_c9	chr18	42533021	42533233	MSK_RL_AMP71
chr12	12043866	12044080	ETV6_c10	chr19	13054545	13054710	MSK_RL_AMP72
chr7	1.49E+08	1.49E+08	EZH2_c1	chr20	31022219	31022401	MSK_RL_AMP73
chr7	1.49E+08	1.49E+08	EZH2_c2	chr20	31022525	31022701	MSK_RL_AMP74
chr7	1.49E+08	1.49E+08	EZH2_c3	chr20	31022898	31023107	MSK_RL_AMP75
chr7	1.49E+08	1.49E+08	EZH2_c4	chr21	36164939	36165160	MSK_RL_AMP76
chr7	1.49E+08	1.49E+08	EZH2_c5	chr21	36171482	36171697	MSK_RL_AMP77
chr7	1.49E+08	1.49E+08	EZH2_c6	chr21	36206703	36206893	MSK_RL_AMP78
chr7	1.49E+08	1.49E+08	EZH2_c7	chr21	36231609	36231827	MSK_RL_AMP79
chr7	1.49E+08	1.49E+08	EZH2_c8	chr21	36252808	36253008	MSK_RL_AMP80
chr7	1.49E+08	1.49E+08	EZH2_c9	chr21	44514699	44514914	MSK_RL_AMP81
chr7	1.49E+08	1.49E+08	EZH2_c10	chr21	44524280	44524488	MSK_RL_AMP82
chr7	1.49E+08	1.49E+08	EZH2_c11	chr22	29083873	29084069	MSK_RL_AMP83
chr7	1.49E+08	1.49E+08	EZH2_c12	chr22	29091685	29091879	MSK_RL_AMP84
chr7	1.49E+08	1.49E+08	EZH2_c13	chrX	1.23E+08	1.23E+08	MSK_RL_AMP85
chr7	1.49E+08	1.49E+08	EZH2_c14	chrX	1.23E+08	1.23E+08	MSK_RL_AMP86
chr7	1.49E+08	1.49E+08	EZH2_c15	chrX	1.23E+08	1.23E+08	MSK_RL_AMP87
chr7	1.49E+08	1.49E+08	EZH2_c16	chrX	1.23E+08	1.23E+08	MSK_RL_AMP88
chr7	1.49E+08	1.49E+08	EZH2_c17	chrX	1.23E+08	1.23E+08	MSK_RL_AMP89
chr7	1.49E+08	1.49E+08	EZH2_c18	chrX	1.23E+08	1.23E+08	MSK_RL_AMP90
chr7	1.49E+08	1.49E+08	EZH2_c19	chrX	1.23E+08	1.23E+08	MSK_RL_AMP91
chr13	28592544	28592767	FLT3_c1	chrX	1.34E+08	1.34E+08	MSK_RL_AMP92
chr13	28602179	28602404	FLT3_c2	chrX	1.34E+08	1.34E+08	MSK_RL_AMP93
chr13	28608018	28608153	FLT3_c3	chr5	1.71E+08	1.71E+08	MSK_RL_AMP94
chr13	28608203	28608425	FLT3_c4	chr2	2.09E+08	2.09E+08	MSK_RL_AMP95
chr13	28609547	28609769	FLT3_c5	chr2	25467391	25467609	MSK_RL_AMP96
chr3	1.28E+08	1.28E+08	GATA2_c1	chr4	1.06E+08	1.06E+08	MSK_RL_AMP97
chr3	1.28E+08	1.28E+08	GATA2_c2	chr4	1.06E+08	1.06E+08	MSK_RL_AMP98
chr2	2.09E+08	2.09E+08	IDH1_c1	chr4	1.06E+08	1.06E+08	MSK_RL_AMP99
chr15	90631759	90631985	IDH2_c1	chr4	1.06E+08	1.06E+08	MSK_RL_AMP100
chr9	5069966	5070184	JAK2_c1	chr4	1.06E+08	1.06E+08	MSK_RL_AMP101
chr9	5073578	5073805	JAK2_c2	chrX	1.23E+08	1.23E+08	MSK_RL_AMP102

chrX	44820495	44820673	KDM6A_c1	chrX	1.23E+08	1.23E+08	MSK_RL_AMP103
chrX	44833817	44833986	KDM6A_c2	chrX	1.23E+08	1.23E+08	MSK_RL_AMP104
chrX	44879806	44879979	KDM6A_c3	chrX	1.23E+08	1.23E+08	MSK_RL_AMP105
chrX	44896847	44896978	KDM6A_c4	chr4	1.06E+08	1.06E+08	MSK_RL_AMP106
chrX	44910955	44911125	KDM6A_c5	chr17	74732893	74733125	MSK_RL_AMP107
chrX	44913025	44913215	KDM6A_c6	chrX	1.23E+08	1.23E+08	MSK_RL_AMP108
chrX	44918199	44918395	KDM6A_c7	chr7	1.49E+08	1.49E+08	MSK_RL_AMP109
chrX	44919220	44919403	KDM6A_c8				
chrX	44921848	44922010	KDM6A_c9				
chrX	44922903	44923058	KDM6A_c10				
chrX	44928854	44929041	KDM6A_c11				
chrX	44929082	44929312	KDM6A_c12				
chrX	44929375	44929601	KDM6A_c13				
chrX	44938445	44938646	KDM6A_c14				
chrX	44942689	44942899	KDM6A_c15				
chrX	44948938	44949155	KDM6A_c16				
chrX	44949941	44950138	KDM6A_c17				
chrX	44966642	44966798	KDM6A_c18				
chrX	44969341	44969549	KDM6A_c19				
chr4	55561575	55561801	KIT_c1				
chr4	55589690	55589906	KIT_c2				
chr4	55592020	55592244	KIT_c3				
chr4	55593610	55593833	KIT_c4				
chr4	55594135	55594358	KIT_c5				
chr4	55599231	55599448	KIT_c6				
chr12	25378568	25378790	KRAS_c1				
chr12	25380259	25380466	KRAS_c2				
chr12	25398183	25398405	KRAS_c3				
chr1	43814926	43815093	MPL_c1				
chr8	1.29E+08	1.29E+08	MYC_c1				
chr8	1.29E+08	1.29E+08	MYC_c2				
chr8	1.29E+08	1.29E+08	MYC_c3				
chr8	1.29E+08	1.29E+08	MYC_c4				
chr8	1.29E+08	1.29E+08	MYC_c5				
chr8	1.29E+08	1.29E+08	MYC_c6				
chr17	29483050	29483268	NF1_c1				

chr17	29508713	29508833	NF1_c2
chr17	29509391	29509609	NF1_c3
chr17	29527934	29528162	NF1_c4
chr17	29528458	29528681	NF1_c5
chr17	29533177	29533393	NF1_c6
chr17	29552046	29552264	NF1_c7
chr17	29553680	29553877	NF1_c8
chr17	29554239	29554460	NF1_c9
chr17	29554510	29554726	NF1_c10
chr17	29556072	29556295	NF1_c11
chr17	29556664	29556887	NF1_c12
chr17	29557822	29558039	NF1_c13
chr17	29559870	29560093	NF1_c14
chr17	29562528	29562662	NF1_c15
chr17	29562732	29562893	NF1_c16
chr17	29562944	29563096	NF1_c17
chr17	29575904	29576122	NF1_c18
chr17	29588544	29588770	NF1_c19
chr17	29652681	29652896	NF1_c20
chr17	29654400	29654602	NF1_c21
chr17	29654646	29654839	NF1_c22
chr17	29657353	29657574	NF1_c23
chr17	29663533	29663756	NF1_c24
chr17	29667347	29667573	NF1_c25
chr17	29683823	29684032	NF1_c26
chr17	29684082	29684298	NF1_c27
chr17	29685545	29685768	NF1_c28
chr5	1.71E+08	1.71E+08	NPM1_c1
chr1	1.15E+08	1.15E+08	NRAS_c1
chr1	1.15E+08	1.15E+08	NRAS_c2
chrX	1.34E+08	1.34E+08	PHF6_c1
chrX	1.34E+08	1.34E+08	PHF6_c2
chrX	1.34E+08	1.34E+08	PHF6_c3
chrX	1.34E+08	1.34E+08	PHF6_c4
chrX	1.34E+08	1.34E+08	PHF6_c5
chrX	1.34E+08	1.34E+08	PHF6_c6

chrX	1.34E+08	1.34E+08	PHF6_c7
chrX	1.34E+08	1.34E+08	PHF6_c8
chr17	58740194	58740380	PPM1D_c1
chr17	58740423	58740649	PPM1D_c2
chr17	58740696	58740907	PPM1D_c3
chr12	1.13E+08	1.13E+08	PTPN11_c1
chr12	1.13E+08	1.13E+08	PTPN11_c2
chr12	1.13E+08	1.13E+08	PTPN11_c3
chr12	1.13E+08	1.13E+08	PTPN11_c4
chr8	1.18E+08	1.18E+08	RAD21_c1
chr8	1.18E+08	1.18E+08	RAD21_c2
chr8	1.18E+08	1.18E+08	RAD21_c3
chr8	1.18E+08	1.18E+08	RAD21_c4
chr21	36164451	36164621	RUNX1_c1
chr21	36164676	36164884	RUNX1_c2
chr21	36171590	36171810	RUNX1_c3
chr21	36193775	36194003	RUNX1_c4
chr21	36206705	36206884	RUNX1_c5
chr21	36231715	36231936	RUNX1_c6
chr21	36252831	36253058	RUNX1_c7
chr21	36259166	36259401	RUNX1_c8
chr21	36421020	36421247	RUNX1_c9
chr18	42530384	42530606	SETBP1_c1
chr18	42531784	42531951	SETBP1_c2
chr18	42531989	42532197	SETBP1_c3
chr18	42532535	42532764	SETBP1_c4
chr18	42533021	42533240	SETBP1_c5
chr18	42533290	42533514	SETBP1_c6
chr2	1.98E+08	1.98E+08	SF3B1_c1
chr2	1.98E+08	1.98E+08	SF3B1_c2
chr2	1.98E+08	1.98E+08	SF3B1_c3
chr2	1.98E+08	1.98E+08	SF3B1_c4
chr2	1.98E+08	1.98E+08	SF3B1_c5
chrX	53423398	53423625	SMC1A_c1
chrX	53426467	53426688	SMC1A_c2
chrX	53432543	53432748	SMC1A_c3

chr10	1.12E+08	1.12E+08	SMC3_c1
chr10	1.12E+08	1.12E+08	SMC3_c2
chr10	1.12E+08	1.12E+08	SMC3_c3
chr10	1.12E+08	1.12E+08	SMC3_c4
chr17	74732886	74733076	SRSF2_c1
chrX	1.23E+08	1.23E+08	STAG2_c1
chrX	1.23E+08	1.23E+08	STAG2_c2
chrX	1.23E+08	1.23E+08	STAG2_c3
chrX	1.23E+08	1.23E+08	STAG2_c4
chrX	1.23E+08	1.23E+08	STAG2_c5
chrX	1.23E+08	1.23E+08	STAG2_c6
chrX	1.23E+08	1.23E+08	STAG2_c7
chrX	1.23E+08	1.23E+08	STAG2_c8
chrX	1.23E+08	1.23E+08	STAG2_c9
chrX	1.23E+08	1.23E+08	STAG2_c10
chrX	1.23E+08	1.23E+08	STAG2_c11
chrX	1.23E+08	1.23E+08	STAG2_c12
chrX	1.23E+08	1.23E+08	STAG2_c13
chr4	1.06E+08	1.06E+08	TET2_c1
chr4	1.06E+08	1.06E+08	TET2_c2
chr4	1.06E+08	1.06E+08	TET2_c3
chr4	1.06E+08	1.06E+08	TET2_c4
chr4	1.06E+08	1.06E+08	TET2_c5
chr4	1.06E+08	1.06E+08	TET2_c6
chr4	1.06E+08	1.06E+08	TET2_c7
chr4	1.06E+08	1.06E+08	TET2_c8
chr4	1.06E+08	1.06E+08	TET2_c9
chr4	1.06E+08	1.06E+08	TET2_c10
chr4	1.06E+08	1.06E+08	TET2_c11
chr4	1.06E+08	1.06E+08	TET2_c12
chr4	1.06E+08	1.06E+08	TET2_c13
chr4	1.06E+08	1.06E+08	TET2_c14
chr4	1.06E+08	1.06E+08	TET2_c15
chr4	1.06E+08	1.06E+08	TET2_c16
chr4	1.06E+08	1.06E+08	TET2_c17
chr4	1.06E+08	1.06E+08	TET2_c18

chr4	1.06E+08	1.06E+08	TET2_c19
chr4	1.06E+08	1.06E+08	TET2_c20
chr4	1.06E+08	1.06E+08	TET2_c21
chr4	1.06E+08	1.06E+08	TET2_c22
chr4	1.06E+08	1.06E+08	TET2_c23
chr4	1.06E+08	1.06E+08	TET2_c24
chr4	1.06E+08	1.06E+08	TET2_c25
chr4	1.06E+08	1.06E+08	TET2_c26
chr17	7576494	7576701	TP53_c1
chr17	7579764	7579966	TP53_c2
chr17	7573880	7574076	TP53_c3
chr17	7576810	7576948	TP53_c4
chr17	7577000	7577225	TP53_c5
chr17	7577424	7577614	TP53_c6
chr17	7578098	7578292	TP53_c7
chr17	7578379	7578587	TP53_c8
chr17	7579348	7579566	TP53_c9
chr21	44514700	44514922	U2AF1_c1
chr21	44524279	44524505	U2AF1_c2
chr11	32413415	32413641	WT1_c1
chr11	32414193	32414411	WT1_c2
chr11	32417779	32418008	WT1_c3
chrX	15808955	15809170	ZRSR2_c1
chrX	15817959	15818143	ZRSR2_c2
chrX	15821773	15821932	ZRSR2_c3
chrX	15822168	15822349	ZRSR2_c4
chrX	15826277	15826495	ZRSR2_c5
chrX	15827302	15827524	ZRSR2_c6
chrX	15833836	15834061	ZRSR2_c7
chrX	15838246	15838463	ZRSR2_c8
chrX	15840789	15840954	ZRSR2_c9
chrX	15841002	15841103	ZRSR2_c10
chrX	15841178	15841403	ZRSR2_c11

Supplementary Table 2: Genes and their corresponding biological pathways used for analysis.

Pathway	Gene
NPM1	NPM1
DNA methylation	DNMT3A
DNA methylation	IDH1
DNA methylation	IDH2
DNA methylation	TET2
RTK/RAS/MAP kinase pathway	NRAS
RTK/RAS/MAP kinase pathway	NF1
RTK/RAS/MAP kinase pathway	KRAS
RTK/RAS/MAP kinase pathway	FLT3
RTK/RAS/MAP kinase pathway	PTPN11
RTK/RAS/MAP kinase pathway	KIT
RTK/RAS/MAP kinase pathway	CBL
RTK/RAS/MAP kinase pathway	SETBP1
RTK/RAS/MAP kinase pathway	BRAF
JAK-STAT	JAK2
JAK-STAT	MPL
JAK-STAT	CSF3R
JAK-STAT	CALR
Transcription factor	RUNX1
Transcription factor	WT1
Transcription factor	GATA2
Transcription factor	PHF6
Transcription factor	ETV6
Chromatin/cohesin	ASXL1
Chromatin/cohesin	BCOR
Chromatin/cohesin	STAG2
Chromatin/cohesin	KDM6A
Chromatin/cohesin	EZH2
Chromatin/cohesin	SMC3
Chromatin/cohesin	SMC1A
Splicing	SRSF2
Splicing	U2AF1

Splicing	ZRSR2
Splicing	SF3B1
Apoptosis	TP53
Apoptosis	PPM1D
Apoptosis	MYC
Apoptosis	ATM
Apoptosis	CHEK2
Apoptosis	RAD21

Supplementary Table 3: Connections in each tree that are poorly supported, specifically that <50% cells with later mutation contain early mutation.

Path	Fraction	Cells	Patient
DNMT3A:p.R882H->WT1:p.R369X	0.498168498	136	MSK_P28
KRAS:p.G12V->ASXL1:p.T639fs	0.487179487	76	MD_Anderson_AML-22
KRAS:p.G12V->ASXL1:p.T639fs	0.487179487	76	MD_Anderson_AML-22
SRSF2:p.P95L->IDH2:p.R140W	0.483870968	15	MD_Anderson_AML-66
SRSF2:p.P95L->NRAS:p.G13V	0.482758621	14	MD_Anderson_AML-66
SRSF2:p.P95L->NRAS:p.G12D	0.481481481	13	MD_Anderson_AML-66
RUNX1:p.T246fs->FLT3:p.V491L	0.474380165	287	MSK_P14
KIT:p.D816V->EZH2:p.E747X	0.463414634	19	MD_Anderson_AML-112
KIT:p.D816V->ZRSR2:p.Q124fs	0.461538462	30	MD_Anderson_AML-112
TET2:p.R1387fs->ZRSR2:p.Q124fs	0.454545455	30	MD_Anderson_AML-112
NPM1:p.L287fs->ZRSR2:p.M367delinsIVX	0.454545455	5	MD_Anderson_AML-112
DNMT3A:p.R882H->EZH2:p.E747X	0.45	18	MD_Anderson_AML-112
TET2:p.R1387fs->ZRSR2:p.M367delinsIVX	0.45	9	MD_Anderson_AML-112
NRAS:p.G13V->SRSF2:p.P95L	0.449744463	264	MSK_P80
DNMT3A:p.R882H->TP53:p.G244S	0.447368421	51	MSK_P28
KIT:p.D816V->ZRSR2:p.M367delinsIVX	0.428571429	9	MD_Anderson_AML-112
RUNX1:p.I366fs->BCOR:p.P1621fs	0.428571429	3	MD_Anderson_AML-42
DNMT3A:p.R882H->FLT3-ITD	0.427350427	100	MSK_P65
SRSF2:p.P95L->IDH1:p.R132C	0.422535211	30	MD_Anderson_AML-99
NPM1:p.L287fs->EZH2:p.E195X	0.421052632	8	MD_Anderson_AML-112
DNMT3A:p.R882H->NRAS:p.G12D	0.420560748	45	MSK_P70
SRSF2:p.P95L->RUNX1:p.S318fs	0.417721519	66	MD_Anderson_AML-99
DNMT3A:p.R882H->IDH1:p.R132C	0.417177914	68	MSK_P70

TET2:p.R1387fs->KIT_55561677_splicing	0.409090909	9	MD_Anderson_AML-112
TET2:p.R1387fs->EZH2:p.E747X	0.375	15	MD_Anderson_AML-112
NPM1:p.L287fs->ZRSR2:p.K138X	0.375	12	MD_Anderson_AML-112
SRSF2:p.P95L->FLT3-ITD	0.373737374	37	MD_Anderson_AML-10
SRSF2:p.P95L->FLT3-ITD	0.371972318	215	MD_Anderson_AML-99
DNMT3A:p.R882H->SRSF2:p.P95H	0.366666667	22	MSK_P101
SRSF2:p.P95L->CSF3R:p.Q768X	0.362573099	62	MD_Anderson_AML-99
NPM1:p.L287fs->EZH2:p.E649X	0.36	18	MD_Anderson_AML-112
NPM1:p.L287fs->ZRSR2:p.Q124fs	0.357142857	15	MD_Anderson_AML-112
NPM1:p.L287fs->EZH2:p.E747X	0.344827586	10	MD_Anderson_AML-112
NPM1:p.L287fs->TET2:p.Q1568fs	0.333333333	1	MD_Anderson_AML-118
NPM1:p.L287fs->TET2:p.Q1574X	0.333333333	1	MD_Anderson_AML-118
NRAS:p.G13D->STAG2:p.N1046fs	0.309090909	51	MD_Anderson_AML-42
SRSF2:p.P95L->CSF3R:p.Q776X	0.295081967	18	MD_Anderson_AML-99
FLT3-ITD->FLT3:p.D835V	0.292307692	19	MD_Anderson_AML-88
NRAS:p.G13D->RUNX1:p.A142fs	0.287769784	40	MD_Anderson_AML-42
NRAS:p.G13D->NRAS:p.G12D	0.282051282	11	MD_Anderson_AML-42
KIT:p.D816Y->KRAS:p.G12V	0.27607362	45	MSK_P21
GATA2:p.L359V->JAK2:p.V617F	0.24122807	55	MD_Anderson_AML-89
KIT:p.D816Y->FLT3:p.D835H	0.218487395	52	MSK_P21
SRSF2:p.P95R->TP53:p.V197E	0.214285714	3	MSK_P47
SF3B1:p.K666N->JAK2:p.V617F	0.212903226	33	MD_Anderson_AML-02
FLT3:p.N841I->FLT3:p.V491L	0.211783439	133	MSK_P14
SRSF2:p.P95L->NRAS:p.Q61P	0.210526316	4	MD_Anderson_AML-66
TP53:p.R213X->TP53:p.C176S	0.20661157	25	MD_Anderson_AML-85
TP53:p.V216M->DNMT3A:p.R882H	0.198731501	94	MD_Anderson_AML-78
PTPN11:p.E76V->FLT3:p.D835Y	0.193771626	112	MD_Anderson_AML-82

IDH2:p.R172K->NRAS:p.G12V	0.193181818	17	MD_Anderson_AML-77
TP53:p.V216M->PPM1D:p.C478X	0.1875	12	MD_Anderson_AML-78
RUNX1:p.S141fs->JAK2:p.V617F	0.182481752	25	MD_Anderson_AML-02
FLT3:p.D835V->JAK2:p.V617F	0.181818182	28	MD_Anderson_AML-02
PTPN11:p.E76V->PTPN11:p.G60V	0.180354267	112	MD_Anderson_AML-82
NRAS:p.G12D->TET2:p.L697fs	0.178571429	10	MD_Anderson_AML-90
IDH1:p.R132C->WT1:p.R369fs	0.170212766	16	MD_Anderson_AML-04
NRAS:p.G13D->RUNX1:p.S322X	0.165384615	86	MD_Anderson_AML-69
FLT3:p.D835A->FLT3:p.D835Y	0.136363636	6	MD_Anderson_AML-05
GATA2:p.L359V->DNMT3A:p.I495fs	0.130434783	6	MD_Anderson_AML-89
NRAS:p.G13D->FLT3:p.N676K	0.121212121	4	MD_Anderson_AML-05
FLT3-ITD->FLT3:p.834_835del	0.118181818	13	MD_Anderson_AML-88
KRAS:p.G12V->KRAS:p.G12S	0.106666667	8	MD_Anderson_AML-22
IDH1:p.R132H->IDH2:p.R140Q	0.10376569	124	MD_Anderson_AML-28
KRAS:p.G12V->NRAS:p.G13C	0.101449275	7	MD_Anderson_AML-22
IDH2:p.R172K->KRAS:p.V14I	0.1	7	MD_Anderson_AML-48
MYC:p.P74A->MYC:p.P74L	0.097972973	87	MD_Anderson_AML-86
NPM1:p.L287fs->TET2:p.L697fs	0.096153846	5	MD_Anderson_AML-90
NRAS:p.G12S->KRAS:p.G12D	0.09516943	132	Stanford_SU359
NRAS:p.Q61H->NRAS:p.G12A	0.090909091	12	MD_Anderson_AML-76
FLT3:p.D835A->FLT3-ITD	0.090909091	4	MD_Anderson_AML-05
NRAS:p.G12D->FLT3-ITD	0.089147287	23	MD_Anderson_AML-06
NRAS:p.G12D->PTPN11:p.A72V	0.087378641	9	MD_Anderson_AML-35
NRAS:p.G12D->NRAS:p.Q61R	0.081081081	6	Stanford_SU290
FLT3-ITD->NRAS:p.G12A	0.080645161	10	Stanford_SU442
NRAS:p.G13D->KRAS:p.G12A	0.077294686	16	MD_Anderson_AML-69
KRAS:p.G13D->NRAS:p.G12D	0.074074074	4	MD_Anderson_AML-81
IDH1:p.R132S->WT1:p.R369fs	0.071428571	6	MD_Anderson_AML-04
NRAS:p.G12D->NRAS:p.G12C	0.068965517	4	Stanford_SU290
PTPN11:p.G503E->NRAS:p.G13V	0.065217391	6	MD_Anderson_AML-66
SRSF2:p.P95R->KRAS:p.G13D	0.064516129	2	MD_Anderson_AML-57
RUNX1:p.K152fs->RUNX1:p.D198N	0.063492063	8	MD_Anderson_AML-59
NRAS:p.G12D->NRAS:p.G13V	0.063063063	7	Stanford_SU290

NRAS:p.G12D->FLT3-ITD	0.058823529	35	Stanford_SU290
NRAS:p.G12D->NRAS:p.G13R	0.053763441	5	MD_Anderson_AML-53
NRAS:p.G12S->KRAS:p.G12D	0.052083333	5	MD_Anderson_AML-66
NRAS:p.G13R->PTPN11:p.G503A	0.047619048	1	MSK_P39
FLT3:p.V491L->TP53:p.A159V	0.041666667	6	MSK_P57
KRAS:p.G13D->NRAS:p.G12C	0.040983607	5	MD_Anderson_AML-81
KRAS:p.G13D->NRAS:p.G12S	0.040816327	4	MD_Anderson_AML-81
NRAS:p.G12D->IDH1:p.R132S	0.04034135	52	MD_Anderson_AML-04
KRAS:p.G13D->FLT3:p.D835Y	0.037037037	5	MD_Anderson_AML-81
FLT3-ITD->NRAS:p.Q61R	0.036585366	3	Stanford_SU290
KRAS:p.G12C->KRAS:p.G13D	0.032520325	4	MSK_P53
NPM1:p.L287fs->KRAS:p.G13D	0.03125	2	MD_Anderson_AML-57
NRAS:p.G12D->FLT3-ITD	0.022222222	10	MD_Anderson_AML-53
NRAS:p.G12S->NRAS:p.G13V	0.020408163	2	MD_Anderson_AML-66
NRAS:p.G12D->NRAS:p.Q61H	0.018867925	1	Stanford_SU290
NRAS:p.G12D->KIT:p.N822K	0.018348624	2	Stanford_SU290
NRAS:p.G12D->KIT:p.N822K	0.018348624	2	Stanford_SU290
FLT3-ITD->KIT:p.N822K	0.017094017	2	Stanford_SU290
FLT3:p.D835E->NRAS:p.G12S	0.016460905	8	MD_Anderson_AML-36
FLT3:p.D835E->FLT3:p.836_837del	0.014925373	1	MD_Anderson_AML-81
FLT3:p.D835E->NRAS:p.G12D	0.010752688	1	MD_Anderson_AML-36
NRAS:p.G12S->NRAS:p.G12D	0.010638298	1	MD_Anderson_AML-36
PTPN11:p.G503E->IDH2:p.R140W	0.010204082	1	MD_Anderson_AML-66
KRAS:p.G12V->FLT3:p.D835Y	0.009174312	1	Stanford_SU320
KRAS:p.G12V->FLT3:p.836_837del	0.008519702	8	Stanford_SU320
FLT3-ITD->WT1:p.V371fs	0	0	MD_Anderson_AML-04
IDH1:p.R132C->IDH1:p.R132S	0	0	MD_Anderson_AML-04
NRAS:p.G12C->NRAS:p.G12S	0	0	MD_Anderson_AML-22
IDH1:p.R132H->PTPN11:p.G503A	0	0	MD_Anderson_AML-38
PTPN11:p.D61H->PTPN11:p.G503A	0	0	MD_Anderson_AML-38
FLT3-ITD->NRAS:p.G13R	0	0	MD_Anderson_AML-53
TP53:p.A138V->TP53_7577498_splicing	0	0	MD_Anderson_AML-79
FLT3:p.D835E->KIT:p.N822K	0	0	MD_Anderson_AML-81

FLT3:p.D835E->FLT3:p.N676K	0	0	MD_Anderson_AML-81
JAK2:p.V617F->TET2:p.Q1624X	0	0	MSK_P47
SRSF2:p.P95R->TET2:p.Q1624X	0	0	MSK_P47
SRSF2:p.P95R->RUNX1:p.L317fs	0	0	MSK_P47
KRAS:p.G12C->KRAS:p.G12D	0	0	MSK_P53
IDH1:p.R132C->TET2:p.K685fs	0	0	MSK_P61
IDH1:p.R132G->DNMT3A:p.R736C	0	0	MSK_P97
PTPN11:p.A72T->WT1:p.R369fs	0	0	Stanford_SU067

Supplementary Table 4: Table showing whether one mutation tends to occur before another, among mutations occurring in the same clones and with mutations summarized to genes. P-values were derived using a binomial test and adjusted to Q-values using the Benjamini-Hochberg method (37).

Gene1	Gene2	Number of clones	Proportion Gene1 first	P-value	Q-value
IDH2	NRAS	18	0.9444444444	0.000144958	0.002512614
FLT3	IDH2	20	0.1	0.000402451	0.004231771
KRAS	NPM1	12	0	0.000488281	0.004231771
NRAS	TET2	12	0	0.000488281	0.004231771
IDH2	SRSF2	19	0.894736842	0.000728607	0.00541251
IDH2	NPM1	21	0.857142857	0.001489639	0.008645051
FLT3	NPM1	54	0.2777777778	0.001496259	0.008645051
KRAS	TP53	10	0	0.001953125	0.009232955
PTPN11	TP53	10	0	0.001953125	0.009232955
DNMT3A	NPM1	29	0.793103448	0.0023157	0.0100347
FLT3	IDH1	13	0.076923077	0.003417969	0.012695313
FLT3	SF3B1	9	0	0.00390625	0.012695313
FLT3	TET2	9	0	0.00390625	0.012695313
NPM1	TET2	9	0	0.00390625	0.012695313
DNMT3A	KRAS	12	0.916666667	0.006347656	0.01941636
NPM1	NRAS	32	0.75	0.007000367	0.020223282
NRAS	TP53	8	0	0.0078125	0.0203125
NRAS	U2AF1	8	0	0.0078125	0.0203125
DNMT3A	EZH2	6	1	0.03125	0.065
NPM1	SF3B1	6	0	0.03125	0.065
NRAS	SF3B1	6	0	0.03125	0.065
PTPN11	TET2	6	0	0.03125	0.065
TET2	TP53	6	1	0.03125	0.065
NRAS	RUNX1	15	0.2	0.03515625	0.0703125
IDH2	KRAS	9	0.888888889	0.0390625	0.075231481
IDH1	NRAS	14	0.785714286	0.057373047	0.106549944
IDH2	PTPN11	8	0.875	0.0703125	0.126077586
IDH1	NPM1	16	0.75	0.076812744	0.128847184

NPM1	PTPN11	16	0.75	0.076812744	0.128847184
ASXL1	NRAS	7	0.857142857	0.125	0.203125
IDH2	RUNX1	12	0.75	0.145996094	0.230054451
DNMT3A	TET2	9	0.222222222	0.1796875	0.274816176
DNMT3A	SRSF2	6	0.833333333	0.21875	0.325
FLT3	WT1	18	0.666666667	0.237884521	0.343610975
SRSF2	TET2	8	0.25	0.2890625	0.40625
DNMT3A	IDH2	25	0.6	0.424356222	0.576436857
DNMT3A	U2AF1	7	0.714285714	0.453125	0.576436857
FLT3	SRSF2	7	0.285714286	0.453125	0.576436857
NPM1	WT1	16	0.625	0.454498291	0.576436857
IDH1	RUNX1	9	0.333333333	0.5078125	0.614098837
NRAS	WT1	9	0.333333333	0.5078125	0.614098837
FLT3	RUNX1	11	0.363636364	0.548828125	0.648615057
DNMT3A	WT1	6	0.666666667	0.6875	0.777173913
IDH2	JAK2	6	0.666666667	0.6875	0.777173913
DNMT3A	IDH1	14	0.428571429	0.790527344	0.874625997
ASXL1	RUNX1	7	0.571428571	1	1
ASXL1	TET2	7	0.428571429	1	1
DNMT3A	RUNX1	15	0.533333333	1	1
RUNX1	SRSF2	9	0.555555556	1	1
RUNX1	TET2	7	0.428571429	1	1
DNMT3A	FLT3	33	0.909090909	1.40E-06	3.64E-05
DNMT3A	NRAS	32	0.9375	2.46E-07	1.28E-05

Supplementary Table 5: Triplet mutation orderings. A trio of mutations was considered for ordering analysis if more than two patients had the three mutations in the same clone. P-values were derived from the exact multinomial test, except for when the binomial coefficient was greater than 10^6 , in which case a Monte Carlo approach was used. Both the number of clones with the three mutations (“Number clones”) and the number of clones with the most common ordering (“Ordering count”) are shown. P-values were calculated both at the A) gene level and B) pathway level and were adjusted using the Benjamini-Hochberg method (37).

A) Analysis by gene

Top mutation order for trio	Number clones	Ordering count	P-value for non-uniform chance of ordering	FDR-adjusted p-value
DNMT3A->NPM1->FLT3	20	13	6.62E-05	0.002712307
IDH2->NPM1->FLT3	12	8	0.000213772	0.004382334
TET2->DNMT3A->NRAS	5	5	0.000771605	0.010545267
RUNX1->DNMT3A->NRAS	8	6	0.003647262	0.023726852
DNMT3A->IDH1->NRAS	9	6	0.004189053	0.023726852
DNMT3A->NPM1->NRAS	9	6	0.004189053	0.023726852
IDH2->NPM1->NRAS	9	6	0.004189053	0.023726852
TET2->ASXL1->NRAS	4	4	0.00462963	0.023726852
DNMT3A->NPM1->WT1	6	4	0.013631687	0.062099909
DNMT3A->IDH1->FLT3	8	5	0.016275149	0.066728109
IDH1->NPM1->FLT3	10	6	0.019692596	0.068544239
DNMT3A->IDH2->FLT3	5	4	0.020061728	0.068544239
NRAS->NPM1->FLT3	3	3	0.027777778	0.081349206
IDH2->SRSF2->NRAS	3	3	0.027777778	0.081349206
DNMT3A->SF3B1->FLT3	5	3	0.058641975	0.150270062
DNMT3A->U2AF1->NRAS	5	3	0.058641975	0.150270062
DNMT3A->IDH2->NRAS	7	3	0.090792181	0.181186869
DNMT3A->RUNX1->FLT3	4	3	0.097222222	0.181186869
IDH2->DNMT3A->SRSF2	4	3	0.097222222	0.181186869
DNMT3A->U2AF1->RUNX1	4	3	0.097222222	0.181186869
SF3B1->RUNX1->FLT3	4	3	0.097222222	0.181186869
NPM1->IDH1->PTPN11	4	3	0.097222222	0.181186869
DNMT3A->IDH1->NPM1	5	3	0.212962963	0.363811728
RUNX1->TET2->NRAS	6	3	0.212962963	0.363811728
DNMT3A->ASXL1->RUNX1	3	2	0.444444444	0.607407407
DNMT3A->NPM1->KRAS	3	2	0.444444444	0.607407407
DNMT3A->NPM1->PTPN11	3	2	0.444444444	0.607407407

<i>DNMT3A->SF3B1->RUNX1</i>	3	2	0.444444444	0.607407407
<i>JAK2->IDH2->SRSF2</i>	3	2	0.444444444	0.607407407
<i>IDH2->NPM1->SRSF2</i>	3	2	0.444444444	0.607407407
<i>DNMT3A->IDH2->NPM1</i>	7	2	0.58590535	0.774907076
<i>DNMT3A->FLT3->WT1</i>	4	2	0.722222222	0.870915033
<i>IDH1->NPM1->NRAS</i>	4	2	0.722222222	0.870915033
<i>IDH2->NPM1->PTPN11</i>	4	2	0.722222222	0.870915033
<i>DNMT3A->RUNX1->IDH1</i>	6	2	0.75308642	0.882186949
<i>WT1->FLT3->WT1</i>	3	2	0.777777778	0.885802469
<i>NRAS->NPM1->WT1</i>	5	2	0.907407407	1
<i>FLT3->NPM1->WT1</i>	11	3	0.979370285	1
<i>RUNX1->IDH2->SRSF2</i>	6	2	0.984567901	1
<i>IDH2->JAK2->RUNX1</i>	3	1	1	1
<i>DNMT3A->TET2->RUNX1</i>	4	1	1	1

B) Analysis by pathway

<i>Top mutation order for trio</i>	Number clones	Ordering count	P-value for non-uniform chance of ordering	FDR-adjusted p-value
DNA methylation->DNA methylation->RTK/RAS/MAP kinase pathway	54	47	8.78E-07	5.50E-06
<i>DNA methylation->Chromatin/cohesin->RTK/RAS/MAP kinase pathway</i>	29	20	1.00E-06	5.50E-06
<i>DNA methylation->NPM1->RTK/RAS/MAP kinase pathway</i>	89	55	1.00E-06	5.50E-06
<i>DNA methylation->Splicing->RTK/RAS/MAP kinase pathway</i>	48	23	1.00E-06	5.50E-06
<i>Transcription factor->DNA methylation->RTK/RAS/MAP kinase pathway</i>	46	22	1.00E-06	5.50E-06
<i>Splicing->RTK/RAS/MAP kinase pathway->Transcription factor</i>	28	12	1.00E-06	5.50E-06
<i>DNA methylation->NPM1->Transcription factor</i>	14	11	4.81E-06	2.27E-05
<i>DNA methylation->Apoptosis->RTK/RAS/MAP kinase pathway</i>	16	10	7.47E-05	0.000307969
<i>DNA methylation->RTK/RAS/MAP kinase pathway->RTK/RAS/MAP kinase pathway</i>	15	13	9.43E-05	0.000345741
<i>Splicing->NPM1->RTK/RAS/MAP kinase pathway</i>	11	8	0.000266529	0.000879546
<i>Chromatin/cohesin->RTK/RAS/MAP kinase pathway->Transcription factor</i>	13	6	0.000399027	0.001197082

DNA methylation->DNA methylation->NPM1	16	12	0.000601649	0.001654534
Chromatin/cohesin->Splicing->Transcription factor	9	6	0.004189053	0.010459884
Splicing->NPM1->Transcription factor	4	4	0.00462963	0.010459884
DNA methylation->Chromatin/cohesin->Transcription factor	13	6	0.004754493	0.010459884
DNA methylation->Chromatin/cohesin->Splicing	14	8	0.005655148	0.011663742
DNA methylation->DNA methylation->JAK-STAT	6	5	0.053497942	0.103848947
DNA methylation->NPM1->Splicing	9	3	0.066786694	0.122442273
RTK/RAS/MAP kinase pathway->NPM1->RTK/RAS/MAP kinase pathway	7	5	0.0781893	0.135802469
Chromatin/cohesin->Chromatin/cohesin->RTK/RAS/MAP kinase pathway	10	7	0.093126048	0.152777778
JAK-STAT->DNA methylation->Splicing	4	3	0.097222222	0.152777778
RTK/RAS/MAP kinase pathway->NPM1->Transcription factor	22	9	0.103342077	0.155013116
DNA methylation->DNA methylation->Apoptosis	3	3	0.111111111	0.15942029
DNA methylation->DNA methylation->Splicing	19	10	0.158055066	0.217325716
DNA methylation->Chromatin/cohesin->DNA methylation	17	8	0.16938742	0.223591394
DNA methylation->Splicing->Transcription factor	25	9	0.226187774	0.287084482
DNA methylation->Chromatin/cohesin->Chromatin/cohesin	8	5	0.295839049	0.348667451
RTK/RAS/MAP kinase pathway->Chromatin/cohesin->RTK/RAS/MAP kinase pathway	8	5	0.295839049	0.348667451
DNA methylation->Transcription factor->JAK-STAT	16	6	0.30647262	0.348744706
Splicing->RTK/RAS/MAP kinase pathway->RTK/RAS/MAP kinase pathway	7	4	0.519890261	0.571879287
RTK/RAS/MAP kinase pathway->Transcription factor->Transcription factor	4	2	0.555555556	0.591397849
RTK/RAS/MAP kinase pathway->RTK/RAS/MAP kinase pathway->Transcription factor	5	3	0.62962963	0.649305556
DNA methylation->DNA methylation->Transcription factor	18	7	0.955724758	0.955724758

Supplementary Table 6: Multivariable regression analyses. A) Linear regression of DNA methylation mutation order compared to bone marrow blast, granulocyte, and monocyte percentages, before and after adjusting for patient age and DNA methylation mutation burden (% mutated cells). B) Similar regressions as in (A), but predictor variable is signaling mutation order instead of DNA methylation mutation order, and response variable is peripheral white blood cell, granulocyte, and monocyte counts. C) *WT1* mutation order at diagnosis vs. patient age, adjusting for signaling mutation order. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, [†] $p < 0.1$

A) DNA methylation mutations vs. cell counts

Variable	Single variable regression		Multivariable regression	
	Bone marrow blast %	Bone marrow blast % p-value	Bone marrow blast %	Bone marrow blast % p-value
DNA methylation mutation late	-11.8	0.0938 [†]	-8.73	0.206
No DNA methylation mutation	-6.99	0.129	11.6	0.191
DNA methylation mutation clone size			29.7	0.00792**
Age			-0.275	0.0649 [†]
	Bone marrow granulocyte %	Bone marrow granulocyte % p-value	Bone marrow granulocyte %	Bone marrow granulocyte % p-value
DNA methylation mutation late	4.92	0.0824 [†]	1.52	0.545
No DNA methylation mutation	3.75	0.0442	2.43	0.462
DNA methylation mutation clone size			-0.652	0.876
Age			0.148	0.00868**
	Bone marrow monocyte %	Bone marrow monocyte % p-value	Bone marrow monocyte %	Bone marrow monocyte % p-value
DNA methylation mutation late	1.69	0.506	4.8	0.093 [†]
No DNA methylation mutation	1.74	0.308	1.08	0.764
DNA methylation mutation clone size			-3.29	0.467
Age			-0.0538	0.373

**B) Signaling mutations vs.
cell counts**

Variable	Single variable regression		Multivariable regression	
	Log blast count coefficient	Log blast count p-value	Log blast count coefficient	Log blast count p-value
Signaling mutation late	-0.756	0.15	-0.47	0.364
No signaling mutation	-2.01	0.000677***	-0.718	0.307
Signaling mutation clone size			2	0.00842**
Age			-0.0188	0.171
Signaling mutation late No signaling mutation Signaling mutation clone size Age	Log granulocyte count coefficient	Log granulocyte count p-value	Log granulocyte count coefficient	Log granulocyte count p-value
	-0.5	0.117	-0.545	0.0884†
	-1.16	0.00106**	-1.04	0.0164*
			0.648	0.16
			0.0172	0.0434*
Signaling mutation late No signaling mutation Signaling mutation clone size Age	Log monocyte count coefficient	Log monocyte count p-value	Log monocyte count coefficient	Log monocyte count p-value
	-0.777	0.0335*	-0.793	0.0348*
	-1.24	0.00245**	-1.24	0.0157*
			0.104	0.846
			0.00415	0.675

C) WT1 mutations vs. patient age and cell counts

Variable	Single variable regression		Multivariable regression	
	Log blast count coefficient	Log blast count p-value	Log blast count coefficient	Log blast count p-value
WT1 mutation late	22.3	0.00864**	22.6	0.00601**
No WT1 mutation	19.5	0.00171**	18.1	0.00282**
Signaling mutation late			7.08	0.0329*
No signaling mutation			12.3	0.000844***
	Log blast count coefficient	Log blast count p-value	Log blast count coefficient	Log blast count p-value
WT1 mutation late	-0.878	0.516	0.0958	0.941
No WT1 mutation	-0.0231	0.981	1.22	0.208
Signaling mutation late			-0.41	0.433
No signaling mutation			-0.678	0.337
Signaling mutation clone size			2.18	0.00451***
Age			-0.0222	0.12
	Log granulocyte count coefficient	Log granulocyte count p-value	Log granulocyte count coefficient	Log granulocyte count p-value
WT1 mutation late	-1.6	0.0488*	-1.97	0.0131*
No WT1 mutation	-0.7	0.232	-0.786	0.179
Signaling mutation late			-0.647	0.0422*
No signaling mutation			-1.17	0.00657**
Signaling mutation clone size			0.569	0.215
Age			0.0218	0.0122*
	Log monocyte count coefficient	Log monocyte count p-value	Log monocyte count coefficient	Log monocyte count p-value
WT1 mutation late	-1.92	0.0359*	-2.24	0.016*
No WT1 mutation	-1.16	0.0801†	-1.28	0.0632†
Signaling mutation late			-0.928	0.0135*
No signaling mutation			-1.39	0.00625**
Signaling mutation clone size			-0.0451	0.933
Age			0.0105	0.299

Supplementary Table 7: Variants from whole exome or extended targeted sequencing data from 17 cases with signaling mutations first that would have met criteria for inclusion in this study but were missed on the sequencing panel.

Sample	Variant	Notes
MSK120	DNMT3A W581R	Limited literature to support pathogenicity, based on computational algorithms ¹
MSK17	DNMT3A Q402*	Not known to be associated with AML
MSK47	TET2 R1261H	Limited literature suggests pathogenicity in AML ²
SU353	DNMT3A G543C, ASXL1 Q377stop	DNMT3A mutation thought to be oncogenic based on computational algorithms ¹ , but ASXL1 mutation not previously associated with AML

Citations

1

Papaemmanuil, E. *et al.* Genomic Classification and Prognosis in Acute Myeloid Leukemia. *N Engl J Med* **374**, 2209–2221 (2016).

2

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