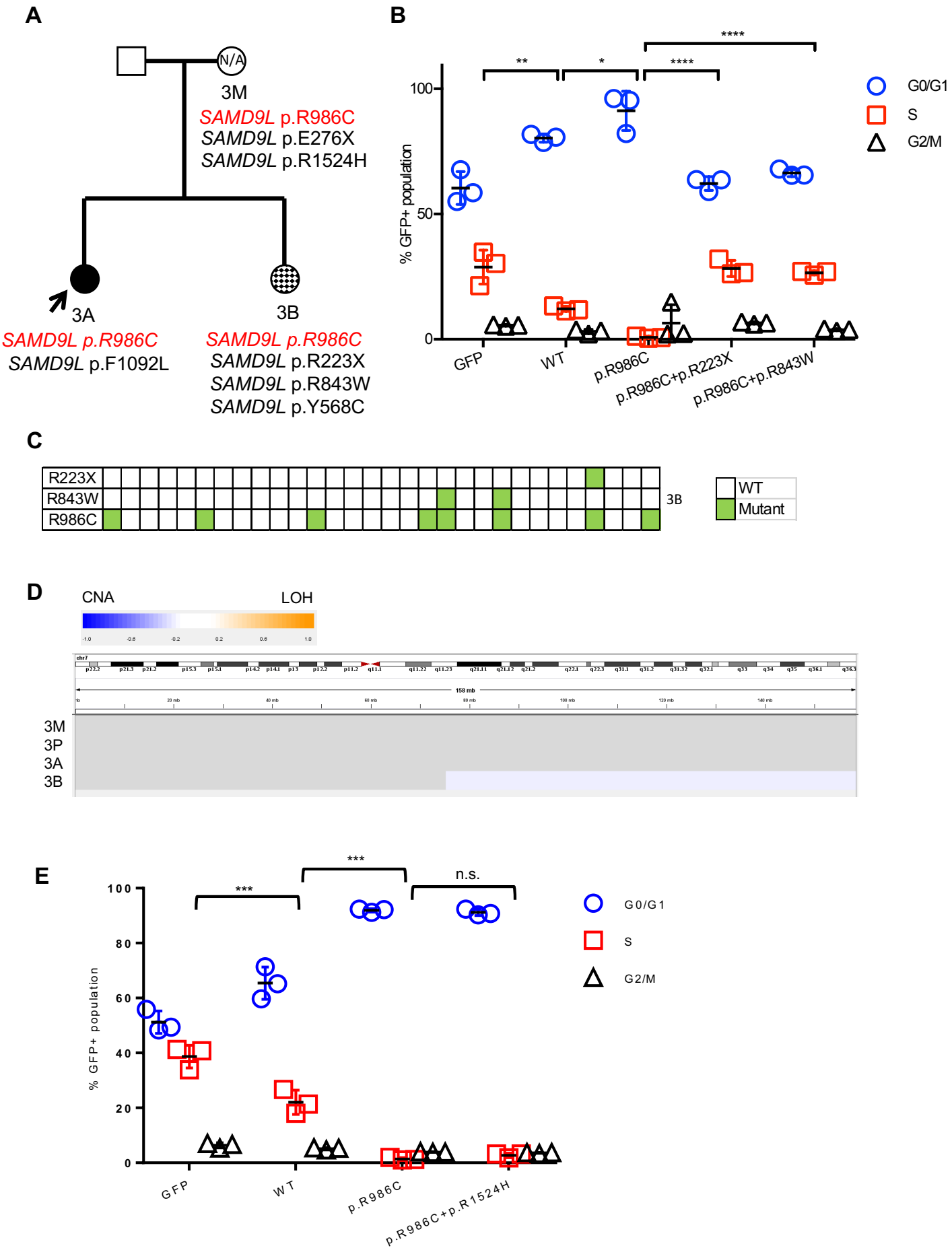
Supplementary File:

Germline *SAMD9* and *SAMD9L* Mutations Are Associated with Extensive Genetic Evolution and Diverse Hematologic Outcomes

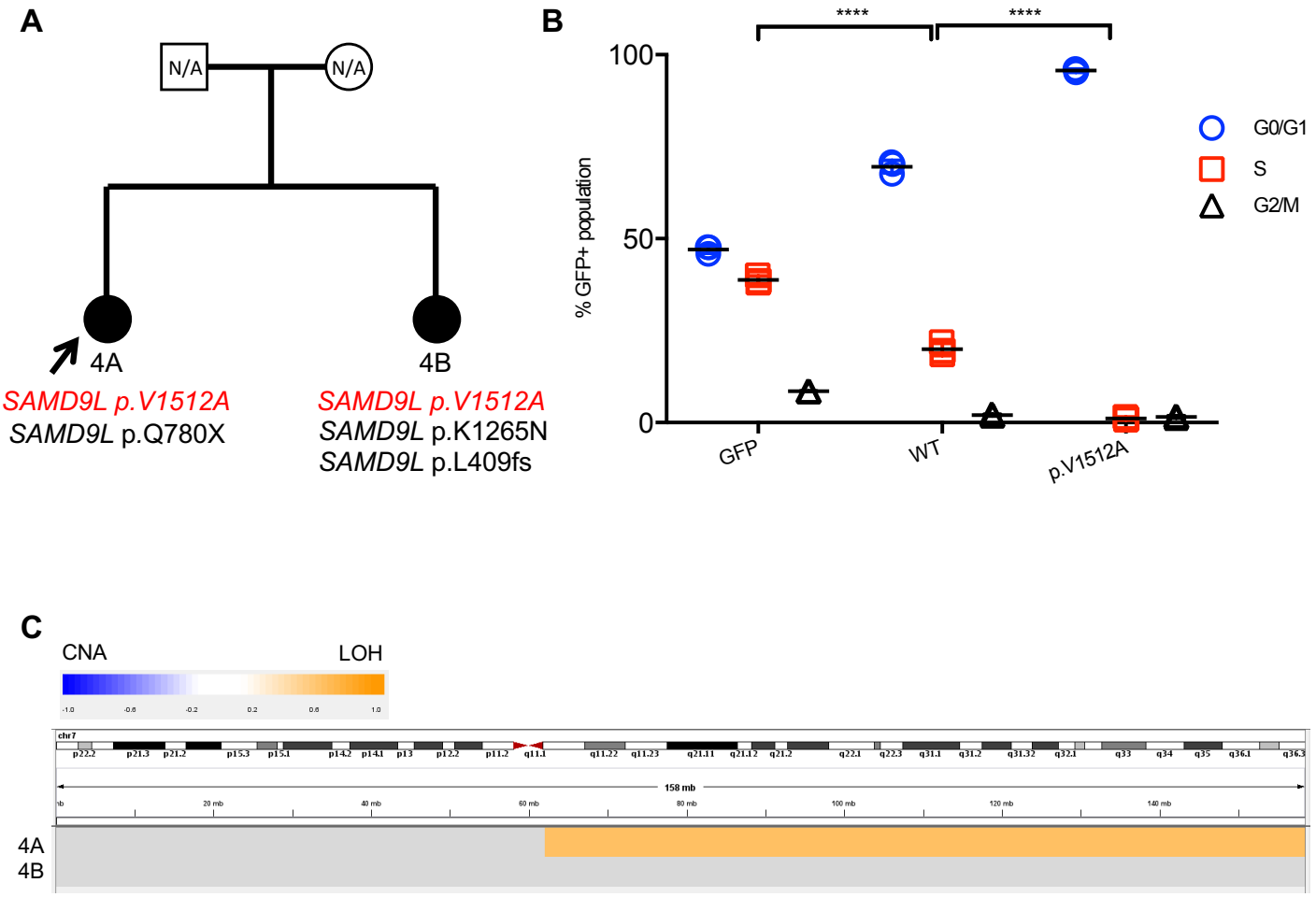
Jasmine C. Wong[1,4*], Victoria Bryant[2*], Tamara Lamprecht[2], Jing Ma[2], Michael Walsh[2], Jason Schwartz[3], Maria del pilar Alzamora[1,4], Charles G. Mullighan[2], Mignon L. Loh[1,4], Raul Ribeiro[3], James R. Downing[2], William L. Carroll[5], Jeffrey Davis[6], Stuart Gold[7], Paul C. Rogers[8], Sara Israels[9], Rochelle Yanofsky[9], Kevin Shannon[1,4] and Jeffery M. Klco[2]

Supplemental Figure 1



Supplemental Figure 1. *SAMD9L* R986C Mutation in MLSM7 Family 3. A. Pedigree of Family 3 with a germline *SAMD9L* p.R986C mutation. Pedigree symbol usage are the same as in Figure 2A. Symbol marked with a diamond fill pattern indicates interstitial deletion on chromosome 7q, while "N/A" indicates that clinical history is not available. Possible revertant mutations in *SAMD9L* are found in 3M, 3A and 3B. **B**. EdU cell cycle results showing empty GFP vector, *SAMD9L* WT, *SAMD9L* p.R986C, p.R986C *in cis* with p.R223X, and p.R986C *in cis* with p.R843W. Data representative of 3 experiments completed in triplicate. **C**. Sequencing results of individual PCR products from the amplified genomic DNA of patient 3B. Green box indicates mutation found, white box indicates WT sequence. Each column is an individual clone. **D**. SNP array data of chromosome 7 showing extent of LOH in patient 3B. ***E.*** EdU cell cycle results showing empty GFP vector, *SAMD9L* WT, *SAMD9L* p.R986C, p.R986C in *cis* with p.R1524H. Data representative of 2 experiments completed in triplicate. For B and E, the percentages of cells in the S phase of the cell division cycle were compared using one-way ANOVAs with repeated measures followed by Tukey's posthoc multiple comparisons test, significance was based on alpha = 0.05. A $p<0.05$ was considered significant. (*:$p<0.05$, **: $p<0.01$, ****: $p<0.0001$, N=3). Individual data points, and mean ± SD are shown.

Supplemental Figure 2



Supplemental Figure 2. ***SAMD9L* V1512A Mutation in MLSM7 Family 4. A**. Pedigree of Family 4 with a germline *SAMD9L* p.V1512A mutation. Pedigree symbol usage are the same as in Figure 2A. Symbol marked with "N/A" indicates that clinical history is not available. In addition, no DNA was available from the parents for analysis. Potential revertant mutations in *SAMD9L* are found in patients 4A and 4B. **B**. EdU cell cycle results showing empty GFP vector, *SAMD9L* WT and *SAMD9L* p.V1512A. Percentages of cells in the S phase of the cell division cycle were compared using one-way ANOVAs with repeated measures followed by Tukey's posthoc multiple comparisons test, significance was based on alpha = 0.05. A $p<0.05$ was considered significant. (****: $p<0.0001$, N=3). Individual data points, and mean ± SD are shown. Data representative of 2 experiments completed in triplicate. **C**. SNP array data of chromosome 7 showing extent of LOH in patient 4A.

Supplemental Figure 3

A

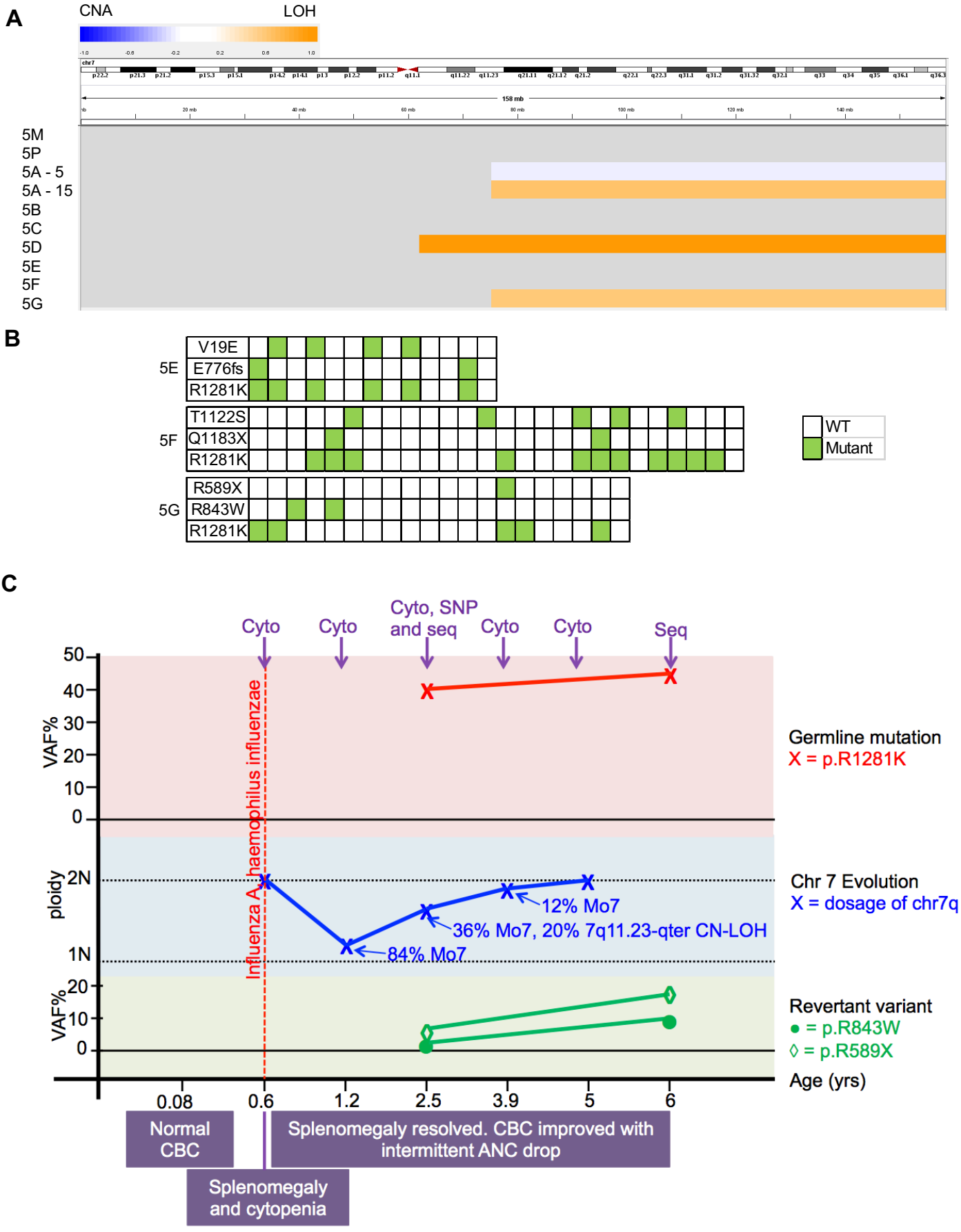
Probe	Enzyme	Gene	Location	1M	1A	1B	1P
NJ3	Eco RI	COL1A2	7q21.3	13.5/9.5	9.5/-	9.5/-	13.5/13.5
PAI-1	HindIII	SERPINE	7q22.1	18/22	22/-	22/-	18/18
B79a (D7S13)	Msp I	unknown	7q31.2	8.4/8.4	8.4/-	8.4/-	10.6/10.6
J3.11 (D7S8)	Msp I	Non-coding	7q31.31	4.1/1.7	1.7/-	4.1/-	4.1/4.1
C33	Eco RI	unknown	7q31.1-31.3	3.0/3.0	3.0/-	3.5/-	3.5/3.0

B

Probe	Enzyme	Gene	Location	2M	2A	2B	2P
MDR-2 (ABCB4)	Eco RI	ABCB4	7q21.12	4.5/3.1	3.1/-	4.5/-	4.5/3.1
NJ3	Eco RI	COL1A2	7q21.3	9.5/13.5	13.5/-	9.5/-	9.5/9.5
PAI-1	HindIII	SERPINE	7q22.1	18/22	22/-	18/-	22/22
B79a (D7S13)	Msp I	unknown	7q31.2	11.6/8.4	8.4/-	11.6/-	8.4/8.4
Met D	Taq I	MET	7q31.2	4.3/5.5	5.5/-	4.3/-	5.5/4.3
J3.11 (D7S8)	Msp I	Non-coding	7q31.31	4.1/1.7	1.7/-	4.1/-	4.1/4.1

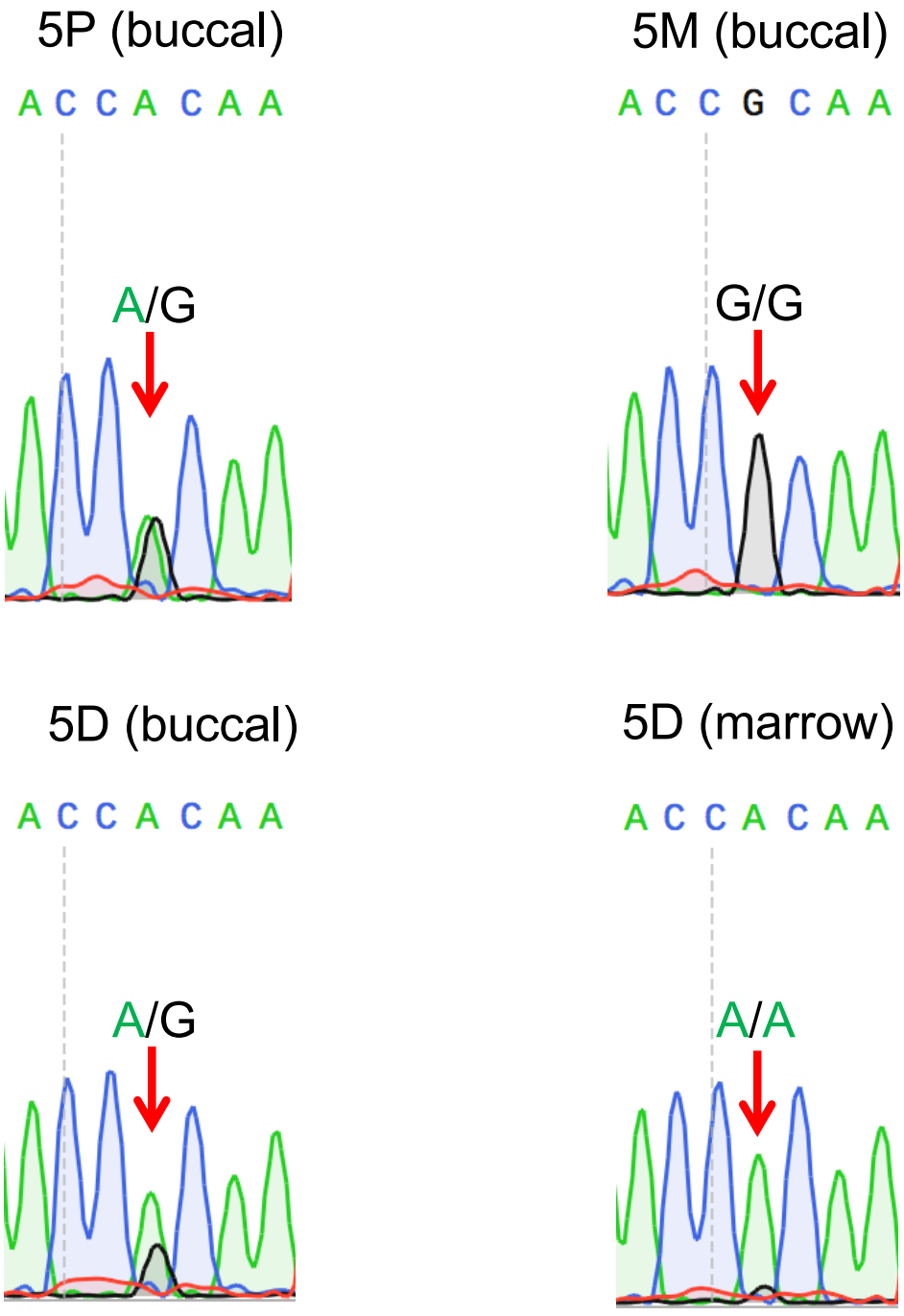
Supplemental Figure 3 . RFLP Analysis of DNA Extracted from Parental Leukocytes and Patient Monosomy 7 Cells in Families 1 and 2. RFLP analysis for families 1 and 2 are shown in panels A and B, respectively. Adapted from Shannon et al. (1989). JCI (84): 984 – 989. Probes MDR-2 and NJ3 (denoted in red) detects RFLP in the *ABCB4* and *COL1A2* genes located in chromosome 7q21.12 and 7q21.3 respectively, which are approximately 5.7Mb proximal and 1.3Mb distal from *SAMD9* and *SAMD9L* on 7q21.2.

Supplemental Figure 4



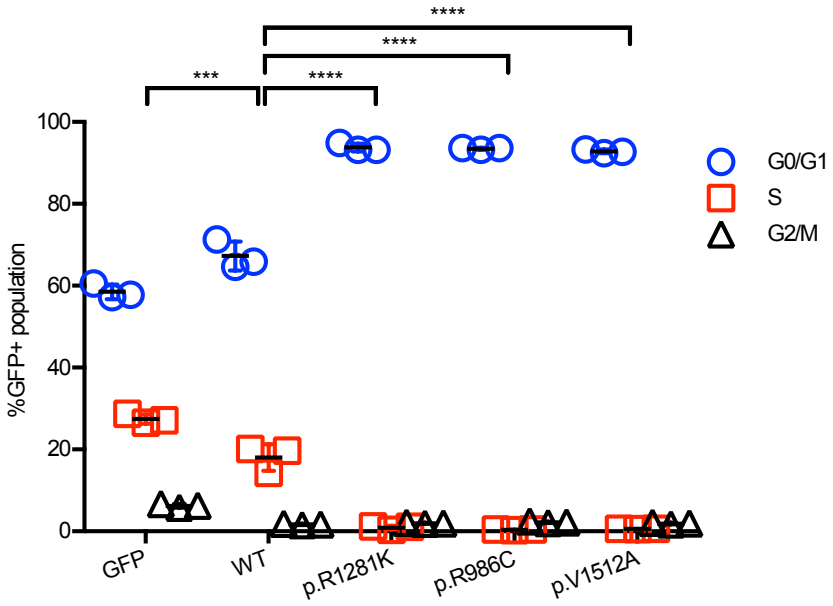
Supplemental Figure 4. **Clonal Evolution of Chromosome 7 and *SAMD9L* gene in MLSM7 Family 5. A.** SNP array data of chromosome 7 showing domains of deletion or LOH in the blood or BM cells of patients 5A (at ages 5 and 15), 5D, and 5G. **B**. Sequencing results of individual PCR products from the amplified genomic DNA of patient 5E, 5F and 5G. The green boxes indicate individual missense mutations and the white boxes depicts the normal sequence. Each column is an individual clone. **C**. Clonal evolution of the R1281K mutation, chromosome 7 and potential *SAMD9L* revertants in patient 5G over clinical course. Purple arrows indicate the timepoints at which cytogenetics (Cyto), SNP array (SNP) or *SAMD9L* sequencing (Seq) were performed. ANC: Absolute Neutrophil Count.

Supplemental Figure 5



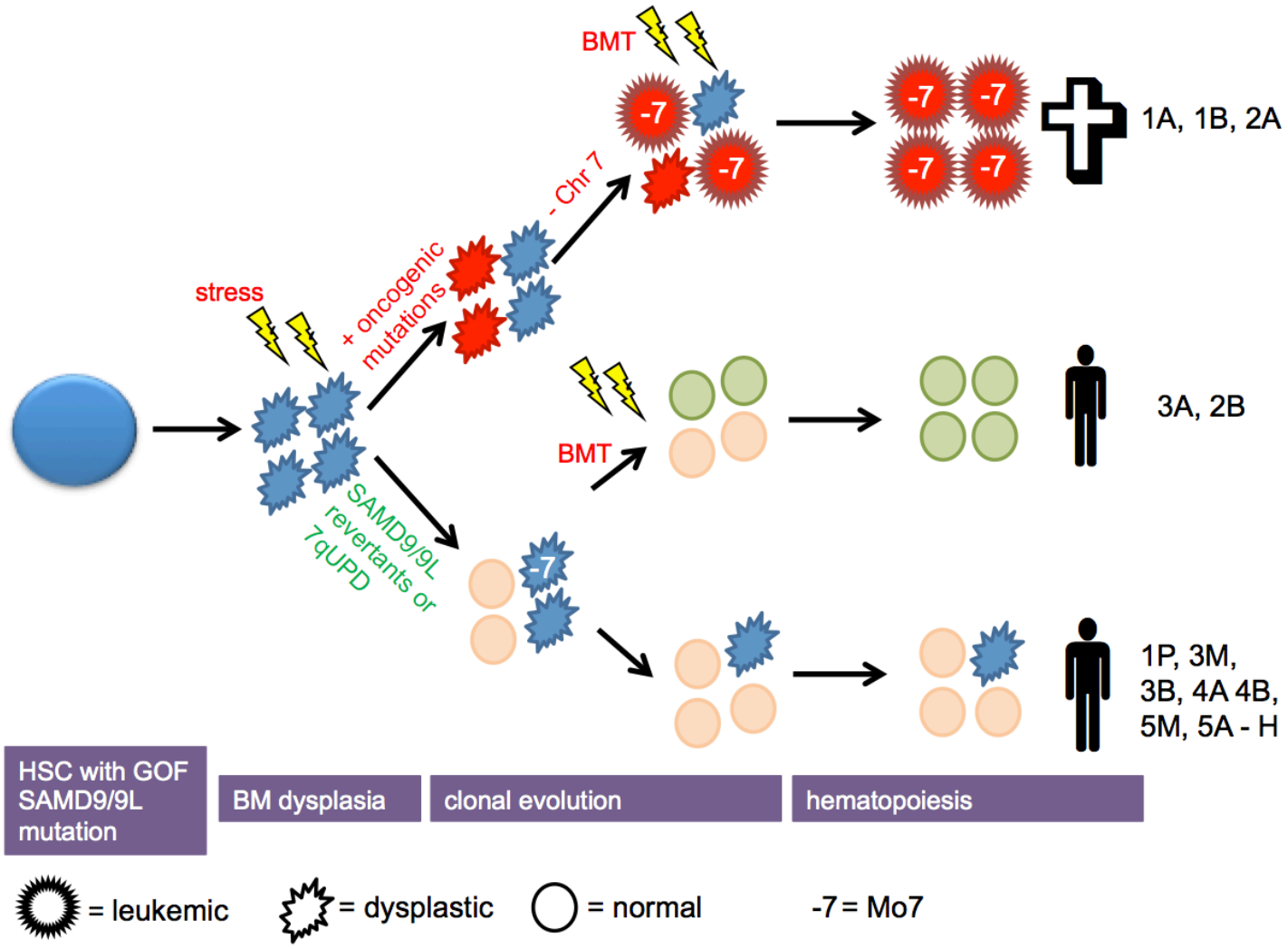
Supplemental Figure 5. Validation of Acquired UPD in 5D. **A**. Acquired UPD detected by SNP array was validated by sequencing within the UPD region. PCR results demonstrate uniparental disomy for the father's normal chromosome 7 homolog in 7q11.21 in the bone marrow from 5D but not in her buccal DNA.

Supplemental Figure 6



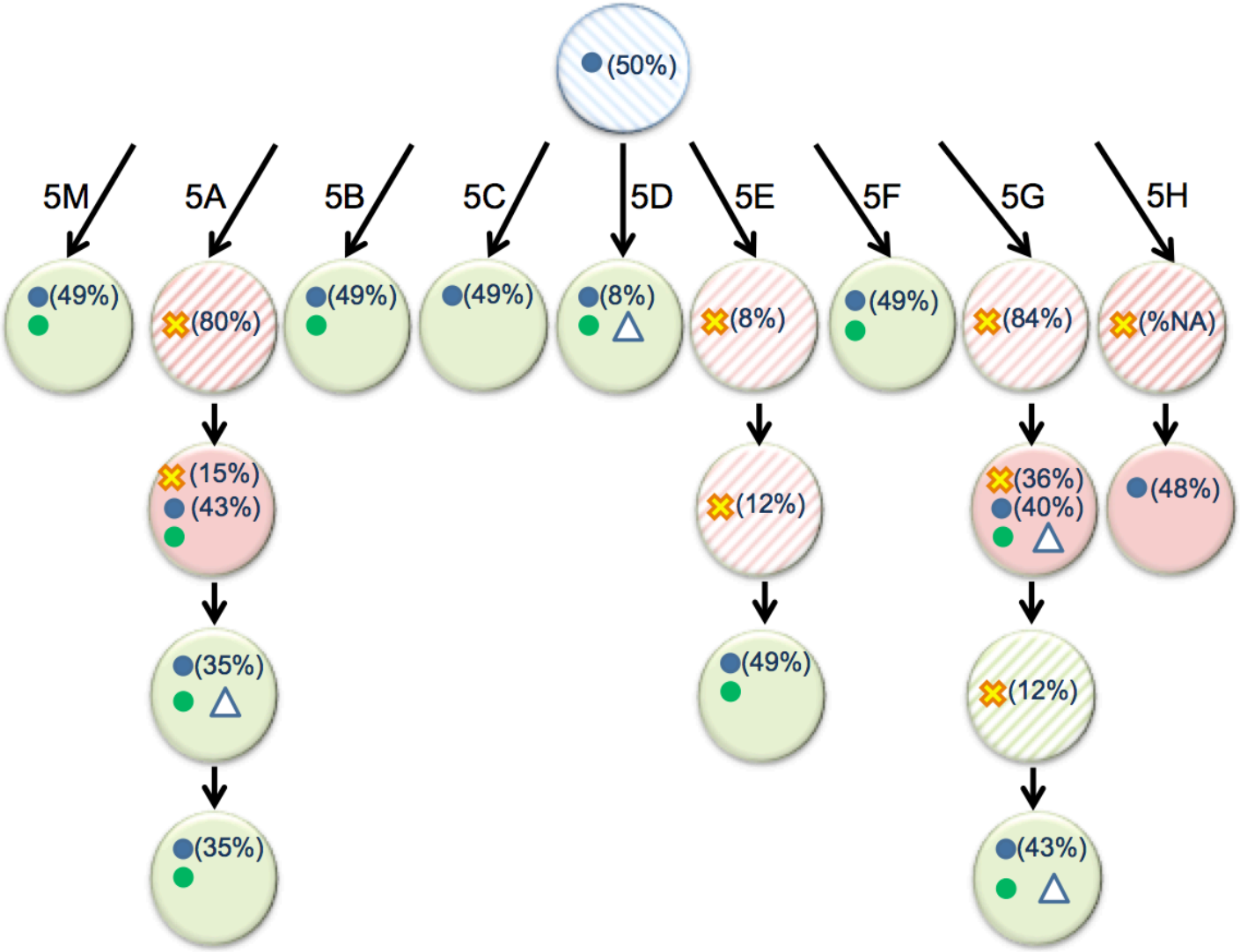
Supplemental Figure 6. **Functional comparison of three germline SAMD9L mutations.** Despite the benign clinical course to date in the members of Family 5, the p.R1281K variant induced a similar cell cycle arrest phenotype in transduced 293T cells as the p.R986C and p.V1512A *SAMD9L* mutations. The percentages of cells in the S phase of the cell division cycle were compared using one-way ANOVAs with repeated measures followed by Tukey's posthoc multiple comparisons test, significance was based on alpha = 0.05. A $p<0.05$ was considered significant. (*:$p<0.05$, **: $p<0.01$, ****: $p<0.0001$, N=3). There was no statistically significant difference between the S-phase fractions of cells expressing the different germline mutations. Individual data points, and mean ± SD are shown.

Supplemental Figure 7



Supplemental Figure 7. Illustration of clonal evolution and disease outcome of *SAMD9/9L* GOF mutation carriers. This figure provides a synopsis of the possible outcomes of an HSC from a GOF SAMD9/9L mutation carrier. The initial stage is usually BM dysplasia, but the cells have the possibility to undergo different clonal evolution pathways, leading to very diverse outputs of hematopoietic cells (hematopoiesis). Cells are color-coded to indicate their mutation status. Blue: *SAMD9/9L* GOF mutation, red: oncogenic mutation, beige: SAMD9/9L revertant or 7qUPD, green: BMT donor cells with no mutations. Shapes of cells indicate their disease status. 32-point star indicates leukemic cells, explosion shape indicates dysplastic, and circles indicates normal. “-7” indicates cells with monosomy 7. Symbol of a human indicates healthy individuals, while symbol of a cross indicates deceased individuals.

Supplemental Figure 8



= monosomy 7 or 7q deletion

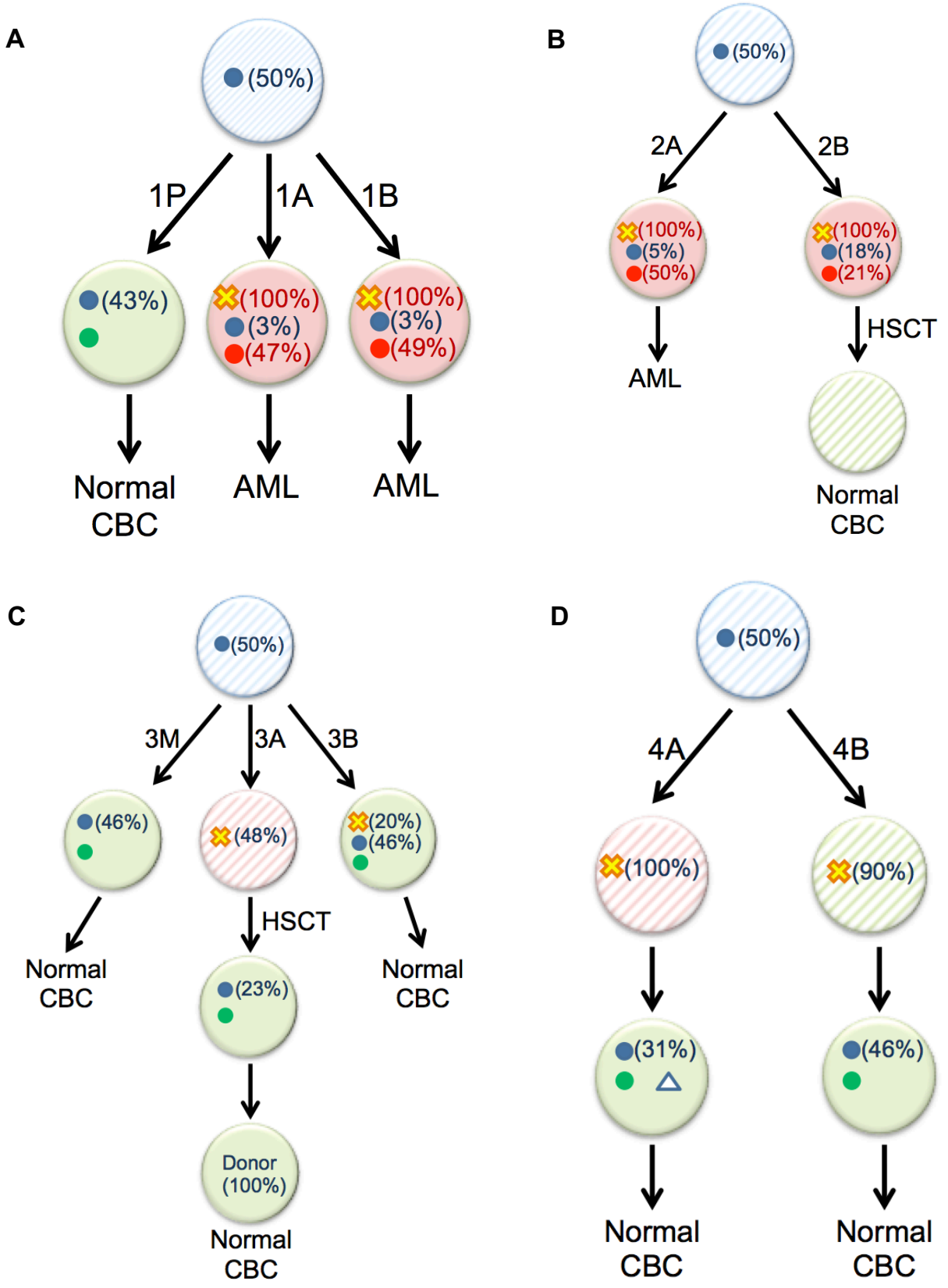
= CN-LOH chr 7

= germline *SAMD9/9L* mutation

= potential revertant *SAMD9/9L* allele(s)

Supplemental Figure 8. Serial Genetic Changes on Chromosome 7 and Disease Outcome of *SAMD9/9L* Mutation Carriers in Family 5. Hematopoietic cells are color-coded in blue to indicate the germ line configuration (50% mutant allele frequency and normal cytogenetics), and the disease status of the different blood and bone marrow specimens analyzed. Large green circles depict specimens from individuals without hematologic abnormalities at the time of sample collection and large red circles from patients with hematologic abnormalities. Cells shaded with diagonal parallel lines indicate that only cytogenetic information is available for that sample. The colored symbols indicate specific genetic changes observed in each sample and are followed by numbers showing the variant allelic frequency (VAF) from sequencing data or the percentage of cells with monosomy 7 or a del(7q) detected by cytogenetic or SNP array analysis. Blue circles indicate the respective germline *SAMD9/9L* mutation; yellow crosses indicate the presence of monosomy 7 or a del(7q); green circles depict potential SAMD9/9L revertant alleles; and white triangles specify 7q copy neutral loss of heterozygosity (CN-LOH). VAFs were not included for the revertant mutations due to the fact the multiple potential revertants exist in many cases, some of which are in cis and some in trans. Copy number analyses by SNP array are presented in Supplemental Table 3, while VAFs for different potential revertant alleles are presented in Supplemental Table 4. For patients in whom multiple samples were analyzed over time, the samples collected at the youngest age are at the top and subsequent samples are shown below them. Abbreviation used include NA (not available).

Supplemental Figure 9



Supplemental Figure 9. Serial Genetic Changes on Chromosome 7 and Disease Outcome of *SAMD9/9L* Mutation Carriers. Families 1-4 are shown in panels A-D, respectively. Hematopoietic cells are color-coded in blue to indicate the germ line configuration in each family (50% mutant allele frequency and normal cytogenetics), and the disease status of the different blood and bone marrow specimens analyzed. Large green circles depict specimens from individuals without hematologic abnormalities and large red circles from patients with hematologic abnormalities. Cells shown in solid colors were investigated using a combination of cytogenetic, DNA sequencing, and SNP array analyses, while those shaded with a diagonal parallel line indicate that only cytogenetic information from the medical record was available. The colored symbols indicate specific genetic changes observed in each sample and are followed by numbers showing the variant allele frequency (VAF) from sequencing data or the percentage of cells with monosomy 7 or a del(7q) detected by cytogenetic or SNP array analysis. Blue circles indicate the respective germline *SAMD9/9L* mutation; red circles show the somatic mutations in known oncogenes (highest VAF is listed); yellow crosses indicate the presence of monosomy 7 or a del(7q); green circles depict potential SAMD9/9L revertant alleles; and white triangles specify 7q copy neutral loss of heterozygosity (CN-LOH). VAFs were not included for the revertant mutations due to the fact the multiple potential revertants exist in many cases, some of which are in cis and some in trans. Copy number analyses by SNP array are presented in Supplemental Table 3, while VAFs for different potential revertant alleles are presented in Supplemental Table 4. Abbreviations used include HSCT (hematopoietic stem cell transplant), CBC (complete blood count), MDS (myelodysplastic syndrome), and AML

(acute myeloid leukemia). Note that the middle sample for patient 3A was obtained ~1 year after a matched unrelated donor transplant, and the lower VAF likely reflects incomplete reconstitution with normal cells at that time point. This patient now reportedly has full donor chimerism (bottom circle).

Supplemental Table 1
Clinical and Molecular Characteristics of *SAMD9* or *SAMD9L* Mutation Carriers

Family	Germline mutations	Individuals and Germline VAFs	Potential revertant mutations	Additional mutations	Age at Diagnosis (years)	Current Age (years)	Initial Findings and Diagnosis	Subsequent Course and Notes
1[A]	*SAMD9L* H880Q	1P (dad) 43.17%	Q569P	ND	NA	NA	No hematologic abnormalities or ataxia	NA
		1A (proband) 3.26%	Mo7	*RUNX1*(D171N), *SETBP1*(G870S) *CBL* (E366_E8splice)	0.75	D	Petechiae, suspected ITP but developed anemia after prednisone treatment	Died with refractory AML
		1B (sibling) 3.22%	Mo7	*RUNX1*(N139fs), *SETBP1*(D868N), *BRAF*(N581Y), *KRAS*(T58I)	5.5	D	Mo7[B]	Developed AML and died from infection after BMT
2[A]	*SAMD9* K676E	2A (proband) 5.22%	Mo7	del 12p13.2 (*ETV6*), *SETBP1* (D876N) *ASXL1* (K686fs)	4	D	AML	Prolonged aplasia followed induction. Died of sepsis.
		2B (sibling) 18.46%	Mo7	*ETV6* (R369Q)	2.5	33	Pancytopenia, Mo7[B]	Persistent MDS, transplanted at age 9, doing well with minimal GVHD
3	*SAMD9L* R986C	3M (mom) 45.57%	E276X R1524H	ND	NA	NA	NA	NA
		3A (proband) 23.44%	Mo7 (historical) F1092L	ND	2.5	27	MDS Mo7	Received BMT and recovered with donor engraftment. Well at last followup.
		3B (sibling) 45.51%	del(7q11-32) R223X R843W Y568C	ND	5.6	D	del(7)(q11;q32) [B]	No hematologic abnormalities, died at age 27 of unrelated cause

4	*SAMD9L* V1512A	4A (proband) 31.17%	Mo7 Q780X	ND	3	21	Cytopenia, MCV >100, Mo7	Recovered with resolution of Mo7
		4B (sibling) 46.06%	Mo7 (historical) K1265N L409fs	ND	1.5	19	Transient Mo7[B]	Mo7 resolved
5	*SAMD9L* R1281K	5M (mom) 48.75%		ND		NA	Never had hematologic abnormalities	No hematologic abnormalities
		5A (proband) 43.11%	Mo7 (historical) Del7q 7q CN-LOH R70C A280T R359Q T1053I F1092V D1171N	ND	0.33	26	CMV infection at 4 months, anemia, cytopenia, dyspoiesis but normal cytogenetics. Mo7 diagnosed at 1.5yrs	Blood counts gradually improved and Mo7 resolved
		5B (sibling) 48.97%	V361fs	ND	13.25	24	Hypocellular BM and dysplastic changes, normal cytogenetics[B]	Bilateral camptodactyly but overall healthy
		5C (sibling) 48.54%	ND	ND	10.75	22	Hypocellular BM and dysplastic changes, normal cytogenetics[B]	Healthy
		5D (sibling) 7.87%	7q CN-LOH 1152_1153del R986L	ND	9.6	21	Hypocellular BM and dysplastic changes, normal cytogenetics[B]	Healthy
		5E (sibling) 49.24%	Mo7 (historical) V19E E562K E776fs	ND	2.9	18	Mildly neutropenic and thrombocytopenic at age 2.9, recurrent chest infections in first	Blood counts gradually improved and Mo7 resolved; sensory and motor peripheral neuropathy.

							few years of life and Mo7 at age 3	
		5F (sibling) 49.42%	Q1183X T1122S 1122_1124 del S1397P	ND	6	17	Hypocellular BM and dysplastic changes, normal cytogenetics[B]	Healthy
		5G (sibling) 40.21%	Mo7 (historical) 7q CN-LOH R843W R589X	ND	0.6	14	Pancytopenia and recurrent chest infections in first few years of life and Mo7 at age 1.2	Normal cytogenetics but hypocellular BM
		5H (sibling) 48.25%	Mo7(historical)	ND	3.5	8	Pancytopenia and easy bruising, hypocellular BM and Mo7	Overall healthy with mild thrombocytopenia

[A] - These families were initially reported in Refs 1 and 2.

[B] - Patients in this group were undergoing evaluation as potential transplant donors because they had one or more affected siblings, and did not have overt MDS or AML. ITP = idiopathic thrombocytopenic purpura, NA= not applicable or not available

D - deceased

ND – none detected

Supplemental Table 2 - Germline SAMD9/D9L mutations

Representative samples

Family	Individual	Relationship	Gender	Chr	Start	End	Ref	Alt	AAChange.refGene	snp138	esp6500si_all	exac03	cosmic68	SIFT_pred	Polyphen2_HDIV_pred	Polyphen2_HVAR_pred	Reads1_ref	Reads2_var	VAF	Tissue Source
H880Q	1P	parent	male	7	92762645	92762645	G	T	SAMD9L:NM_152703:exon5:c.C2640A:p.H880Q	NA	NA	NA	NA	D	D	P	5498	4181	43.17%	PB
H880Q	1M	parent	female	7	92762645	92762645	G	T	SAMD9L:NM_152703:exon5:c.C2640A:p.H880Q	NA	NA	NA	NA	D	D	P	5890	5	0.08%	PB
H880Q	1A	proband	female	7	92762645	92762645	G	T	SAMD9L:NM_152703:exon5:c.C2640A:p.H880Q	NA	NA	NA	NA	D	D	P	8645	291	3.26%	BM
H880Q	1B	sibling	male	7	92762645	92762645	G	T	SAMD9L:NM_152703:exon5:c.C2640A:p.H880Q	NA	NA	NA	NA	D	D	P	9509	316	3.22%	BM
K676E	2P	parent	male	7	92733385	92733385	T	C	SAMD9:NM_017654:exon3:c.A2026G:p.K676E	NA	NA	NA	NA	D	P	B	5973	10	0.17%	PB
K676E	2M	parent	female	7	92733385	92733385	T	C	SAMD9:NM_017654:exon3:c.A2026G:p.K676E	NA	NA	NA	NA	D	P	B	25481	50	0.20%	PB
K676E	2A	proband	male	7	92733385	92733385	T	C	SAMD9:NM_017654:exon3:c.A2026G:p.K676E	NA	NA	NA	NA	D	P	B	19488	1073	5.22%	BM
K676E	2B	sibling	male	7	92733385	92733385	T	C	SAMD9:NM_017654:exon3:c.A2026G:p.K676E	NA	NA	NA	NA	D	P	B	15356	3476	18.46%	BM
R986C	3P	parent	male	7	92762329	92762329	G	A	SAMD9L:NM_152703:exon5:c.C2956T:p.R986C	NA	NA	NA	ID=COSM1224632;OCCURENCE=1(large_intestine)	D	B	B	8056	13	0.16%	PB
R986C	3M	parent	female	7	92762329	92762329	G	A	SAMD9L:NM_152703:exon5:c.C2956T:p.R986C	NA	NA	NA	ID=COSM1224632;OCCURENCE=1(large_intestine)	D	B	B	7988	6688	45.57%	PB
R986C	3A	proband	female	7	92762329	92762329	G	A	SAMD9L:NM_152703:exon5:c.C2956T:p.R986C	NA	NA	NA	ID=COSM1224632;OCCURENCE=1(large_intestine)	D	B	B	3197	979	23.44%	BM
R986C	3B	sibling	female	7	92762329	92762329	G	A	SAMD9L:NM_152703:exon5:c.C2956T:p.R986C	NA	NA	NA	ID=COSM1224632;OCCURENCE=1(large_intestine)	D	B	B	2677	2239	45.51%	BM
V1512A	4A	proband	female	7	92760750	92760750	A	G	SAMD9L:NM_152703:exon5:c.T4535C:p.V1512A	NA	NA	NA	NA	D	B	B	5611	2545	31.17%	BM
V1512A	4B	sibling	female	7	92760750	92760750	A	G	SAMD9L:NM_152703:exon5:c.T4535C:p.V1512A	NA	NA	NA	NA	D	B	B	6329	5410	46.06%	BM
R1281K	5P	parent	male	7	92761443	92761443	C	T	SAMD9L:NM_152703:exon5:c.G3842A:p.R1281K	NA	NA	NA	NA	T	B	B	18258	17	0.09%	PB
R1281K	5M	parent	female	7	92761443	92761443	C	T	SAMD9L:NM_152703:exon5:c.G3842A:p.R1281K	NA	NA	NA	NA	T	B	B	8139	7746	48.75%	PB
R1281K	5A-Age 5	proband	male	7	92761443	92761443	C	T	SAMD9L:NM_152703:exon5:c.G3842A:p.R1281K	NA	NA	NA	NA	T	B	B	9173	6952	43.11%	BM
R1281K	5A-Age 15	proband	male	7	92761443	92761443	C	T	SAMD9L:NM_152703:exon5:c.G3842A:p.R1281K	NA	NA	NA	NA	T	B	B	13969	7666	35.42%	PB
R1281K	5A-Age 18	proband	male	7	92761443	92761443	C	T	SAMD9L:NM_152703:exon5:c.G3842A:p.R1281K	NA	NA	NA	NA	T	B	B	14252	7699	35.07%	PB
R1281K	5B	sibling	female	7	92761443	92761443	C	T	SAMD9L:NM_152703:exon5:c.G3842A:p.R1281K	NA	NA	NA	NA	T	B	B	7863	7549	48.97%	BM
R1281K	5C	sibling	male	7	92761443	92761443	C	T	SAMD9L:NM_152703:exon5:c.G3842A:p.R1281K	NA	NA	NA	NA	T	B	B	9561	9023	48.54%	BM
R1281K	5D	sibling	female	7	92761443	92761443	C	T	SAMD9L:NM_152703:exon5:c.G3842A:p.R1281K	NA	NA	NA	NA	T	B	B	13326	1139	7.87%	BM
R1281K	5E	sibling	female	7	92761443	92761443	C	T	SAMD9L:NM_152703:exon5:c.G3842A:p.R1281K	NA	NA	NA	NA	T	B	B	2748	2667	49.24%	BM
R1281K	5F	sibling	female	7	92761443	92761443	C	T	SAMD9L:NM_152703:exon5:c.G3842A:p.R1281K	NA	NA	NA	NA	T	B	B	3907	3820	49.42%	BM
R1281K	5G-Age 1.5	sibling	male	7	92761443	92761443	C	T	SAMD9L:NM_152703:exon5:c.G3842A:p.R1281K	NA	NA	NA	NA	T	B	B	7310	4918	40.21%	BM
R1281K	5G-Age 6	sibling	male	7	92761443	92761443	C	T	SAMD9L:NM_152703:exon5:c.G3842A:p.R1281K	NA	NA	NA	NA	T	B	B	6898	5311	43.47%	PB
R1281K	5H	sibling	female	7	92761443	92761443	C	T	SAMD9L:NM_152703:exon5:c.G3842A:p.R1281K	NA	NA	NA	NA	T	B	B	2320	2165	48.25%	BM

Supplemental Table 3 - Affy SNP6 array CNAs

Family	Individual	Relationship	Gender	Sample	chrom	loc.start	loc.end	num.mark	seg.mean	seg.observedCN	CNAs	CytoBand	NumGene
H880Q	1P	parent	male	13f-4-snp6	6	26488021	29106021	-	-	-	CN-LOH	p22.2;p22.1	74
H880Q	1P	parent	male	13f-4-snp6	12	1.1E+08	1.13E+08	-	-	-	CN-LOH	q24.11;q24.12;q24.13	49
H880Q	1M	parent	female	14f-7-snp6	5	1.29E+08	1.33E+08	-	-	-	CN-LOH	q23.3;q31.1	42
H880Q	1A	proband	female	19l-snp6	7	10238	1.59E+08	99416	-1.0363	-	HetDel	p22.3--q36.3	1315
H880Q	1A	proband	female	19l-snp6	19	43282247	43542819	131	-1.1391	-	HetDel	q13.2;q13.31	6
H880Q	1B	sibling	male	20l-2-snp6	7	10238	1.59E+08	98224	-1.0809	0.95	HetDel	p22.3--q36.3	1315
K676E	2P	parent	male	15f-2-snp6	-	-	-	-	-	-	none	-	0
K676E	2M	parent	female	16f-4-snp6	-	-	-	-	-	-	none	-	0
K676E	2A	proband	male	17l-2-snp6	7	10238	1.59E+08	91641	-0.986	1.01	HetDel	p22.3--q36.3	1315
K676E	2A	proband	male	17l-2-snp6	11	1.25E+08	1.25E+08	27	-0.9658	1.02	HetDel	q24.2	1
K676E	2A	proband	male	17l-2-snp6	12	11703852	13937320	1941	-0.9256	1.05	HetDel	p13.2;p13.1	31
K676E	2A	proband	male	17l-2-snp6	12	99251002	99276000	23	-0.995	1	HetDel	q23.1	2
K676E	2B	sibling	male	18l-5-snp6	7	10238	1.59E+08	99735	-0.7578	1.18	HetDel	p22.3--q36.3	1315
R986C	3P	parent	male	19f-3-snp6	-	-	-	-	-	-	none	-	0
R986C	3M	parent	female	18f-3-snp6	9	10743871	11869293	863	-0.9648	1.02	HetDel	p23	0
R986C	3M	parent	female	18f-3-snp6	9	11869609	12113944	195	-3.1392	0.23	HomoDel	p23	0
R986C	3M	parent	female	18f-3-snp6	9	12115536	12302928	168	-1.0522	0.96	HetDel	p23	0
R986C	3A	proband	female	60l-1-snp6	-	-	-	-	-	-	none	-	0
R986C	3B	sibling	female	79l-3-snp6	7	75308064	1.59E+08	-	-	-	7q HetDel(~20%ofthecells)	q11.23--q36.3	742
R986C	3B	sibling	female	79l-3-snp6	9	10741186	12302928	1228	-0.9351	1.05	HetDel	p23	0
V1512A	4A	proband	female	hm0263-snp6	7	62123565	1.59E+08	-	-	-	7q CN-LOH(~35%ofthecells)	q11.21--q36.3	866
V1512A	4A	proband	female	hm0263-snp6	9	11930000	12193000	-	-1.3	0.8	HetDel	p23	0
V1512A	4B	sibling	female	hm0264-snp6	-	-	-	-	-	-	none	-	0
R1281K	5P	parent	male	54j-1-snp6	18	25158002	27891002	-	-	-	CN-LOH	q12.1	2
R1281K	5M	parent	female	106f-1-snp6	1	1.66E+08	1.95E+08	-	-	-	CN-LOH	q24.1--q31.3	228
R1281K	5M	parent	female	106f-1-snp6	3	39852825	39953907	56	-1.0282	0.98	HetDel	p22.1	1
R1281K	5M	parent	female	106f-1-snp6	7	5341474	9267475	-	-	-	CN-LOH	p22.1;p21.3	49
R1281K	5M	parent	female	106f-1-snp6	13	77565999	1.04E+08	-	-	-	CN-LOH	q22.3--q33.1	143
R1281K	5M	parent	female	106f-1-snp6	13	1.09E+08	1.13E+08	-	-	-	CN-LOH	q33.3;q34	38
R1281K	5M	parent	female	106f-1-snp6	14	96660247	1.07E+08	-	-	-	CN-LOH	q32.2--q32.33	224
R1281K	5A-Age 5	proband	male	107f-1-snp6	3	39852825	39953907	56	-0.9728	1.02	HetDel	p22.1	1
R1281K	5A-Age 5	proband	male	107f-1-snp6	7	75308064	1.59E+08	-	-	-	7q HetDel(~10-15%ofthecells)	q11.23--q36.3	742
R1281K	5A-Age 15	proband	male	hm1239-snp6	3	39852825	39951888	55	-1.0556	0.96	HetDel	p22.1	1
R1281K	5A-Age 15	proband	male	hm1239-snp6	7	75308064	1.59E+08	-	-	-	7q CN-LOH(~30%ofthecells)	q11.23--q36.3	742
R1281K	5B	sibling	female	hm1240-snp6	-	-	-	-	-	-	none	-	0
R1281K	5C	sibling	male	hm1241-snp6	-	-	-	-	-	-	none	-	0
R1281K	5D	sibling	female	hm1242-snp6	7	62123565	1.59E+08	-	-	-	7q CN-LOH	q11.21--q36.3	866
R1281K	5E	sibling	female	hm1243-snp6	-	-	-	-	-	-	none	-	0
R1281K	5F	sibling	female	hm1244-snp6	3	39852825	39951888	55	-1.1222	0.92	HetDel	p22.1	1
R1281K	5F	sibling	female	hm1244-snp6	-	-	-	-	-	-	none	-	0
R1281K	5G	sibling	male	hm1245-snp6	7	75308064	1.59E+08	-	-	-	7q CN-LOH(~20%ofthecells)	q11.23--q36.3	742

Supplemental Table 4 - SAMD9/9L revertant mutations

Family	Individual	Relationship	Gender	Chr	Start	End	Ref	Alt	Gene.refGene	AAChange.refGene	snp138	esp6500si_all	exac03	cosmic68	SIFT_pred	Polyphen2_HDIV_pred	Polyphen2_HVAR_pred	MutationAssessor_pred	Reads1_ref	Reads2_var	VAF
H880Q	1P	parent	male	7	92763579	92763579	T	G	SAMD9L	SAMD9L:NM_152703:exon5:c.A1706C:p.Q569P	NA	NA	NA	NA	D	D	P	M	2741	1966	41.72%
H880Q	1M	parent	female	none detected																	
H880Q	1A	proband	female	none detected																	
H880Q	1B	sibling	male	none detected																	
K676E	2P	parent	male	none detected																	
K676E	2M	parent	female	none detected																	
K676E	2A	proband	male	none detected																	
K676E	2B	sibling	male	none detected																	
R986C	3P	parent	male	none detected																	
R986C	3M	parent	female	7	92764459	92764459	C	A	SAMD9L	SAMD9L:NM_152703:exon5:c.G826T:p.E276X	NA	NA	NA	NA	T	.	.	.	6104	708	10.39%
R986C	3M	parent	female	7	92760714	92760714	C	T	SAMD9L	SAMD9L:NM_152703:exon5:c.G4571A:p.R1524H	rs138088725	0.000154	8.27E-05	NA	D	P	B	L	7114	7561	51.52%
R986C	3A	proband	female	7	92762009	92762009	G	C	SAMD9L	SAMD9L:NM_152703:exon5:c.C3276G:p.F1092L	NA	NA	NA	NA	T	P	B	M	6233	443	6.63%
R986C	3B	sibling	female	7	92762758	92762758	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C2527T:p.R843W	NA	NA	3.30E-05	NA	D	P	B	N	8664	2134	19.76%
R986C	3B	sibling	female	7	92763582	92763582	T	C	SAMD9L	SAMD9L:NM_152703:exon5:c.A1703G:p.Y568C	NA	NA	NA	NA	D	D	D	M	4992	193	3.72%
R986C	3B	sibling	female	7	92764618	92764618	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C667T:p.R223X	NA	NA	NA	ID=COSM1093169;OCCURENCE=1(endometrium)	T	.	.	.	7859	1092	12.20%
V1512A	4A	proband	female	7	92761490	92761490	T	A	SAMD9L	SAMD9L:NM_152703:exon5:c.A3795T:p.K1265N	NA	NA	NA	NA	T	D	P	M	10883	1059	8.86%
V1512A	4A	sibling	female	7	92764060	92764060	G	-	SAMD9L	SAMD9L:NM_152703:exon5:c.1225delC:p.L409fs	NA	NA	NA	NA					2398	201	7.73%
V1512A	4B	sibling	female	7	92762947	92762947	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C2338T:p.Q780X	NA	NA	NA	NA	D	.	.	.	10009	292	2.83%
R1281K	5P	parent	male	none detected																	
R1281K	5M	parent	female	7	92764432	92764432	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C853T:p.R285W	NA	NA	1.66E-05	NA	D	B	B	M	5756	212	3.55%
R1281K	5M	parent	female	7	92761058	92761061	TTGT	-	SAMD9L	SAMD9L:NM_152703:exon5:c.4224_4227del:p.K1408fs	NA	NA	NA	NA					15519	870	5.31%
R1281K	5A-Age 5	proband	male	7	92765077	92765077	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C208T:p.R70C	rs372301151	0.000154	0.0001	ID=COSM1452907;OCCURENCE=1(large_intestine)	D	P	B	L	4771	82	1.69%
R1281K	5A-Age 5	proband	male	7	92762127	92762127	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C3158T:p.T1053I	NA	NA	NA	NA	D	D	D	M	3117	393	11.20%
R1281K	5A-Age 5	proband	male	7	92764209	92764209	C	T	SAMD9L	SAMD9L:NM_152703:exon5:c.G1076A:p.R359Q	NA	NA	8.25E-06	NA	T	D	P	L	5470	262	4.57%
R1281K	5A-Age 5	proband	male	7	92761774	92761774	C	T	SAMD9L	SAMD9L:NM_152703:exon5:c.G3511A:p.D1171N	NA	NA	NA	NA	D	B	B	L	11857	630	5.04%
R1281K	5A-Age 15	proband	male	7	92765077	92765077	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C208T:p.R70C	rs372301151	0.000154	0.0001	ID=COSM1452907;OCCURENCE=1(large_intestine)	D	P	B	L	6562	427	6.11%
R1281K	5A-Age 15	proband	male	7	92762127	92762127	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C3158T:p.T1053I	NA	NA	NA	NA	D	D	D	M	2077	281	11.91%
R1281K	5A-Age 15	proband	male	7	92764209	92764209	C	T	SAMD9L	SAMD9L:NM_152703:exon5:c.G1076A:p.R359Q	NA	NA	8.25E-06	NA	T	D	P	L	7117	604	7.82%
R1281K	5A-Age 15	proband	male	7	92761774	92761774	C	T	SAMD9L	SAMD9L:NM_152703:exon5:c.G3511A:p.D1171N	NA	NA	NA	NA	D	B	B	L	17775	1026	5.46%
R1281K	5A-Age 15	proband	male	7	92764447	92764447	C	T	SAMD9L	SAMD9L:NM_152703:exon5:c.G838A:p.A280T	NA	NA	NA	NA	D	D	P	M	7489	92	1.21%
R1281K	5A-Age 15	proband	male	7	92762011	92762011	A	C	SAMD9L	SAMD9L:NM_152703:exon5:c.T3274G:p.F1092V	NA	NA	NA	NA	D	D	P	M	8972	143	1.57%
R1281K	5A-Age 18	proband	male	7	92765077	92765077	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C208T:p.R70C	rs372301151	0.000154	0.0001	ID=COSM1452907;OCCURENCE=1(large_intestine)	D	P	B	L	7774	405	4.95%
R1281K	5A-Age 18	proband	male	7	92762127	92762127	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C3158T:p.T1053I	NA	NA	NA	NA	D	D	D	M	2931	387	11.66%
R1281K	5A-Age 18	proband	male	7	92764209	92764209	C	T	SAMD9L	SAMD9L:NM_152703:exon5:c.G1076A:p.R359Q	NA	NA	8.25E-06	NA	T	D	P	L	9095	749	7.61%
R1281K	5A-Age 18	proband	male	7	92761774	92761774	C	T	SAMD9L	SAMD9L:NM_152703:exon5:c.G3511A:p.D1171N	NA	NA	NA	NA	D	B	B	L	16563	776	4.48%
R1281K	5A-Age 18	proband	male	7	92764447	92764447	C	T	SAMD9L	SAMD9L:NM_152703:exon5:c.G838A:p.A280T	NA	NA	NA	NA	D	D	P	M	8957	134	1.47%
R1281K	5A-Age 18	proband	male	7	92762011	92762011	A	C	SAMD9L	SAMD9L:NM_152703:exon5:c.T3274G:p.F1092V	NA	NA	NA	NA	D	D	P	M	8001	134	1.65%
R1281K	5B	sibling	female	7	92764203	92764203	A	-	SAMD9L	SAMD9L:NM_152703:exon5:c.1082delT:p.V361fs	NA	NA	NA	NA					6699	146	2.13%
R1281K	5C	sibling	male	none detected																	
R1281K	5D	sibling	female	7	92762328	92762328	C	A	SAMD9L	SAMD9L:NM_152703:exon5:c.G2957T:p.R986L	NA	NA	NA	NA	D	D	P	M	4866	187	3.70%
R1281K	5D	sibling	female	7	92761827	92761829	AGG	-	SAMD9L	SAMD9L:NM_152703:exon5:c.3456_3458del:p.1152_1153del	NA	NA	NA	NA					13206	229	1.70%
R1281K	5E	sibling	female	7	92763601	92763601	C	T	SAMD9L	SAMD9L:NM_152703:exon5:c.G1684A:p.E562K	NA	NA	NA	NA	D	D	D	M	3866	98	2.47%
R1281K	5E	sibling	female	7	92765229	92765229	A	T	SAMD9L	SAMD9L:NM_152703:exon5:c.T56A:p.V19E	NA	NA	NA	NA	D	D	D	M	418	118	22.01%
R1281K	5E	sibling	female	7	92762958	92762958	-	C	SAMD9L	SAMD9L:NM_152703:exon5:c.2326dupG:p.E776fs	NA	NA	NA	NA					7434	1559	17.29%
R1281K	5F	sibling	female	7	92761096	92761096	A	G	SAMD9L	SAMD9L:NM_152703:exon5:c.T4189C:p.S1397P	NA	NA	NA	NA	D	D	D	M	383	13	3.28%
R1281K	5F	sibling	female	7	92761738	92761738	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C3547T:p.Q1183X	NA	NA	NA	NA	T	.	.	.	328	55	14.36%
R1281K	5F	sibling	female	7	92761921	92761921	T	A	SAMD9L	SAMD9L:NM_152703:exon5:c.A3364T:p.T1122S	NA	NA	NA	NA	D	D	D	M	272	21	7.12%
R1281K	5F	sibling	female	7	92761915	92761920	CTAGTG	-	SAMD9L	SAMD9L:NM_152703:exon5:c.3365_3370del:p.1122_1124del	NA	NA	NA	NA					290	30	9.35%
R1281K	5G-Age 1.5	sibling	male	7	92762758	92762758	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C2527T:p.R843W	NA	NA	3.30E-05	NA	D	P	B	N	12768	112	0.87%
R1281K	5G-Age 1.5	sibling	male	7	92763520	92763520	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C1765T:p.R589X	NA	NA	8.31E-06	ID=COSM79411;OCCURENCE=1(ovary),1(large_intestine)	T	.	.	.	8459	481	5.38%
R1281K	5G-Age 6	sibling	male	7	92762758	92762758	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C2527T:p.R843W	NA	NA	3.30E-05	NA	D	P	B	N	3789	412	9.80%
R1281K	5G-Age 6	sibling	male	7	92763520	92763520	G	A	SAMD9L	SAMD9L:NM_152703:exon5:c.C1765T:p.R589X	NA	NA	8.31E-06	ID=COSM79411;OCCURENCE=1(ovary),1(large_intestine)	T	.	.	.	2093	459	17.96%
R1281K	5H	sibling	female	none detected																	

Supplemental Table 5 - Haloplex Calls

	Individual	Relationship	Impacted.Gene	AA	Number.of.Variant.Alleles	Filtered.Read.Depth..per.sample.	Allele.Frequency	HGVS.Coding.	Type	Chrom	Pos	Ref.Allele	Alt.Allele	Function.Class	Codon	Coding	Exon.ID
H880Q	1A	proband	*CBL*	E366_E8splice	78	167	46.70%	NM_005188	SNP	11	119148875	G	T	Splice		CODING	
H880Q	1A	proband	*RUNX1*	D171N	145	424	34.20%	NM_001001890	SNP	21	36231792	C	T	MISSENSE	Gat/Aat	CODING	NM_001001890.ex.3
H880Q	1A	proband	*SETBP1*	G870S	183	453	40.40%	NM_015559	SNP	18	42531913	G	A	MISSENSE	Ggc/Agc	CODING	NM_015559.ex.4
H880Q	1B	sibling	*BRAF*	N581Y	34	135	25.20%	NM_004333	SNP	7	140453987	T	A	MISSENSE	Aat/Tat	CODING	NM_004333.ex.14
H880Q	1B	sibling	*KRAS*	T58I	207	441	46.90%	NM_004985	SNP	12	25380285	G	A	MISSENSE	aCa/aTa	CODING	NM_004985.ex.3
H880Q	1B	sibling	*RUNX1*	N139fs	195	395	49.40%	NM_001001890	Insertion	21	36252945	G	GT	Frameshift		CODING	NM_001001890.ex.2
H880Q	1B	sibling	*SETBP1*	D868N	328	750	43.70%	NM_015559	SNP	18	42531907	G	A	MISSENSE	Gac/Aac	CODING	NM_015559.ex.4
K676E	2A	proband	*ASXL1*	K686fs	370	902	41.00%	NM_015338	Deletion	20	31022572	AGT	A	Frameshift		CODING	NM_015338.ex.12
K676E	2A	proband	*SETBP1*	D868N	479	966	49.60%	NM_015559	SNP	18	42531907	G	A	MISSENSE	Gac/Aac	CODING	NM_015559.ex.4
K676E	2B	sibling	*ETV6*	R369Q	58	275	21.10%	NM_001987	SNP	12	12037475	G	A	MISSENSE	cGg/cAg	CODING	NM_001987.ex.6
K676E	2B	sibling	*SAMD9*	K676E	16	98	16.30%	NM_001193307	SNP	7	92733385	T	C	MISSENSE	Aag/Gag	CODING	NM_001193307.ex.2
K676E	2M	parent	*CDKN2A*	D74A	21	60	35.00%	NM_000077	SNP	9	21971137	T	G	MISSENSE	gAc/gCc	CODING	NM_000077.ex.2
R986C	3A	proband	*SAMD9L*	R986C	49	474	10.30%	NM_001303496	SNP	7	92762329	G	A	MISSENSE	Cgt/Tgt	CODING	NM_001303496.ex.5
R986C	3B	sibling	*SAMD9L*	R986C	292	793	36.80%	NM_001303496	SNP	7	92762329	G	A	MISSENSE	Cgt/Tgt	CODING	NM_001303496.ex.5
R986C	3B	sibling	*SAMD9L*	R843W	31	165	18.80%	NM_001303496	SNP	7	92762758	G	A	MISSENSE	Cgg/Tgg	CODING	NM_001303496.ex.5
R986C	3B	sibling	*SAMD9L*	R223*	44	390	11.30%	NM_001303496	SNP	7	92764618	G	A	NONSENSE	Cga/Tga	CODING	NM_001303496.ex.5
V1512A	4A	proband	*SAMD9L*	V1512A	126	411	30.70%	NM_001303496	SNP	7	92760750	A	G	MISSENSE	gTg/gCg	CODING	NM_001303496.ex.5
V1512A	4B	sibling	*SAMD9L*	V1512A	208	490	42.40%	NM_001303496	SNP	7	92760750	A	G	MISSENSE	gTg/gCg	CODING	NM_001303496.ex.5
R1281K	5A	proband	*SAMD9L*	R1281K	37	70	52.90%	NM_001303496	SNP	7	92761443	C	T	MISSENSE	aGg/aAg	CODING	NM_001303496.ex.5
R1281K	5C	sibling	*SAMD9L*	R1281K	29	63	46.00%	NM_001303496	SNP	7	92761443	C	T	MISSENSE	aGg/aAg	CODING	NM_001303496.ex.5
R1281K	5E	sibling	*SAMD9L*	R1281K	50	99	50.50%	NM_001303496	SNP	7	92761443	C	T	MISSENSE	aGg/aAg	CODING	NM_001303496.ex.5
R1281K	5E	sibling	*SAMD9L*	V19E	34	152	22.40%	NM_001303496	SNP	7	92765229	A	T	MISSENSE	gTg/gAg	CODING	NM_001303496.ex.5
R1281K	5F	sibling	*SAMD9L*	R1281K	43	87	49.40%	NM_001303496	SNP	7	92761443	C	T	MISSENSE	aGg/aAg	CODING	NM_001303496.ex.5
R1281K	5F	sibling	*SAMD9L*	TLG1122S	86	510	16.90%	NM_001303496	Deletion	7	92761914	CCTAGTG	C	Indel	acactaggt/agt	CODING	NM_001303496.ex.5
R1281K	5H	sibling	*SAMD9L*	R1281K	34	68	50.00%	NM_001303496	SNP	7	92761443	C	T	MISSENSE	aGg/aAg	CODING	NM_001303496.ex.5

Supplemental Table 6 - Haloplex Targets

TargetID	Interval	Regions	Size	Databases
ASXL1	chr20:30946569-31025151	17	5060	CCDS, Ensembl, Gencode, RefSeq, VEGA
ASXL2	chr2:25964888-26101101	13	4571	Ensembl, Gencode, RefSeq, VEGA
ATM	chr11:108098342-108236245	62	10411	CCDS, Ensembl, Gencode, RefSeq
BCOR	chrX:39909159-39937192	15	5648	CCDS, Ensembl, Gencode, RefSeq, VEGA
BCORL1	chrX:129139198-129190121	14	5690	CCDS, Ensembl, Gencode, RefSeq, VEGA
BRAF	chr7:140439612-140481493	7	813	CustomRegion
CBL	chr11:119148467-119149423	3	424	CustomRegion
CDKN2A	chr9:21968198-21994463	6	1248	CCDS, Ensembl, Gencode, RefSeq, VEGA
CEBPA	chr19:33792234-33793435	1	1202	CCDS, Ensembl, Gencode, RefSeq, VEGA
CREBBP	chr16:3777711-3799628	8	3233	CustomRegion
CSF3R	chr1:36932221-36933575	4	555	CustomRegion
CTCF	chr16:67644729-67662457	7	1734	CustomRegion
CUX1	chr7:101459301-101926392	34	6113	CCDS, Ensembl, Gencode, RefSeq, VEGA
DDX41	chr5:176939323-176942993	2	139	CustomRegion
DHX15	chr4:24572273-24572480	1	208	CustomRegion
DNMT3A	chr2:25457147-25468203	11	1304	CustomRegion
ETV6	chr12:12022356-12038963	3	815	CustomRegion
EZH2	chr7:148504728-148544400	21	2876	CCDS, Ensembl, Gencode, RefSeq, VEGA
FLT3	chr13:28588588-28610197	13	1619	CustomRegion
GATA2	chr3:128199860-128205219	4	1244	CustomRegion
IDH1	chr2:209113090-209113391	1	302	CustomRegion
IDH2	chr15:90631590-90631985	2	316	CustomRegion
JAK1	chr1:65303613-65312425	9	1276	CustomRegion
JAK2	chr9:5050684-5070055	7	1216	CustomRegion
JAK3	chr19:17943326-17949201	9	1282	CustomRegion
KDM6A	chrX:44732788-44970666	31	5090	CCDS, Ensembl, Gencode, RefSeq, VEGA
KIT	chr4:55589749-55599363	2	250	CustomRegion
KRAS	chr12:25380168-25398320	2	295	CustomRegion
MGA	chr15:41961083-42059488	24	9841	CCDS, Ensembl, Gencode, RefSeq
MPL	chr1:43814930-43815039	1	110	CustomRegion
MYC	chr8:128750486-128753216	2	1391	CustomRegion
NF1	chr17:29422216-29705959	63	10271	CCDS, Ensembl, Gencode, RefSeq, VEGA
NIPBL	chr5:36953789-37065004	46	9380	CCDS, Ensembl, Gencode, RefSeq, VEGA
NRAS	chr1:115256420-115258785	2	300	CustomRegion
PHF6	chrx:133512032-133551336	7	978	CustomRegion
PIK3C2A	chr11:17111284-17136026	14	1919	CustomRegion
PTEN	chr10:89623697-89725239	9	1912	CCDS, Ensembl, Gencode, RefSeq, VEGA
PTPN11	chr12:112888120-112926983	2	360	CustomRegion
RAD21	chr8:117859729-117878978	13	2156	CCDS, Ensembl, Gencode, RefSeq, VEGA
RIT1	chr1:155874095-155874295	1	201	CustomRegion
RRAS	chr19:50140081-50140185	1	105	CustomRegion
RUNX1	chr21:36164422-36421206	11	1804	CCDS, Ensembl, Gencode, RefSeq, VEGA
SAMD9	chr7:92730631-92735420	1	4790	CCDS, Ensembl, Gencode, RefSeq, VEGA
SAMD9L	chr7:92760520-92765294	1	4775	CCDS, Ensembl, Gencode, RefSeq, VEGA
SETBP1	chr18:42449195-42533327	2	3542	CustomRegion
SETD2	chr3:47058573-47205424	23	8200	CCDS, Ensembl, Gencode, RefSeq, VEGA
SF3B1	chr2:198266708-198267559	2	431	CustomRegion
SMC1A	chrX:53407014-53449559	26	4402	CCDS, Ensembl, Gencode, RefSeq, VEGA
SMC3	chr10:112327565-112364070	29	4234	CCDS, Ensembl, Gencode, RefSeq, VEGA
SOS1	chr2:39249709-39251287	2	814	CustomRegion
SRSF2	chr17:74732865-74733253	1	389	CustomRegion
STAG2	chrX:123156468-123234457	34	4541	CCDS, Ensembl, Gencode, RefSeq, VEGA
TET2	chr4:106111617-106197686	10	6365	CCDS, Ensembl, Gencode, RefSeq, VEGA
TP53	chr17:7565247-7579922	14	1658	CCDS, Ensembl, Gencode, RefSeq, VEGA
WT1	chr11:32410594-32456901	11	1788	CCDS, Ensembl, Gencode, RefSeq, VEGA
ZRSR2	chrX:15808609-15841375	12	1930	CCDS, Ensembl, Gencode, RefSeq, VEGA

Supplemental Table 7 - Haloplex coverage

Family	Individual	Relationship	HighQualityReads	MedianReadDepth
H880Q	1M	parent	460263	140
H880Q	1A	proband	533302	172
H880Q	1B	sibling	777695	246
K676E	2P	parent	624785	194
K676E	2M	parent	1202839	378
K676E	2A	proband	961997	294
K676E	2B	sibling	582880	185
R986C	3A	proband	896876	301
R986C	3B	sibling	897232	300
V1512A	4A	proband	696854	235
V1512A	4B	sibling	962792	295
R1281K	5A	proband	888462	283
R1281K	5B	sibling	483439	161
R1281K	5C	sibling	753589	241
R1281K	5D	sibling	463747	158
R1281K	5E	sibling	1161641	398
R1281K	5F	sibling	1152491	395
R1281K	5G	sibling	255242	82
R1281K	5H	sibling	854382	287

Supplemental Table 8 - Amplicon coverage

				Primer set 1							Primer set 2					
Family	Individual	Relationship	Tot_reads	Mapped_reads	UnMpd_reads	Mapped_ratio	D9 Primer 1	D9 Primer 3	9L Primer 2	Tot_reads	Mapped_reads	UnMpd_reads	Mapped_ratio	D9 Primer 2	9L Primer 1	9L Primer 3
H880Q	1P	parent	211300	211228	72	99.97%	7187	13353	8723	169153	169100	53	99.97%	10614	8275	3850
H880Q	1M	parent	361170	360990	327	99.95%	8689	18955	10819	373936	373732	484	99.95%	16161	12885	5528
H880Q	1A	proband	227757	227691	66	99.97%	7350	15714	7758	152578	152538	40	99.97%	9168	6977	3702
H880Q	1A	proband	140250	140208	42	99.97%	5055	8559	6017	393267	393126	141	99.96%	19283	16694	8635
H880Q	1A	proband	292855	292781	74	99.97%	9491	17705	11977	239706	239616	90	99.96%	13398	11394	5974
H880Q	1A	proband	295792	295669	123	99.96%	8891	19385	9696	277594	277480	114	99.96%	16395	12786	4644
H880Q	1B	sibling	273265	273171	94	99.97%	7721	19613	8971	201494	201404	90	99.96%	12237	9519	4325
H880Q	1B	sibling	165397	165332	65	99.96%	5766	10939	6340	266347	266254	93	99.97%	14273	11541	5750
H880Q	1B	sibling	366047	365950	97	99.97%	10040	24757	13226	349501	349367	134	99.96%	19059	15442	7126
H880Q	1B	sibling	280525	280426	99	99.96%	8393	18311	9180	381457	381289	168	99.96%	21060	16486	6191
K676E	2P	parent	279595	279507	88	99.97%	9152	14109	13195	125699	125656	43	99.97%	5153	6023	3189
K676E	2M	parent	332289	332135	154	99.95%	8012	20256	9793	374160	374009	151	99.96%	22192	17520	7444
K676E	2A	patient	235863	235793	70	99.97%	9018	15458	9047	4679	4674	5	99.89%	283	246	112
K676E	2A	patient	196442	196394	48	99.98%	6733	13375	7912	223767	223683	84	99.96%	17468	8719	3440
K676E	2A	patient	297573	297495	78	99.97%	10258	20814	11035	259822	259754	68	99.97%	15860	12430	5922
K676E	2B	patient	229770	229716	54	99.98%	8959	14290	10577	295097	295010	87	99.97%	16150	13250	6930
R986C	3P	parent	301981	301906	75	99.98%	9763	18180	12747	253061	252962	99	99.96%	18331	11514	5364
R986C	3M	parent	428198	427929	435	99.94%	9051	24124	12279	329938	329817	323	99.96%	13978	11398	5756
R986C	3A	proband	220180	220093	87	99.96%	4316	13736	11547	283080	282984	96	99.97%	18046	13106	5660
R986C	3A	proband	198829	198777	52	99.97%	5031	14445	7013	309204	309087	117	99.96%	20654	14068	5431
R986C	3B	proband	253062	252831	231	99.91%	4361	17015	12318	229070	228893	177	99.92%	15290	11159	3869
R986C	3B	sibling	258289	258201	88	99.97%	7394	17194	8878	335071	334945	126	99.96%	21666	16984	6816
R986C	3B	sibling	254501	254443	58	99.98%	9127	16762	10941	223909	223822	87	99.96%	15431	11167	4346
V1512A	4A	patient	245222	245138	84	99.97%	10099	13070	8301	252168	252056	112	99.96%	13210	13094	3574
V1512A	4B	patient	316172	316096	76	99.98%	8771	22421	8706	176636	176569	67	99.96%	10750	9814	2716
R1281K	5P	parent	197853	197758	95	99.95%	5920	13802	7852	268475	268407	68	99.97%	17390	13340	4899
R1281K	5M	parent	325851	325782	69	99.98%	11187	21206	13072	271348	271251	97	99.96%	16479	13383	6265
R1281K	5A	patient	82343	82319	24	99.97%	3230	5570	3961	392230	392111	119	99.97%	24491	18898	7656
R1281K	5A	patient	299330	299247	83	99.97%	9558	18086	10887	380386	380255	131	99.97%	22083	17414	9195
R1281K	5A	patient	249439	249306	133	99.95%	7137	11601	9537	215038	214969	69	99.97%	12149	9993	4559
R1281K	5A	patient	278253	278193	60	99.98%	9946	16136	11652	267027	266942	85	99.97%	17519	12905	5464
R1281K	5B	sibling	228536	228467	69	99.97%	5410	14569	10795	233407	233345	62	99.97%	14843	11387	5753
R1281K	5B	sibling	221371	221307	64	99.97%	7716	14717	9803	255639	255574	65	99.97%	15843	12450	6473
R1281K	5C	sibling	289083	289021	62	99.98%	10187	20497	11891	209812	209741	71	99.97%	13106	10477	5015
R1281K	5C	sibling	229406	229359	47	99.98%	6236	18641	7034	345490	345397	93	99.97%	21762	15768	5600
R1281K	5D	sibling	302360	302278	82	99.97%	8958	22032	9463	281002	280923	79	99.97%	17862	13573	5923
R1281K	5D	sibling	251684	251608	76	99.97%	6423	19681	8619	236075	236004	71	99.97%	15136	11479	5709
R1281K	5E	patient	225344	225289	55	99.98%	6917	17343	7567	143839	143765	74	99.95%	13349	4247	1398
R1281K	5F	sibling	64693	64674	19	99.97%	1335	3688	3277	13225	13215	10	99.92%	545	380	153
R1281K	5F	sibling	126919	126868	51	99.96%	3595	9038	4955	113207	113163	44	99.96%	8395	5344	1925
R1281K	5G	patient	91590	91565	25	99.97%	3103	5627	3632	188504	188441	63	99.97%	13129	8893	3826
R1281K	5G	patient	332174	332114	60	99.98%	12088	21700	11810	224797	224719	78	99.97%	16500	10105	3562
R1281K	5H	patient	293092	293018	74	99.97%	9151	19953	10112	228812	228742	70	99.97%	23304	4016	1059
R1281K	5H	patient	73993	73929	64	99.91%	2006	5988	3644	66823	66764	59	99.91%	4416	3759	1747
R1281K	5H	patient	89969	89952	17	99.98%	2783	7480	4181	102580	102549	31	99.97%	9502	1357	289

Group 1	SAMD9 amp1 F	ATGGCAAAGCAACTTAACCTTCC
	SAMD9 amp1 R	GAAATACCACCAAAAACTTCCC
	SAMD9 amp3 F	TGAAGGTGAAACAGGAAATTGG
	SAMD9 amp3 R	TTAAACAATTTCAATGTCATAAGC
	SAMD9L amp2 F	CCTCTAGAACCACATTTATG
	SAMD9L amp2 R	GCATTTTGTGGGAATCGTCTAC
Group 2	SAMD9 amp2 F	GAGCTTCTGATGTCAGGAAACTG
	SAMD9 amp2 R	CTTCAACTGCTTCATTTCCTTC
	SAMD9L amp1 F	ATGAGTAAACAAGTATCTCTACCTG
	SAMD9L amp1 R	CCACTGAAGAGAGTAATAGA
	SAMD9L amp3 F	CAAGGTGTATGGAGATGAAAC
	SAMD9L amp3 R	TTAAATTACTTCTATATCATATGCCAGA

Platinum SuperFi (cat# 12358-010)

C1000 machine

	x1
2x SuperFi Mix	12.5
10uM primer mix	2.5
25ng DNA	10
Total vol:	25

98°C x 30"	
98°C x 10"	30 cycles
60°Cx 10"	
72°C x 1.5'	
72°C x 5'	
4°C x ∞	

Supplemental Table 9 - SNP coverage

Family	Individual	Relationship	Gender	Tissue	Total Reads	Mapped Reads	Unmapped Reads	Mapped Ratio
H880Q	1B	sibling	male	spleen	5497	5487	10	99.82%
H880Q	1B	sibling	male	liver	8983	8974	9	99.90%
K676E	2P	parent	male	unknown	8539	8530	9	99.89%
K676E	2M	parent	female	blood	10680	10672	8	99.93%
R986C	3P	parent	male	blood	20716	19380	1336	93.55%
R986C	3P	parent	male	blood	13898	13176	722	94.81%
R986C	3P	parent	male	blood	21928	21333	595	97.29%
R986C	3M	parent	female	unknown	8735	7533	1202	86.24%
R986C	3M	parent	female	unknown	15452	14854	598	96.13%
R986C	3M	parent	female	blood	20320	19380	940	95.37%
R1281K	5P	parent	male	buccal	12204	11966	238	98.05%
R1281K	5M	parent	female	buccal	16318	16005	313	98.08%
R1281K	5D	sibling	female	buccal	13300	13048	252	98.11%

Chrom	Pos	Ref.Allele	Alt.Allele	Impacted.Gene	AA	name	seq	name	seq	size
7	92762645	G	T	SAMD9L	H880Q	tagged H880Q F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGGGAATCCAGATGAAAGTGC	tagged H880Q R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGAGTCAGTAACATAAGAGC	277
7	92763579	T	G	SAMD9L	Q569P	tagged Q569P F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGGGCAGAGAGAAAGAGCTTC	tagged Q569P R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGCTGTGGTTTGTTAGTTCATC	274
7	92733385	T	C	SAMD9	K676E	tagged K676E F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGGGCTTTTGCCATCTATTGG	tagged K676E R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGGTACTTGTTGGTTTAGAAG	302
7	92761443	C	T	SAMD9L	R1281K	tagged R1281K F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCTGATCCCAGAAATGAATGT	tagged R1281K R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGCTAGCTTTTTCCTGCAATTC	279
7	92732005	C	G	SAMD9	E1136Q	tagged E1136Q F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGGTTCAACCCAAATGCATTC	tagged E1136Q R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGCCTTTTTGACTTCGGATAC	332
7	92762329	G	A	SAMD9L	R986C	tagged R986C F	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCATATACACTAGTACACCC	tagged R986C R	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGCCTTGCGCTGTCTTGTAAG	293

C1000 machine	x1
2x SuperFi Mix	12.5
10uM primer mix	2.5
H2O	6
25ng DNA	4
Total vol:	25

98°C x 30"	
98°C x 10"	30 cycles
60°Cx 10"	
72°C x 30"	
72°C x 5'	
4°C x ∞	

Supplemental Table 10 - mutagenesis primers

Name	Sequence
SAMD9 K676E F	AAATTCCTTGAATTCGAGGCATCAAAAGAGG
SAMD9 K676E R	CCTCTTTTGATGCCTCGAATTCAAGGAATTT
SAMD9L R843W F	AACTGCATGAGATCCTGGAATCCAGATGAAA
SAMD9L R843W R	TTTCATCTGGATTCCAGGATCTCATGCAGTT
SAMD9L R986C F	AGATACACAGGTGTGTGTATCATTCACCCTC
SAMD9L R986C R	GAGGGTGAATGATACACACACCTGTGTATCT
SAMD9L V1512A F	GGCACAGTGGGGATGCGTGGAAAAAAAATGA
SAMD9L V1512A R	TCATTTTTTTTCCACGCATCCCCACTGTGCC
SAMD9L V19E F	CCAAAGAGCATGAGAAAAAATGGGT
SAMD9L V19E R	ACCCATTTTTTCTCATGCTCTTTGG
SAMD9L R223* F	AGCAATGAAGTCTTCTGATTTGCATCAGCTT
SAMD9L R223* R	AAGCTGATGCAAATCAGAAGACTTCATTGCT
SAMD9L H880Q F	GAAATTGAAAAGCAGCAAAAGAACTGTGAAAACTT
SAMD9L H880Q R	AAGTTTTCACAGTTCTTTTGCTGCTTTTCAATTTC
SAMD9L R1281K F	GTTCTTCTGAAAATGAAGTATACCCAAAAAGAA
SAMD9L R1281K R	TTCTTTTTGGGTATACTTCATTTTCAGAAGAAC
SAMD9L Q569P F	TCTGGGCTTTCTATCCAGCTCTCAAAGGAAT
SAMD9L Q569P R	ATTCCTTTGAGAGCTGGATAGAAAGCCCAGA

Supplemental Table 11 - samples

Representative samples

Family	Individual	Relationship	Gender	Source
H880Q	1P	parent	male	PB
H880Q	1M	parent	female	PB
H880Q	1A	proband	female	BM
H880Q	1B	sibling	male	BM
K676E	2P	parent	male	PB
K676E	2M	parent	female	PB
K676E	2A	proband	male	BM
K676E	2B	sibling	male	BM
R986C	3P	parent	male	PB
R986C	3M	parent	female	PB
R986C	3A	proband	female	BM
R986C	3B	sibling	female	BM
V1512A	4A	proband	female	BM
V1512A	4B	sibling	female	BM
R1281K	5P	parent	male	PB
R1281K	5M	parent	female	PB
R1281K	5A	proband	male	BM -5 years old
R1281K	5A	proband	male	PB- 15 years old
R1281K	5A	proband	male	PB- 18 years old
R1281K	5B	sibling	female	BM
R1281K	5C	sibling	male	BM
R1281K	5D	sibling	female	BM
R1281K	5E	sibling	female	BM
R1281K	5F	sibling	female	BM
R1281K	5G	sibling	male	BM - 2.5 years old
R1281K	5G	sibling	male	PB - 6 years old
R1281K	5H	sibling	female	PB