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Germline Predisposition Gene Analysis in Pediatric Acute Myeloid Leukemia

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Germline Predisposition Gene Analysis in Pediatric Acute Myeloid Leukemia

by

Dajeong Jeong

A thesis submitted to the Department of Medicine in partial fulfillment of the requirements for the Degree of Master of Medicine (Laboratory Medicine) at Seoul National University College of Medicine

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Approved by Thesis Committee:

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Abstract

Background: The pediatric acute myeloid leukemia (AML) is different from adult AML in that germline predisposition genes heavily contribute to leukemogenesis. Since AML with germline predisposition gene mutations requires different clinical management, detection of it is growing important.

Methods: In present study, we investigated the prevalence of germline predisposition gene mutations in context with somatic mutations in Korean pediatric AML. Seventeen bone marrow (BM) samples at initial diagnosis of pediatric AML and 16 paired BM specimens of remission and 1 saliva sample were collected. Cytogenetic studies of G-banding and FISH and targeted multi-gene sequencing using 507 in-house gene panel were performed.

Results: A total of 18 germline predisposition gene variants in 11 patients were detected: 3 likely pathogenic variants in 2 patients and 15 variants of unknown significance in 9 patients. Meanwhile, 12 out of 17 (70.6%) patients carried somatic mutations and 10 out of 17 (58.8%) patients had gene fusions.

Conclusions: Prevalence of germline predisposition gene mutations in Korean pediatric AML was estimated to be approximately 11.8%, which suggests that work-up for germline mutation is necessary in pediatric AML.

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Keywords: Germline predisposition; pediatric acute myeloid leukemia; genetic susceptibility; somatic mutation; multi-gene sequencing

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Abbreviations

AML	Acute myeloid leukemia
NGS	Next generation sequencing
BM	Bone marrow
FAB	French–American–British
MDS	Myelodysplastic syndrome
IRB	Institutional review board
APC	Allophycocyanin
PE	Phycoerythrin
PC5	Phycoerythrin–cyanine 5
FITC	Fluorescein isothiocyanate
cyt	cytoplasmic
TdT	Terminal deoxynucleotidyl transferase
MPO	Myeloperoxidase
WBC	White blood cells
ISCN	International System for Human Cytogenetic Nomenclature
FISH	Fluorescence in situ hybridization
QC	Quality control
GATK	Genome Analysis Toolkit
VAF	Variant allele frequency
SNP	Single nucleotide polymorphism
MAF	Minor allele frequency
SIFT	Sorting Tolerant From Intolerant

FATHMM	Functional Annotation Through
CADD	Combined Annotation Dependent Depletion
ICGC	International Cancer Genome Consortium
COSMIC	Catalogue of Somatic Mutations in
DIC	Disseminated intravascular coagulopathy
Hb	Hemoglobin
LP	Likely pathogenic
VUS	Variant of unknown significance

Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematopoietic stem cell disorder of which development is acquired or inherited. In adults, AML has been regarded as an acquired disease, while infantile leukemia and familial leukemia has elucidated a role of genetic predisposition to leukemia [1]. With an introduction of next generation sequencing (NGS), unrecognized patients with genetic predisposition to myeloid malignancies are being unveiled and it is likely that patients with genetic predisposition to myeloid malignancies will be increasing.

Although children occupy minor portion of AML than adults, mutational landscape and genetic background is expected to remarkably differ between elderly and pediatrics [2]. Furthermore, a recent study on the molecular landscape of pediatric AML highlighted the development of age-tailored target therapies for pediatric AML [3].

The importance of germline predisposition in myeloid malignancy is being more and more emphasized due to its clinical significance. For the allogeneic hematopoietic stem cell donor, family members of the patient should be thoroughly screened or excluded because the same mutation with the proband can result in donor cell leukemia. The family members are recommended to take genetic counseling and may benefit from the early and regular surveillance [4,5].

Recent study demonstrated the prevalence of genetic susceptibility genes in pediatric cancers and inherited bone marrow failure [6,7]. However, the prevalence of germline predisposition genes in AML has not been reported both

in adults and children.

We aimed to investigate the prevalence of germline predisposition gene mutations in pediatric AML and compared the mutational profile of somatic mutation with that of adult AML in Korea.

Materials and Methods

1. Study populations

Seventeen patients who visited the department of pediatrics in Seoul National University Children's Hospital and were diagnosed with AML from 2013 to 2015 were enrolled in this study. They went through the bone marrow (BM) examination and the diagnosis was made based on the WHO 2012, which was retrospectively reviewed according to WHO 2016. Flow cytometry was performed to demonstrate the myeloid lineage of the blasts. A total of 31 children were diagnosed with AML and two of whom with therapy-related AML were excluded. In addition, three AML French–American–British (FAB) classification of M6 patients were reclassified as myelodysplastic syndrome (MDS) with excessive blasts-1 or -2. Among 26 candidate study subjects, 17 patients' BM specimens were retrospectively available. Seventeen BM samples at initial diagnosis and 16 paired BM specimens of remission (less than 5% blasts in BM with no evidence of residual cells by immunohistochemical stain) and 1 saliva sample were collected. For patients' clinical features, electronic medical records were retrospectively reviewed.

This study was approved by the institutional review board (IRB) of Seoul National University Hospital (IRB 1508-075-695), and the requirement for obtaining informed consent was waived.

2. Flow cytometry

Fifteen kinds of surface markers and 6 kinds of cytoplasmic markers were used for acute leukemia lineage study: anti-CD45- Allophycocyanin (APC) (Beckman coulter, France), anti-CD33- Phycoerythrin (PE) (Beckman coulter), anti-CD34-Phycoerythrin–cyanine 5 (PC5) (Beckman coulter), anti-CD2- Fluorescein isothiocyanate (FITC) (Beckman coulter), anti-CD10-PE (Beckman coulter), anti-CD3-PC5 (Beckman coulter), anti-CD56-FITC (Becton-Dickinson, USA), anti-CD117-PE (Beckman coulter), anti-CD41-PC5 (Beckman coulter), anti-CD13-FITC (Beckman coulter), anti-CD19-PE (Beckman coulter), anti-CD7-PC5 (Beckman coulter), anti-CD20-FITC (Beckman coulter), anti-CD5-PE (Beckman coulter), anti-terminal deoxynucleotidyl transferase (TdT)-FITC (Beckman coulter), anti- cytoplasmic (cyt) CD79a-PE (Beckman coulter), anti-cytCD3-PC5 (Beckman coulter), anti-cytIgM-PE (Southern Biotech, USA), anti-cytCD22-PC5 (Beckman coulter) and anti- myeloperoxidase (MPO)-FITC (Beckman coulter). Seven tubes for surface markers and 5 tubes for cytoplasmic markers were used. A total of 10 uL of anti-CD45-APC was added on each tube. Two surface tubes and one cytoplasmic tube were for isotype control. Three kinds of markers with FITC, PE and PC5 fluorescence were added in each tubes. Then, BM aspirate (100 uL) was dispensed in each tube. After 15 minutes, RBCs in the specimen were lysed using VersaLys Lysing Solution (Beckman Coulter, Marseille, France). Then centrifugation at 3000 rpm for 1 minute was done. After removing the supernatant, washing was performed using sheath fluid (2 mL). The centrifugation at 3000 rpm for 1 minute and the removal of upper layer was carried out again. Lastly, sheath fluid (500 uL) was added in each tube. For cytoplasmic tubes, reagents for fixation and permeabilization were used. Flow cytometric analysis was performed using Beckman Coulter Navios flow cytometer (Beckman Coulter) and the Kaluza

(Beckman Coulter) software. A minimum of 30,000 cells were analyzed.

3. Immunohistochemical stain

Immunohistochemical staining for CD34 and CD117 was performed on both initial diagnosis and remission BM biopsy sections. The paraffin-embedded tissue block got trimmed and sliced into 2-μm. The tissues on slides were incubated at 56°C for 30 minutes. Hydration by xylene, 100% EtOH, 95% EtOH and 70% EtOH was performed. Then, each slide was stained using Ventana BenchMark ULTRA (Ventana Medical Systems Inc., Tucson, AZ, USA). The mouse anti-CD34 monoclonal antibody (Novocastara, Newcastle, UK) and rabbit anti-CD117 monoclonal antibody (DAKO, Glostrup, Denmark) were applied for 15 minutes at room temperature. Subsequently, the slides were dehydrated using 70% EtOH, 95% EtOH, 100% EtOH and Xylene.

4. G-banding

Chromosome analysis was carried out by the conventional G-banding technique. The heparinized BM samples were collected and white blood cells (WBCs) were sorted by centrifugation and cultured in RPMI-1640 medium (Gibco, USA) at 37℃, in 5% CO2 for 24 hours. Colcemid treatment was done to inhibit the mitosis. The specimen in the medium was centrifuged and the upper layer was decanted. Then, KCl was added at 37℃ for 20 minutes. For fixation, 1 mL of Carnoy's solution was used. After preparation of the slide,

Leishman's G-banding stain was performed according to the standard protocol. A minimum of 20 metaphase cells per patient was analyzed using the software Metafer 4 (MetaSystems, Altlussheim, FRG). The karyotype designation was based on the principles of the International System for Human Cytogenetic Nomenclature (ISCN 2013).

5. Fluorescence *in situ* hybridization (FISH)

Interphase FISH analysis was done on mononuclear cells of BM aspirates to detect common cytogenetic abnormalities related to AML and/or MDS using the LSI *RUNX1T1*/*RUNX1* (Vysis Inc., Downers Grove, IL, USA), LSI *PML*/*RARA* (Vysis), LSI *MLL* DualColor (Vysis), LSI *CBFB* (Vysis), LSI *EGR*, LSI D7S522 (Vysis), LSI 20 (Vysis), LSI CEP 8 (Vysis) and LSI 1q25 (Vysis). For FISH slide preparation, each bone marrow aspirate specimen with 10 mL of 0.075M KCl was centrifuged at 1200 rpm for 8 minutes. After removing the upper layer, the pellet with 0.075M KCl was incubated at 37°C water bath for 30 minutes. For fixation, methanol and acetic acid (3:1) was used. The slides were immersed in 0.1% nonylphenol polyethylene glycol (NP40) and 2x sodium saline citrate (SSC) at 37°C for 30 minutes and dehydrated with 70%, 85% and 100% ethanol for 3 minutes each. Then, the slides were air-dried. Meanwhile, the probes were made using 7 μL of hybridization buffer, 1 uL of LSI probe and deionized water in the dark. A total of 10 μL of the probe mixture solution was dropped on each FISH slide. Then co-denaturation of slides and probes were done at 75°C for 3 minutes. After overnight hybridization at 39°C,

the slides were pre-warmed in a solution containing 0.3% NP40 and 0.4% SSC at 73°C for 2 minutes. A total of 6.6 μL of 4′,6-diamidino-2-phenylindole (DAPI II) (Vysis) was dropped on each slide for counterstaining. The fluorescent signals were read using a fluor

escent microscope (Zeiss, Germany). At least 200 cells in each specimen were analyzed. The FISH results were recorded according to the ISCN 2013.

6. Multigene sequencing and variant calling strategy

A total of 33 BM and 1 saliva specimen of 17 patients was analyzed by multigene targeted NGS. In-house gene panel which consists of 507 leukemia and other cancer-related genes was used (Table S1). The algorithm searching for germline and somatic variants are shown in Figure 1.

Sequence quality control (QC) was performed using FastqQC 0.11.2 [8] and was mapped to human reference genome sequence NCBI b37 using BWA-MEM 0.7.12 [9]. Potential PCR duplicates were removed using Picard MarkDuplicates (http://broadinstitute.github.io/picard). BAM files were realigned using the Genome Analysis Toolkit (GATK) 3.3 IndelRealigner, and base quality scores were recalibrated using the GATK base quality recalibration tools [10]. For germline variant calling, GATK's HaplotypeCaller was used. To filter out low quality variants, variants that had either depth <10, variant count <2 or variant allele frequency (VAF) <1% were excluded. Then common single nucleotide polymorphisms (SNPs) were filtered out by removing variants that were annotated as having a minor allele frequency (MAF) of > 1% in either of the following databases: dbSNP, 1000 Genomes, Exome Variant Server, Exome Aggregation Consortium, or in-house Korean SNP database consisting of diabetes mellitus patients (n=917). Annotation of the variants were done using ANNOVAR [11].

The functional effects of the missense variants were predicted using in silico tools: Sorting Tolerant From Intolerant (SIFT), PolyPhen-2 HDIV, Mutation Taster, MutationAssessor, Functional Annotation Through Hidden Markov Model (FATHMM) and Combined Annotation Dependent Depletion (CADD).

Variants that existed both in initial and remission BM or saliva specimen with VAF of 30-70% were sorted out as potential germline variants. A total of 95 genes were analyzed for germline mutation analysis (Table S2). Namely, genes that are known to be associated with Fanconi anemia (*FANCA*, *FANCB*, *FANCC*, *BRCA2*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *BRIP1*, *FANCL*, *PALB2*, *RAD51C*, *SLX4* and *ERCC4*), severe congenital neutropenia (*ELANE*, *CSF3R*, *GFI1*, *HAX1*, *G6PC3*, *WAS*, *CXCR4*, *AP3B1*, *USB1*, *SLC37A4*, *VPS13B* and *RMRP*), Shwachman-Diamond syndrome (SBDS), Diamond-Blackfan anemia (*RPS19*, *RPS17*, *RPS24*, *RPL35A*, *RPL5*, *RPL11*, *RPS7*, *RPS26*, *RPS10* and *GATA1*), telomere biology disorders (*DKC1*, *TERT*, *TERC*, *TINF2*, *RTEL1*, *NOP10*, *NHP2*, *WRAP53* and *CTC1*), myeloid neoplasms (*CEBPA*, *DDX41*, *RUNX1*, *ANKRD26*, *ETV6*, *GATA2*, *SRP72* and *SAMD9*) and other cancers (*TP53*, *NF1*, *SMARCB1*, *WT1*, *ASXL1*, *RB1*, *APC*, *MUTYH*, *SMAD4*, *BMPR1A*, *STK11*, *MSH2*, *MSH6*, *MLH1*, *PMS2*, *VHL*, *CDC73*, *ATM*, *BLM*, *NBN*, *PTEN*, *PTPN11*, *SOS1*, *KRAS*, *MET*, *HRAS*, *EZH2*, *CREBBP*, *EP300*, *SETBP1*, *CHEK2*, *FANCM*, *ATR*, *BARD1*, *BRCA1*, *LIG4*, *PRKDC*, *CDH1*, *PAX5* and *CDKN2A*) were filtered. In case of genes of which inheritance mode is autosomal dominant, variants with > 0.1% MAF were excluded.

Conversely, variants that were present only in initial diagnosis BM and absent in remission samples or saliva were classified as potential somatic mutations.

Then, variants that were previously reported as pathogenic or likely pathogenic in ClinVar, International Cancer Genome Consortium (ICGC) or Catalogue of Somatic Mutations in Cancer (COSMIC) were regarded as a somatic mutation

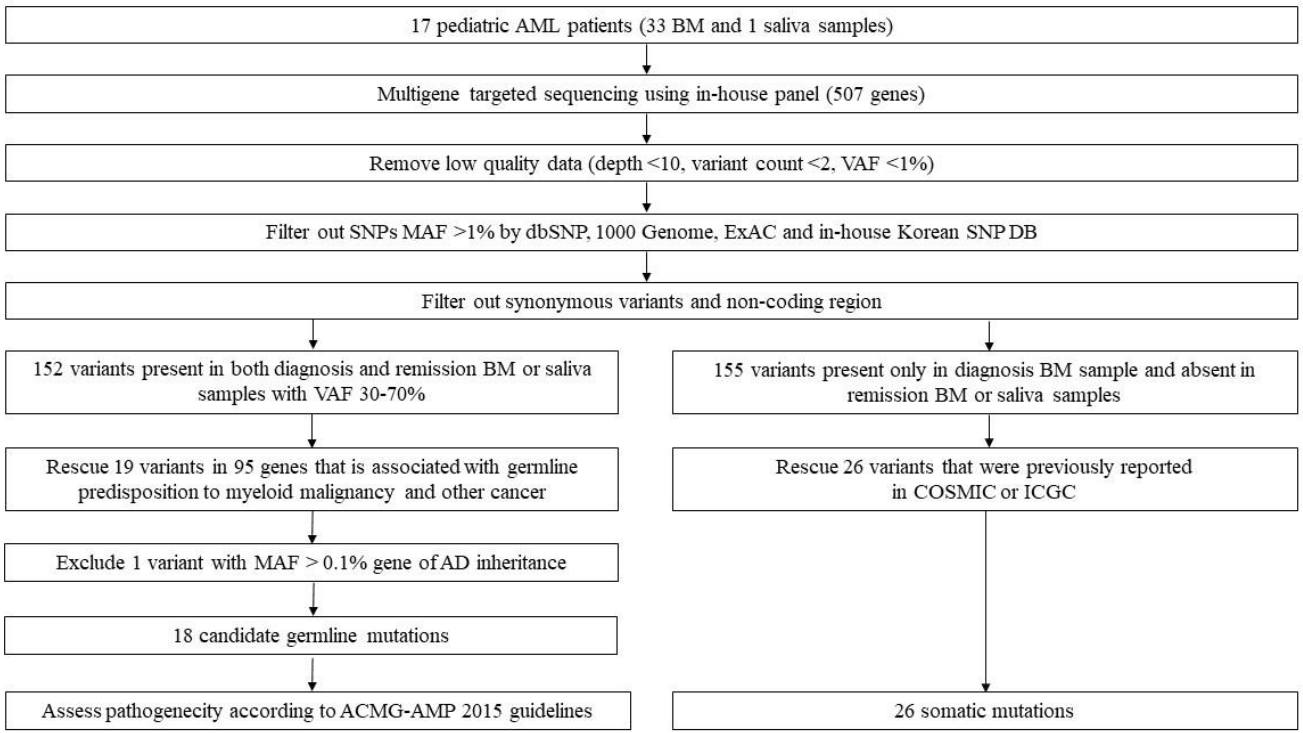

Figure 1. Algorithms searching for candidate germline and somatic mutations in 17 pediatric AML patients

Results

1. Clinical characteristics of patients

The median age of the 17 patients was 7 years old (range 0-17) and M:F ratio was 0.9. There was only one (5.9%) patient whose age was less than 1 year. Eight (47.1%) patients had organomegaly; 6 patients with hepatosplenomegaly and 2 with hepatomegaly only. One (5.6%) patient had skin involvement of AML. No patients showed disseminated intravascular coagulopathy (DIC) feature. Family history of cancer was present in 5 (29.4%) patients: one leukemia and four other cancers. The median value of hemoglobin (Hb) was 8.3 g/l (range 6.0-10.6), WBC count 7.29 $x10^9$/l (range 1.55-209.49) and platelet count $62x10^9$/l (range 23-291) at the time of initial diagnosis. The median value of blast percentage of BM aspirate was 73.5% (range 21.2-94.6). FAB classification of M4 was the most common (n=7, 41.2%), followed by M2 (n=4, 23.5%), M5 (n=2, 11.8%), M7 (n=2, 11.8%), M1 (n=1, 5.9%) and M3 (n=1, 5.9%) (Table 1).

Table 1. Clinical characteristics of 17 pediatric AML patients

Characteristics	Total (N =17)
Age, years*	7 (0-17)
< 1 year, n (%)	1 (5.9)
Sex, n (%)	
Male	8 (47.1)
Female	9 (52.9)
Organomegaly, n (%)†	
Hepatomegaly	8 (47.1)
Splenomegaly	6 (35.3)
Extramedullary involvement	
Skin	1 (5.9)
Family history, n (%)	
Leukemia	1 (5.9)
Other cancers	4 (23.5)
Hematologic parameters*	
Hb (g/l)	8.3 (6.0-10.6)
WBC ($x10^9$/l)	7.29 (1.55-209.49)
Platelet ($x10^9$/l)	62 (23-291)
BM blast (%)‡	73.5 (21.2-94.6)
FAB classification, n (%)	
M1	1 (5.9)
M2	4 (23.5)
M3	1 (5.9)
M4	7 (41.2)
M5	2 (11.8)
M6	0 (0.0)
M7	2 (11.8)

*Values presented as the median (range).

†Six patients had hepatosplenomegaly.

‡Two diluted samples were excluded.

2. Cytogenetics by G-banding & FISH

G-banding analysis revealed that 16 out of 17 (94.1%) patients had abnormal karyotype and only 1 patient carried normal karyotype. In 2 patients (patient #6 and #9), *RUNX1-RUNX1T1* rearrangement and *KMT2A* rearrangement were identified by FISH but not by G-banding. Based on both G-banding and FISH results, 10 (58.8%) patients showed gene fusions: 6 (35.3%) *KMT2A* rearrangements, 3 (17.6%) *RUNX1-RUNX1T1* fusions and one (5.9%) *FUS-ERG* fusion. Moreover, hyperdiploidy (n=1, 5.9%), trisomy 8 (n=1, 5.9%), trisomy 21 (n=1, 5.9%), add(4p) (n=1, 5.9%) and 7q aberration (n=1, 5.9%) were detected. Six (37.5%) patients had complex karyotype (≥3 cytogenetic abnormalities) and 5 (23.5%) patients carried karyotype with two numerical and/or structural abnormalities (Figure 2, Table 2).

3. Germline variants

A total of 18 germline predisposition gene variants were detected in 11 patients: six (33.3%) variants in Fanconi anemia genes (*FANCA*, *FANCD2*, *FANCI*, *PALB2* and *SLX4*), 4 (22.2%) variants in genes related to telomere biology disorder (*CTC1*, *RTEL1*, and *WRAP53*), 2 (11.1%) variants in germline myeloid neoplasm-associated genes (*DDX41* and *RUNX1*), 2 (11.1%) variants in severe congenital neutropenia-related gene (*VPS13B*) and 4 (22.2%) variants in other cancer-related genes (*ATM*, *BRCA1*, *MLH1* and *MSH6*) (Figure 2, Table 2). Germline variants of inherited bone marrow failure-related genes were most common (n=8, 44.4%), followed by other cancer-related genes (n=4, 22.2%),

telomere biology disorder-associated genes (n=4, 22.2%) and myeloid neoplasm predisposition genes (n=2, 11.1%). Mean number of mutated germline predisposition genes per one patient was 1.1. Evaluating pathogenicity based on the 2015 American College of Medical Genetics and Genomics and the Association for Molecular Pathology guideline, 3 (16.7%) variants in 2 patients, that is, *DDX41* mutation (c.1547A>G, p.Y516C), *SLX4* mutation (c.5071_5073del, p.1691_1691del) and *WRAP53* mutation (c.1565delC, p.A522Gfs*26), were classified as likely pathogenic (LP) [12]. Fifteen (83.3%) variants in 9 patients were assessed as variant of unknown significance (VUS) [12]. (Figure 2, Table 4).

4. Somatic variants

Twelve out of 17 (70.6%) patients carried somatic mutations. Nine out of 12 (75.0%) patients harbored germline mutation as well. A total of 26 somatic mutations in 19 genes were detected: 14 (53.8%) variants of 7 signaling genes (*FLT3, KIT*, *KRAS*, *ATR*, *BCR*, *MAP3K1* and *ALPK2*), 2 (7.7 %) variants of chromatin-modifying genes (*BRD4* and *NCOA3*), 3 (11.5%) variants of transcription factors (*CREBBP*, *GATA1* and *ZNF93*), 1 (3.8%) variant in cohesin complex gene (*RAD21*), 2 (7.7%) variants in spliceosome-complex genes (*SF1* and *TRA2B*) and 4 (14.8%) variants in other genes (*DDX54*, *WRAP53*, *ZNF676* and *MUC16*) (Figure 2, Table 2). *FLT3* mutations were most common (n=4, 14.8%) followed by *KRAS* (n=3, 11.1%), *KIT* (n=2, 7.4%) and *BCR* (n=2, 7.4%. Mean number of somatic variants per one patient was 1.5.

When we compared the somatic variants between Korean adult AML and pediatric AML, genes of somatic mutations were overlapped with those of adult AML in 33.3% (*FLT3*, *KRAS*, *KIT*, *RAD21*, *ATR* and *CREBBP*), while 13 genes (*BCR*, *ALPK2*, *BRD4*, *DDX54*, *GATA1*, *MAP3K1*, *MUC16*, *NCOA3*, *SF1*, *TRA2B*, *WRAP53*, *ZNF93*, and *ZNF676*) were identified only in pediatric AML (Figure 3) [13]. Meanwhile, mutations that are commonly found in adult AML such as *NPM1*, DNA methylation modifying genes (*IDH1*, *IDH2*, *TET2* and *DNMT3A*), tumor suppressor genes (*TP53* and *WT1*) were not present in children [14].

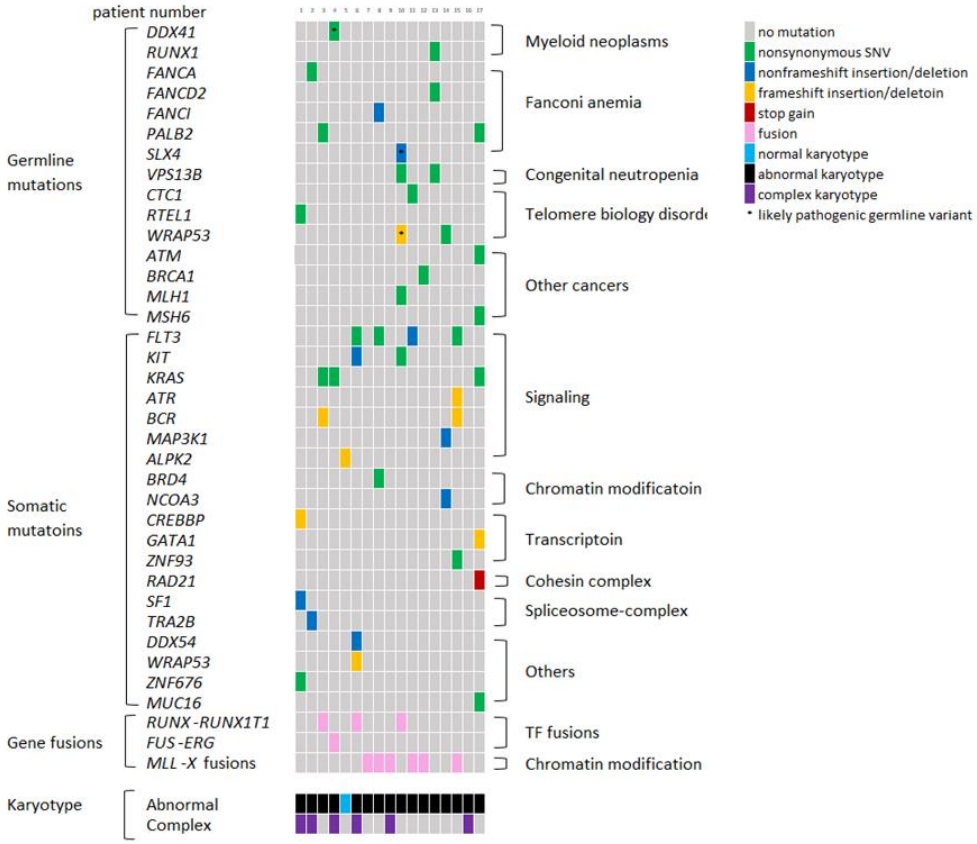

Figure 2. Germline, somatic mutations and cytogenetics of 17 pediatric AML patients

Table 2. Cytogenetic and molecular profiles of 17 pediatric AML patients

Patient number	Cytogenetics (initial)	Mutation Category	Gene	Position	Nucleotide change	Protein change	Variant type	MAF*	SIFT	PolyPhen-2 HDIV	PolyPhen-2 HVAR	MT	MA	FATHMM	CADD
1	46,XY,der(7)r(7;?)(p22q36;?),-13,+mar[17]/46,XY[3]	Germline	*RTEL1*	62309666	c.335C>G	p.P112R	missense	0.0006	T	D	D	D	M	D	23.8
		Somatic	*CREBBP*	3779211	c.5723delC	p.P1908fs	fs	0.0038	.	.	.	.	.	.	.
		Somatic	*SF1*	64534503	c.1824_1826del	p.608_609del	in-frame del	0.0078	.	.	.	.	.	.	.
		Somatic	*ZNF676*	22363617	c.902G>T	p.R301I	missense	.	T	B	B	D	L	T	1.86
2	51,XX,+6,+15,+19,der(20)t(1;20)(q25;q13.3),+21,+22[2]/51,idem,del(3)(q13.2q21)[6]/46,XX[3]	Germline	*FANCA*	89836366	c.2383A>G	p.R795G	missense	4.177E-05	T	B	B	N	M	D	13.38
		Somatic	*TRA2B*	185637260	c.445_447del	p.149_149del	in-frame del	0.0010	.	.	.	.	.	.	.

3	46,XX,t(8;21)(q22;q22)[17	Germline	*PALB2*	23625404	c.3122A>C	p.K1041	missense	1.73E-	D	D	B	D	M	T	25.8
	]/45,idem,-X[5]/46,XX[1]+					T		05							
		Somatic	*KRAS*	25398281	c.38G>A	p.G13D	missense	.	D	P	P	D	M	T	28.8
		Somatic	*BCR*	23653975	c.3142_314	p.S1048fs	fs	.	.	.	.	.	.	.	.
					3insCCGG										
4	46,XX,t(16;21)(p11.2;q22)	Germline	*DDX41*†	17693949	c.1547A>G	p.Y516C	missense	.	D	D	D	D	H	T	27.1
	[8]/47,sl,+10[9]/48,sdl,+12			9											
	[3]	Somatic	*KRAS*	25398284	c.35G>A	p.G12D	missense	0.0001	D	P	B	D	M	T	25.3
5	46,XX,16qh+†† [19]	Somatic	*ALPK2*	56246440	c.1568delA	p.K523fs	fs	.	.	.	.	.	.	.	.
6	46,XY,add(7)(q32)[7]/45,i	Somatic	*FLT3*	28592641	c.2504A>T	p.D835V	missense	.	D	D	D	D	N	D	33
	dem,-Y[18]														
	nuc	Somatic	*KIT*	55589771	c.1253_125	p.Y418de	in-frame	.	.	.	.	.	.	.	.
	ish(ETOX3,AML1X2)(ET				4insCTTCC	linsYFL	ins								
	O con AML1X1)[195/200]				T										
		Somatic	*WRAP53*	7606722	c.1565delC	p.A522fs	fs	0.0010	.	.	.	.	.	.	.
		Somatic	*DDX54*	11360189	c.1916_191	p.639_64	in-frame	.	.	.	.	.	.	.	.
				2	8del	0del	del								

7	46,XX,t(11;19)(q23;p13.3)[20]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
8	46,XX,t(9;11)(p22;q23)[9]/47,idem,+8[10]/46,XX[1]	Germline	*FANCI*	89843605	c.2698_2699insGGCAAT	p.R900delinsRQW	in-frame ins	0.0009	.	.	.	.	.	.	.
		Somatic	*FLT3*	28592623	c.2522A>T	p.N841I	missense	.	D	P	P	D	L	D	32
		Somatic	*BRD4*	15375544	c.883A>C	p.T295P	missense	.	D	D	D	D	M	T	23.4
9	47,XX,+8,del(12)(p?12p13)[11]/46,XX[9] nuc ish(MLLX2)(5'MLL sep 3'MLLX1)[51/200]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
10	45,X,-Y,t(8;21)(q22;q22)[20]	Germline	*MLH1*	37042521	c.283T>G	p.S95A	missense	0.0001	T	B	B	D	N	D	7.565
		Germline	*VPS13B*	100454723	c.3305G>A	p.S1102N	missense	0.0001	T	D	D	D	L	T	27.6
		Germline	*SLX4*†	3633178	c.5071_5073del	p.1691_1691del	in-frame del	.	.	.	.	.	.	.	.
		Germline	*WRAP53*†	7606722	c.1565delC	p.A522fs	fs	0.0011	.	.	.	.	.	.	.
		Somatic	*KIT*	55599320	c.2446G>C	p.D816H	missense	.	D	P	B	D	L	D	25.2

11	46,XX,t(11;19)(q23;p13.1)[20]	Germline	*CTC1*	8137847	c.1744C>T	p.P582S	missense	.	T	B	B	N	N	D	0.001
		Somatic	*FLT3*	28608262	c.1793_1794insCTACGTTGATTTCAGAGAATATGA	p.E598delinsDYVDFREYE	in-frame ins	.	.	.	.	.	.	.	.
12	46,XY,t(11;19)(q23;p13.3),21pstk+[14]/46,XY,21pstk+[6]	Germline	*BRCA1*	41219631	c.4927A>C	p.K1643Q	missense	0.0006	D	D	D	D	L	D	23.6
13	46,XY,?ins(1;14)(q32;q31q13),del(9)(q13q22)[19]/46,XY[2]	Germline	*FANCD2*	10116340	c.2842A>G	p.T948A	missense	0.0001	D	B	B	N	M	T	23.3
		Germline	*VPS13B*	100168893	c.2130G>C	p.Q710H	missense	.	D	B	B	D	L	T	11.03
		Germline	*RUNX1*	36259286	c.124G>C	p.G42R	missense	0.0005	T	D	D	D	L	D	24.8
14	46,XY,add(4)(p16),add(7)(p13)[17]/46,XY[3]	Germline	*WRAP53*	7606402	c.1360G>A	p.V454M	missense	0.0002	T	P	B	N	M	T	12.14
		Somatic	*NCOA3*	46279834	c.3757_3759del	p.1253_1253del	in-frame del	0.0003	.	.	.	.	.	.	.
		Somatic	*MAP3K1*	56177848	c.2821_2823del	p.941_941del	in-frame del	.	.	.	.	.	.	.	.

15	46,XX,t(9;11)(p22;q23)[13]/46,XX[9]	Somatic	*FLT3*	28592640	c.2505T>G	p.D835E	missense	.	D	D	D	D	N	D	24.2
		Somatic	*ATR*	142274740	c.2320delA	p.I774fs	fs	0.0084	.	.	.	.	.	.	.
		Somatic	*BCR*	23653975	c.3142_3143insCCGG	p.S1048fs	fs	.	.	.	.	.	.	.	.
		Somatic	*ZNF93*	20045067	c.1303G>A	p.V435I	missense	.	T	B	B	N	N	T	0.006
16	46,XY,add(11)(q23)[2]/49,idem,+6,+8,+22[7]/46,XY[11]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
17	47,XY,9qh-,+21[14]/46,XY,9qh-[6]	Germline	*MSH6*	48023107	c.532C>T	p.R178C	missense	.	T	D	B	D	L	T	27.7
		Germline	*ATM*	108142088	c.3032C>G	p.T1011R	missense	.	D	B	B	N	M	T	16.66
		Germline	*PALB2*	23641346	c.2129C>T	p.T710M	missense	8.637E-05	D	D	D	N	M	T	24.2
		Somatic	*KRAS*	25398284	c.35G>A	p.G12D	missense	0.0001	D	P	B	D	M	T	25.3
		Somatic	*RAD21*	117878960	c.9C>G	p.Y3X	stop	.	.	.	.	A	.	.	39

Somatic	*GATA1*	48649655	c.139delT	p.S47fs	fs	.	.	.	.	.	.	.	.
Somatic	*MUC16*	8999554	c.40621G>C	p.D13541H	missense	4.66E-005	T	D	D	N	L	T	12.63

Abbreviations: A., disease-causing automatic (MT); B., benign (Polyphen-2); CADD., Combined Annotation Dependent Depletion; Chr., chromosome; D., damaging (Polyphen-2); D., deleterious (SIFT, FATHMM); D., disease-causing (MT); del., deletion; FHx., family history; FATHMM., Functional Annotation Through Hidden Markov Model; fs., frameshift indel; H., predicted functional, high (MA); ins., insertion; L., predicted non-functional, low (MA); LP., likely pathogenic; M., predicted functional, medium (MA); MA., MutationAssessor; MAF., minor allele frequency; MT., Mutation Taster; N., predicted non-functional, neutral (MA); N., polymorphism (MT); N/A., not applicable; P., probably or possibly damaging (Polyphen-2); SIFT., Sorting Tolerant From Intolerant; T., tolerated (SIFT, FATHMM); VUS., variant of unknown significance

*The highest value among 1000 Genomes, ESP6500 and Exome Aggregation Consortium.

†Likely pathogenic variants according to ACMG-AMP 2015 guidelines.

†† Normal variant

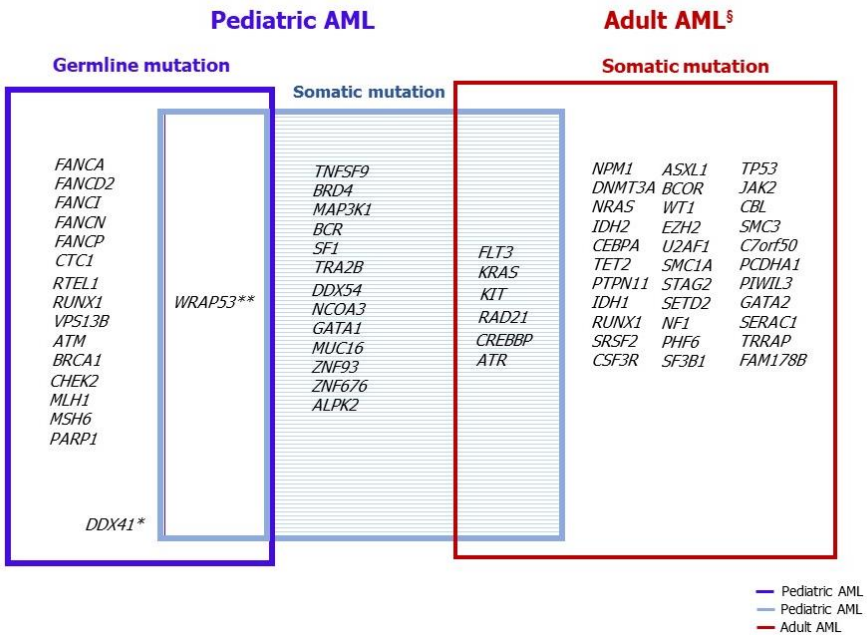

Figure 3. Germline and somatic mutations detected in 17 pediatric AML patients and comparisons with known adult-onset germline predisposition genes and Korean adult AML somatic mutations

* Late-onset germline predisposition gene [16]

***WRAP53** mutations were detected as both germline and somatic variants in different pediatric patients in our data.

§ Somatic mutations of Korean adult AML [13]

Abbreviations: AML., acute myeloid leukemia

Discussion

The prevalence of germline predisposition gene mutation in Korean pediatric AML patients was estimated to be 11.8%. When including VUS, the frequency was 58.8%. Gene fusions and somatic mutations were present in 58.8% and 70.6% of the patients, respectively. Abnormal karyotype was detected in 94.1% of patients, which is much higher than Caucasian AML (54.9% in adults and 76.1% in children) [15]. Such a difference can be attributed to ethnic difference or the degree of G-banding resolution although it was not specified in the Mrózek K et al's report.

Reportedly, the prevalence of germline mutations is 8.5% in pediatric solid tumor and 4.4% in leukemia, using whole genome and/or whole exome sequencing on 1120 children and adolescents with cancer [6]. It was reported that patients with leukemia had the lowest prevalence of germline mutation. Our study revealed higher prevalence (11.8%) of cancer susceptibility gene mutations in pediatric AML using 95 multi-gene panel. Compared to the gene panel of Zhang et al's [6], the panel of the present study additionally included congenital neutropenia-related genes (*CSF3R*, *CXCR4*, *USB1*, *VPS13B*, *GFI1*, *AP3B1*, *SLC37A4* and *RMRP*), more Fanconi anemia gene (*SLX4*), telomere biology genes (*TERC* and *CTC1*) and predisposition genes related to myeloid neoplasm (*DDX41*, *ANKRD26*, *SRP72* and *SAMD9*). As a result, we could identify germline variants in *VPS13B*, *SLX4*, *CTC1* and *DDX41* gene. Also, one of possible causes of different results in germline mutation percentage could be that Zhang et al's report included acute lymphoblastic leukemia (ALL) which consists of majority of pediatric leukemia. This might have made the prevalence

of germline mutation underestimated. Collectively, we suppose that the prevalence of germline predisposition gene mutations is especially high in AML than other solid tumor or other kinds of leukemia.

An average of 1.5 somatic variants per one patient existed in 17 pediatric AML patients, which is lower than that of Korean adult AML that is reported to be about 2.0 by whole exome sequencing [13]. Meanwhile, the mean number of coding variants per individual with pediatric AML have been reported to be approximately 3 by targeted sequencing of 39 cancer-related genes [2]. In short, the number of somatic mutations was relatively lower in our data compared to adult AML as wells as pediatric AML. Considering higher percentage of cytogenetic aberrations (94.1%) in our study, genetic alteration occurring at chromosome level might be more important in the development mechanism of pediatric AML than variants at single nucleotide level. Our results are consistent with the low prevalence of methylation or histone modifying gene mutations in childhood AML [2], though one variant of histone modifying gene (*NCOA3*) was detected in a 7-year-old M3 patient. Histone modifying gene somatic mutation might be involved in leukemogenesis of pediatric AML, although it is rare.

Some germline predisposition genes such as *ANKRD26*, *CEBPA*, *GATA2*, *DDX41* and *ETV6* are known to commonly present in adulthood. In our study, one 16-year-old child carried *DDX41* germline mutation of which presentation has been reported to range from 44 to 88 years old [16]. Although our study focused on pediatric AML, the importance of germline predisposition gene mutation in adult AML remains to be further elucidated. Further studies on adult AML would enable deeper understanding of AML and germline

mutations.

Eleven patients (64.7%) who harbored germline predisposition gene variants all had additional somatic mutations or abnormal cytogenetics (gene fusions or complex karyotype). It suggests that germline predisposition gene mutation is not enough to develop pediatric AML, which fits the “two-hit theory” of cancer development [17].

Our study has a limitation of absence of germline specimen which was replaced by BM aspirate samples at the time of remission. In Korea, access to patients’ families is difficult due to cultural emotion that people attribute abnormal children to maternal cause. However, as to our best knowledge, this is the first study to elucidate the prevalence of germline predisposition genes in pediatric AML. However, as to our best knowledge, this is the first study to elucidate the prevalence of germline predisposition gene mutations in pediatric AML.

In conclusion, prevalence of germline predisposition gene mutations in Korean pediatric AML was estimated to be approximately 11.8%, which suggests that work-up for germline mutation is necessary in pediatric AML.

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Supplementary Tables

Table S1. In-house panel of 507 genes

Genes	HGNC ID	Position	Ontology / Pathway
ABCA7	37	19p13.3	ATPase, transporter
ABCB7	48	Xq13.3	ATPase, heme transporter
ABCC1	51	16p13.11	ATPase, transporter
ABL1	76	9q34.12	Tyrosine kinase, Cell survival
ACTB	132	7p22.1	Other
ACVR2B	174	3p22.2	Tyrosine kinase
ADA	186	20q13.12	Adenosine deaminase
AK2	362	1p35.1	Adenylate kinase
AKAP13	371	15p25.3	Signaling
AKAP9	379	7q21.2	Signaling
ALMS1	428	2p13.1	Cell cycle
ALPK2	20565	18q21.31-q21.32	Serine/threonine kinase
ANKRD24	29424	19p13.3	Other
ANKRD26	29186	10p12.1	Transferase
AP3B1	566	5q14.1	Organelle biogenesis
APC	583	5q22.2	Tumor suppressor, Wnt signaling
ARID1A	11110	1p36.11	Transcription
ARID1B	18040	6q25.3	Transcription
ARID2	18037	12q12	Chromatin regulation, acetylation
ARID3A	3031	19p13.3	Transcription
ARID4B	15550	1q42.3	Transcription
ASXL1	18318	20q11.1	Chromatin modification
ASXL2	23805	2p23.3	Histone modification
ASXL3	29357	18q12.1	Transcription
ATM	795	11q22.3	DNA repair

ATR	882	3q23	Serine/threonine kinase, DNA damage sensor
ATRX	886	Xq21.1	Chromatin remodeling
B2M	914	15q21.1	Other
BARD1	952	2q35	DNA repair
BAX	959	19q13.33	Apoptosis
BCAS3	14347	17q23	Chromatin binding, histone binding
BCL10	989	1p22.3	Apoptosis, NF-KB
BCL11B	13222	14q32.2	Other
BCL2	990	20q11.21	Apoptosis
BCL2L11	994	2q13	Apoptosis
BCL6	1001	3q27.3	Transcription
BCL7A	1004	12q24.31	Other
BCL9	1008	1q21.2	Wnt signaling
BCOR	20893	Xp11.14	Transcription
BCORL1	25657	Xq26.1	Transcription
BCR	1014	22q11.23	Serine/threonine kinase
BIRC3	591	11q22.2	Apoptosis, Signaling
BLM	1058	15q26.1	Helicase, ATPase
BLNK	14211	10q24.1	Other
BLOC1S6	8549	15q21.1	Intracellular vesicle trafficking
BMPR1A	1076	10q23.2	Serine/threonine kinase
BRAF	1097	7q34	Serine/threonine kinase
BRCA1	1100	17q21.31	DNA repair
BRCA2	1101	13q13.1	DNA repair
BRCC3	24185	Xq28	DNA repair
BRD2	1103	6p21.3	Transcription
BRD4	13575	19p13.1	Other
BRD7	14310	16q12.1	Transcription
BRINP3	22393	1q31.1	Other
BRIP1	20473	17q23.2	Nucleic acid binding
BRPF1	14255	3p25.3	Chromatin organization
BTG1	1130	12q21.33	Cell proliferation

BTG2	1131	1q32.1	Cell proliferation
BTG3	1132	21q21.1	Cell proliferation
BTK	1133	Xq22.1	Protein kinase
BTLA	21087	3q13.2	Other
BUB1	1148	2q13	Cell cycle
CACNA1E	1397	1q32.1	Other
CALR	1455	19p13.13	Other
CARD11	16939	19p13.13	Signaling
CARD6	16394	5p13.1	Signaling
CASP10	1500	19p13.13	Apoptosis
CASP8	1509	2q33.1	Apoptosis
CBL	1541	11q23.3	Signaling
CBLB	1542	3q13.11	Other
CBLC	15961	19q13.32	Other
CBX5	1555	12q13.13	Other
CBX7	1557	22q13.1	Chromatin binding
CCDC80	30649	3q13.2	Other
CCND1	1582	11q13.3	Cell cycle
CCND3	1585	6p21.1	Cell cycle
CD200	7203	3q13.2	Other
CD27	11922	3q13.2	Apoptosis
CD36	1663	7q21.11	Other
CD3D	1673	11q23.3	Signaling
CD3E	1674	11q23.3	Signaling
CD40LG	11935	Xq26.3	Signaling
CD58	1688	1p13.1	Signaling
CD70	11937	19p13.3	Signaling
CD79A	1698	19q13.2	Signaling
CD79B	1699	17q23.3	Signaling
CDC73	16783	1q31.2	Transcription, Post-transcription
CDH1	1748	16q22.1	Other
CDH23	13733	10q22.1	Other
CDKN2A	1787	9p21.3	Cell cycle

CDKN2B	1788	9p21.3	Cell cycle
CDKN3	1791	14q22.2	Cell cycle
CEBPA	1833	19q13.1	Transcription
CELSR2	3231	1p13.3	Signaling
CEP164	29182	11q23.3	Cell cycle
CHD1	1915	5q15-q21.1	Chromatin regulation / acetylation
CHD2	1917	15q26.1	Chromatin regulation / acetylation
CHD8	20153	14q11.2	Transcription / Chromatin remodeling
CHEK2	16627	22q12.1	Cell cycle
CHRNA3	1957	15q25.1	Other
CHRNA5	1959	15q25.1	Other
CHRNB4	1964	15q25.1	Other
CIITA	7067	16p13.13	Other
CMYA5	14305	5q14.1	Other
CNOT1	7877	16q21	Other
COL4A2	2203	13q34	Other
COL6A3	2213	2q37.3	Other
CPNE3	2316	8q21.3	Other
CREBBP	2348	16p13.3	Transcription
CRLF2	14281	Xp22.3	Cytokine receptor
CSF1R	2433	5q32	Hematopoietic stem cell survival, proliferation and differentiation
CSF3R	2439	1p34.3	Cytokine receptor
CSTF2T	17086	10q21.1	Splicing
CTC1	26169	17p13.1	Telomere
CTCF	13723	16q22.1	Transcription
CTSS	2545	1q21.3	Other
CUL9	15982	6p21.1	Other
CUX1	2557	7q22.1	Gene expression, cell cycle
CXCR4	2561	2q22.1	Signaling
CYLD	2584	16q12.1	Other
DAP3	2673	1q22	Other
DCLK1	2700	13q13.3	Protein kinase

DCLRE1C	17642	10p13	DNA repair
DDX1	2734	2p24.3	Splicing, Chromatin binding
DDX23	17347	12q13.12	Splicing
DDX3X	2745	Xp11.4	Splicing
DDX41	18674	5q35.3	Splicing
DDX54	20084	12q24.13	Splicing
DHX29	15815	5q11.2	Translation, Chromatin regulation / acetylation
DHX58	29517	5q11.2	Other
DIS3	20604	13q21.33	Other
DKC1	2890	Xq28	Telomerase stabilization
DKK2	2892	4q25	Notch and Wnt signaling
DLEU1	13747	13q14.2-q14.3	Tumor suppressor
DLEU2	13748	13q14.2	Tumor suppressor
DMD	2928	Xp21.2-p21.1	Other
DNAH9	2953	17p12	ATPase
DNMT1	2976	19p13.2	DNA methylation
DNMT3A	2978	2p23	DNA methylation
DNMT3B	2979	20q11.21	DNA methylation
DST	1090	6p12.1	Other
DYRK4	3095	6p12.1	Tyrosine kinase
EBF1	3126	5q33.3	Transcription
ECT2L	21118	6q24.1	Other
EED	3188	11q14.2	Histone methyltransferase
EEF1E1	3212	6p24.3	Other
EGFR	3236	11q14.2	Protein kinase
EGR2	3239	10q21.3	Transcription
ELANE	3309	19p13.3	Other
EP300	3373	22q13.2	Histone acetyltransferase
EPHA2	3386	1p36.13	Tyrosine kinase
EPHA3	3387	3p11.1	Tyrosine kinase

EPHA7	3390	6q16.1	Tyrosine kinase
ERBB2	3430	17q12	Tyrosine kinase
ERCC4	3436	16p13.12	DNA repair
ERCC6	3438	16p13.12	DNA repair
ETS1	3488	11q24.3	Transcription
ETV3	3492	1q23.1	Transcription
ETV6	3495	12p13.2	Transcription
EZH2	3527	7q36.1	Chromatin modification
FANCA	3582	16q24.3	DNA repair
FANCB	3583	Xp22.2	DNA repair
FANCC	3584	9q22.32	DNA repair
FANCD2	3585	3p25.3	DNA repair
FANCE	3586	6p21.31	DNA repair
FANCF	3587	11p14.3	DNA repair
FANCG	3588	9p13.3	DNA repair
FANCI	25568	15q26.1	DNA repair
FANCL	20748	2p16.1	DNA repair
FANCM	23168	14q21.2	DNA repair
FAS	11920	10q23.31	Apoptosis
FASLG	11936	1q24.3	Apoptosis
FAT4	23109	4q28.1	Other
FBXO11	13590	2p16.3	p53 pathway
FBXW7	16712	4q31.3	NOTCH1 signaling
FGFR2	3689	10q26.13	Tyrosine kinase
FLG	3748	1q21.3	Other
FLT3	3765	13q12	Tyrosine kinase, Hematopoiesis
FOXN1	12765	17q11.2	Transcription
FOXO1	3819	13q14.11	Transcription
FOXP3	6106	Xp11.23	Transcription
FYB1	4036	5p13.1	Other
G6PC3	24861	17q21.31	Other
G6PD	4057	Xq28	Other
GATA1	4170	Xp11.23	Transcription

GATA2	4171	3q21.3	Transcription
GATA3	4172	10p14	Transcription
GFI1	4237	1p22.1	Transcription
GLI1	4317	12q13.3	Transcription
GNA13	4381	17q24.1	Signaling
GNAS	4392	20q13.32	Signaling
GNB1	4396	1p36.33	Signaling
GRK2	289	11q13.2	Signaling
HAX1	16915	1q21.3	Other
HCK	4840	20q11.21	Tyrosine kinase
HDAC2	4853	6q21	Histone deacetylase
HDAC3	4854	5q31.3	Histone deacetylase
HDAC7	14067	12q13.11	Histone deacetylase
HEATR1	25517	1q43	rRNA processing
HIST1H1E	4718	6p22.2	Other
HNRNPK	5044	9q21.32	Other
HRAS	5173	11p15.5	Signaling
HUWE1	30892	Xp11.22	Apoptosis
IDH1	5382	2q33.3	DNA methylation
IDH2	5383	15q26.1	DNA methylation
IKZF1	13176	7p13	Transcription
IKZF2	13177	15q26.1	Transcription
IKZF3	13178	17q12-q21.1	Transcription
IL2RG	6010	Xq13.1	Signaling
IL7R	6024	5p13.2	Cytokine receptor
IRAK1	6112	Xq28	Serine/threonine kinase
IRF1	6116	5q31.1	Transcription
IRF4	6119	6p25.3	Transcription
IRF8	5358	16q24.1	Transcription
ITK	6171	5q33.3	Immune response
ITPKB	6179	1q42.12	Signaling
JAK1	6190	1p31.3	Tyrosine kinase
JAK2	6192	9p24.1	Tyrosine kinase

JAK3	6193	19p13.11	Tyrosine kinase
JMJD1C	12313	10q21.3	Histone demethylation
KDM2B	13610	10q21.3	Histone demethylation
KDM3B	1337	5q31.2	Histone demethylation
KDM4C	17071	9p24.1	Histone demethylation
KDM6A	12637	Xp11.3	Histone demethylation
KDM6B	29012	17p13.1	Histone demethylation
KIAA0355	29016	19q13.11	Other
KIF20B	7212	10q23.31	ATPase
KIT	6342	4q12	Cell survival, Proliferation
KLHL6	18653	3q27.1	Other
KLK3	6364	19q13.33	Other
KMT2A	7132	11q23.3	Transcription
KMT2B	15840	19q13.12	Transcription
KMT2C	13726	7q36.1	Histone methyltransferase
KMT2D	7133	12q13.12	Histone methyltransferase
KRAS	6407	12q13.12	GTPase, Cell proliferation
LAMB4	6491	7q31.1	Other
LAMTOR2	29796	1q22	Other
LEF1	6551	4q25	Transcription, Wnt signaling
LIG4	6601	13q33.3	DNA repair
LMO2	6642	11p13	Stem cell differentiation
LRP1B	6693	2q22.1-q22.2	Other
LRRK1	18608	15q26.3	Protein kinase
LSP1	6707	15q26.3	NF-KB
LUC7L2	21608	7q34	Other
LYST	1968	1q42.3	Other
MAGT1	28880	Xq21.1	Transporter
MALT1	6819	18q21.32	NF-KB
MAP3K1	6848	5q11.2	Apoptosis, Signaling
MAP3K14	6853	17q21.31	Apoptosis, Signaling
MAP4K1	6863	19q13.1-	Serine/threonine kinase

		q13.4	
MAPK1	6871	22q11.22	Tyrosine kinase
MDM2	6973	12q15	Apoptosis, Signaling
MED12	11957	Xq13.1	Transcription
MEF2B	6995	19p13.11	Transcription
MEF2C	6996	5q14.3	Transcription
MET	7029	7q31	Tyrosine kinase
METTL3	17563	14q11.2	Splicing
MIR155	31542	21q21.3	Other
MKI67	7107	10q26.2	Cell proliferation
MLH1	7127	10q26.2	DNA repair
MPDZ	7208	9p23	Other
MPL	7217	1p34.2	Signaling receptor, Hematopoietic stem cell differentiation
MSH2	7325	2p21-p16.3	DNA repair
MSH6	7329	2p16.3	DNA repair
MSMB	7372	10q11.22	Other
MST1R	7381	3p21.31	Tyrosine kinase
MTA2	7411	11q12.3	Transcription
MTOR	3942	1p36.22	Serine/threonine kinase
MUC16	15582	19p13.2	Other
MUTYH	7527	1p34.1	DNA repair
MXRA5	7539	Xp22.33	Other
MYB	7545	6q23.3	Transcription
MYC	7553	8q24.21	Apoptosis, Signaling
MYCN	7559	2p24.3	Transcription, Apoptosis
MYD88	7562	3p22.2	Apoptosis, Signaling
MYLK2	16243	20q11.21	Other
MYO3A	7601	10p12.1	Other
NBN	7652	8q21.3	DNA repair
NF1	7765	17q11.2	RAS pathway
NFKB2	7795	10q24.32	Transcription
NFKBIA	7797	14q13.2	Apoptosis, Signaling

NFKBIE	7799	9q34.3	Apoptosis, Signaling
NHEJ1	25737	2q35	DNA repair
NHP2	14377	5q35.3	Ribosome biogenesis, Cell cycle
NCOA3	7670	20q13.12	Histone acetyltransferase
NOP10	14378	15q14	Ribosome biogenesis, Telomere maintenance
NOTCH1	7881	9q34.3	Notch signaling pathway
NOTCH2	7882	1p12	Notch signaling pathway
NOTCH3	7883	19p13.12	Hematopoietic stem cell differentiation
NPM1	7910	5q35	Gene expression, Cell cycle
NR3C1	7978	5q31.3	Transcription
NRAS	7989	1p13.2	GTPase
NRK	25391	Xq22.3	Tyrosine kinase
NUP214	8064	9q34.13	Transporter
OBSCN	15719	1q42.13	Other
OR6K3	15030	1q23.1	Other
ORAI1	25896	12q24.31	Other
P2RY8	15524	Xp22.33	G protein-coupled receptor
PALB2	26144	16p12.2	DNA repair
PARD3	16051	10p11.22-p11.21	Hippo signaling pathway
PARP1	270	1q42.12	DNA repair
PASD1	20686	Xq28	Transcription
PASK	17270	2q37.3	Serine/threonine kinase
PAX5	8619	9p13.2	Transcription
PBRM1	30064	3p21.1	Chromatin remodeling
PCLO	13406	7q21.11	Other
PDGFC	8801	4q32.1	Cell proliferation, Cell migration
PDGFRA	8803	4q12	Cell proliferation
PDGFRB	8804	5q32	Cell proliferation
PDS5B	20418	13q13.1	Cohesin
PDSS2	23041	6q21	Other
PHF6	18145	Xq26.2	Transcription

PHLPP1	20610	18q21.33	Apoptosis, Tumor suppressor
PIGA	8957	Xp22.2	Other
PIGT	14938	20q13.12	Other
PIK3R1	8979	5q13.1	Signaling
PIM1	8986	6p21.2	Signaling, Cell proliferation and survival
PKD1L2	27175	16q23.2	Other
PLCG2	9066	16q24.1	Signaling
PLEKHG5	29105	1p36.31	NF-KB pathway
PLRG1	9089	4q31.3	Splicing
PML	9113	15q24.1	Transcription, Tumor suppressor
PMS2	9122	7p22.1	DNA repair
PNP	7892	14q11.2	Other
POLG	9179	15q25	Mitochondrial DNA replication
POLR2A	9187	17p13.1	Transcription
POSTN	16953	13q13.3	Cancer stem cell maintenance, Metastasis
POT1	17284	7q31.33	Telomere maintenance
POU2F2	9213	19q13.2	Transcription
PRDM1	9346	6q21	Other
PRDM16	14000	1p36.32	Transcription
PRDM9	13994	5p14.2	Histone methyltransferase
PRF1	9360	10q22.1	Apoptosis, Signaling
PRKCG	9402	19q13.42	Tyrosine kinase
PRKD3	9408	2p22.2	Serine/threonine kinase
PRKDC	9413	8q11.21	DNA repair
PRPF3	17348	1q21.2	Splicing
PRPF40B	25031	12q13.12	Splicing
PRPF8	17340	17p13.3	Splicing
PRSS1	9475	7q34	Other
PTEN	9588	10q23.31	Tumor suppressor
PTPN11	9644	12q24.1	Signaling
PTPN14	9647	1q32.3-q41	Signaling
PTPRC	9666	1q31.3-	Signaling

		q32.1	
PTPRT	9682	20q12-q13.11	Signaling
PWWP3A	29641	19p13.2	DNA repair
RAB27A	9766	15q21.3	GTPase, Signaling
RAC2	9802	22q13.1	GTPase
RAD21	9811	8q24.11	Cohesin, DNA repair
RAD51C	9820	17q22	DNA repair
RAG1	9831	11p12	Other
RAG2	9832	11p13	Other
RAPGEF1	4568	9q34.13	Signaling
RARA	9864	17q21.2	Other
RB1	9984	13q14.2	Cell cycle
RBBP4	9887	1p35.1	Chromatin assembly / remodeling, Histone deacetylase
RBMX	9910	Xq26.3	Splicing
REL	9954	2p16.1	Transcription
RELN	9957	7q22.1	Cell-cell interaction
RFTN1	30278	3p24.3	Other
RFX7	25777	15q21.3	Transcription
RFXAP	9988	13q13.3	Other
RIPK1	10019	6p25.2	Serine/threonine kinase
RMRP	10031	9p13.3	Other
RNF213	14539	17q25.3	Protein-protein interaction
RPL11	10301	1p36.11	Ribosome structure
RPL27	10328	17q21	Ribosome structure
RPL35A	10345	3q29	Ribosome structure
RPL5	10360	1p22.1	Ribosome structure
RPN1	10381	3q21.3	Other
RPS10	10383	6p21.31	Ribosome structure
RPS14	10387	5q33.1	Ribosome structure
RPS17	10397	15q25.2	Ribosome structure
RPS19	10402	19q13.2	Ribosome structure

RPS24	10411	10q22.3	Ribosome structure
RPS26	10414	10q22.3	Ribosome structure
RPS27	10416	1q21.3	Ribosome structure
RPS6KA6	10435	Xq21.1	Serine/threonine kinase
RPS7	10440	2p25.3	Ribosome structure
RTEL1	15888	20q13.33	Telomere-length regulation
RUNX1	10471	21q22.3	Transcription
SAMD9	1348	7q21.2	Cell proliferation, Apoptosis
SAMHD1	15925	20q11.23	Other
SAP130	29813	2q14.3	Histone deacetylase
SBDS	19440	7q11.21	Ribosome biogenesis
SCML2	10581	Xp22.13	Transcription
SCRIB	30377	8q24.3	Hippo signaling pathway
SENP6	20944	Xp22.13	Other
SETBP1	15573	18q12.3	Other
SETD2	18420	3p21.31	Histone methyltransferase
SF1	12950	11q13.1	Splicing
SF3A1	10765	22q12.2	Splicing
SF3B1	10768	2q33.1	Splicing
SGK1	10810	6q23.2	Serine/threonine kinase
SH2B3	29605	12q21.12	Hematopoietic stem cell differentiation
SH2D1A	10820	Xq25	Signaling
SLC37A4	4061	11q23.3	Transporter
SLC7A7	11065	14q11.2	Transporter
SLITRK6	23503	13q31.1	Other
SLX4	23845	16p13.3	DNA repair
SMAD1	6767	4q31.21	Signaling
SMAD4	6770	18q21.2	Signaling
SMAD7	6773	18q21.1	Signaling
SMARCA2	11098	9p24.3	Transcription
SMARCA4	11100	19p13.2	Transcription
SMARCB1	11103	22q11.23	Tumor suppressor
SMC1A	11111	Xp11.22	Cohesin

SMC3	2468	10q25.2	Cohesin
SMC5	20465	9q21.12	DNA repair
SMG1	30045	16p12.3	Serine/threonine kinase
SNRNP200	30859	2q11.2	Splicing
SOCS1	19383	16p13.13	Signaling
SOS1	11187	2p22.1	RAS pathway
SPEN	17575	1p36.21-p36.13	Transcription
SPINK1	11244	5q32	Other
SRP72	11303	4q12	Signaling
SRRM2	16639	16p13.3	Splicing
SRSF2	10783	17q25.1	Splicing
SRSF6	10788	20q13.11	Splicing
SRSF8	16988	11q21	Splicing
STAG2	11355	Xq25	Cohesin
STAT3	11364	17q21.2	Signaling, Transcription
STAT5B	11367	17q21.2	Signaling, Transcription
STAT6	11368	12q13	Signaling, Transcription
STIM1	11386	11p15.4	Other
STK11	11389	19p13.3	Tumor suppressor
STK32A	28317	5q32	Serine/threonine kinase
STK33	14568	11p15.4	Serine/threonine kinase
STK36	17209	2q35	Serine/threonine kinase
STRIP2	22209	7q32.1	Other
STX11	11429	6q24.2	Protein transport
STXBP2	11445	19p13.2	Intracellular trafficking
SUDS3	39545	12q24.23	Other
SUMO2	11125	17q25	Other
SUPT5H	11469	19q13.2	Other
SUZ12	17101	17q11.2	Other
SYK	11491	9q22.2	Tyrosine kinase
SYNE1	17089	6q25.2	Other
TAF1	11535	Xq13.1	Transcription

TAL1	11556	1p33	Transcription, Hematopoietic differentiation
TAZ	11577	Xq28	Other
TBL1XR1	29529	3q26.32	Transcription
TBX1	11592	22q11.21	Transcription
TCF12	11623	15q21.3	Transcription
TCF4	11634	18q21.2	Transcription
TENT4B	30758	16q12.1	mRNA decay
TENT5C	24712	1p12	mRNA stability
TERC	11727	3q26.2	Telomere maintenance
TERT	11730	5p15.33	Telomere maintenance
TET1	29484	10q21.3	DNA methylation
TET2	25941	4q24	DNA methylation
TGFB2	11773	3p24.1	Protein kinase
TGM6	16255	20p13	Other
TGM7	30790	15q15.2	Other
THPO	11795	3q27.1	Other
THRB	11799	3p24.2	Other
TINF2	11824	14q12	Telomere maintenance
TMEM30A	16667	6q14.1	TNF signaling
TNFAIP3	11896	6q23.3	TNF signaling
TNFRSF14	11912	1p36.32	Cytokine signaling
TNFSF9	11939	19p13.3	Cytokine signaling
TOX3	11972	16q12.1	Other
TP53	11998	17p13.1	Cell cycle, Apoptosis
TRA2B	10781	3q27.2	Splicing
TRAF3	12033	14q32.32	TNF signaling
TRIO	12303	5p15.2	Transferase
TTBK1	19140	6p21.1	Transferase
TTC27	25986	2p22.3	Other
TTN	12403	2q31.2	Other
TYK2	12440	19p13.2	Signaling
TYW1	25598	7q11.21	Other

U2AF1	12453	21q22.3	Splicing
U2AF1L4	23020	19q13.13	Splicing
U2AF2	23156	19q13.42	Splicing
UBA3	12470	3p14.1	Other
UBE2A	12472	Xq24	Other
UGGT1	15663	2q14.3	Other
ULK4	15784	3p22.1	Serine/threonine kinase
UNC13B	12566	9p13.3	Vesicle maturation
UNC13D	23147	17q25.3	Vesicle maturation
UNC5C	12569	4q22.3	Netrin receptor
UNC5D	18634	8p12	Netrin receptor, cell-cell adhesion
USB1	25792	16q21	Nuclease
VHL	12687	3p25.3	Other
VPS13A	1908	9q21.2	Protein cycling
VPS13B	2183	8q22.2	Protein sorting
VPS45	14579	1q21.2	Protein trafficking
WAC	17327	10p12.1	Protein ubiquitination
WAPAL	23293	10q23.2	Cohesin
WAS	12731	Xp11.23	Signaling
WEE1	12761	11p15.4	Cell cycle
WIPF1	12736	2q31.1	Other
WNK3	14543	Xp11.22	Serine/threonine kinase
WNK4	14544	17q21.2	Serine/threonine kinase
WRAP53	25522	17p13.1	Telomere maintenance
WT1	12796	11p13	Transcription
XIAP	592	Xq25	Apoptosis
XPO1	12825	2p15	Protein transport
ZAP70	12858	2q11.2	Immune response
ZBTB33	16682	Xq24	Transcription
ZBTB7B	18668	1q21.3	Transcription
ZFHX3	777	16q22.2-q22.3	Transcription
ZMYM3	13054	Xq13.1	Other

ZNF93	13169	19p12	Transcription
ZNF608	29238	5q23.2	Transcription
ZNF708	12945	19p12	Transcription
ZRSR2	23109	Xp22.1	Splicing

Table S2. 95 genes selected for germ line mutation analysis

HGNC ID	Gene	Location	Familial syndrome	PMID	Inheritance
29186	*ANKRD26*	10p12.1	*ANKRD26*-related thrombocytopenia	29927566	Autosomal dominant
566	*AP3B1*	5q14.1	Hermansky-Pudlak Syndrome	20301464	Autosomal recessive
583	*APC*	5q22.2	Familial adenomatous polyposis	11135435	Autosomal dominant
18318	*ASXL1*	20q11.1	Bohring-Opitz syndrome	21706002	Autosomal dominant
795	*ATM*	11q22.3	Ataxia-telangiectasia	7792600	Autosomal recessive
882	*ATR*	3q23	Cutaneous telangiectasia and cancer syndrome	22341969	Autosomal dominant
952	*BARD1*	2q35	Familial cancer of breast	15342711	Autosomal dominant
1058	*BLM*	15q26.1	Bloom syndrome	5770175	Autosomal recessive
1076	*BMPR1A*	10q23.2	Juvenile polyposis syndrome	11381269	Autosomal dominant
1100	*BRCA1*	17q21.31	Familial cancer of breast	17033622	Autosomal dominant
1101	*BRCA2*	13q13.1	Fanconi anemia, complementation group D1	12065746	Autosomal recessive
			Hereditary breast and ovarian cancer syndrome	8589730	Autosomal dominant
20743	*BRIP1*	17q23.2	Fanconi anemia, complementation group J	16116424	Autosomal recessive
			Hereditary breast and ovarian cancer syndrome	11301010	Autosomal dominant
16783	*CDC73*	1q31.2	Hyperparathyroidism-jaw tumor syndrome	12434154	Autosomal dominant

1748	*CDH1*	16q22.1	Hereditary diffuse gastric cancer	9537325	Autosomal dominant
			Familial cancer of breast	17660459	Autosomal dominant
1787	*CDKN2A*	9p21.3	Pancreatic cancer/melanoma syndrome	7666917	Autosomal dominant
1833	*CEBPA*	19q13.1	CEBPA-Associated Familial Acute Myeloid Leukemia	15575056	Autosomal dominant
16627	*CHEK2*	22q12.1	Li-Fraumeni syndrome	10617473	Autosomal dominant
2348	*CREBBP*	16p13.3	Rubinstein-Taybi syndrome	9294190	Autosomal dominant
2439	*CSF3R*	1p34.3	Severe congenital neutropenia	24753537	Autosomal recessive
26169	*CTC1*	17p13.1	Cerebroretinal microangiopathy with calcifications and cysts	22267198	Autosomal recessive
2561	*CXCR4*	2q22.1	WHIM syndrome	12692554	Autosomal dominant
18674	*DDX41*	5q35.3	Familial myeloproliferative/lymphoproliferative neoplasms	25920683	Autosomal dominant
2890	*DKC1*	Xq28	Dyskeratosis congenita	10364516	X-linked recessive
3309	*ELANE*	19p13.3	Severe congenital neutropenia, Cyclic neutropenia	11001877	Autosomal dominant
3373	*EP300*	22q13.2	Rubinstein-Taybi syndrome	15706485	Autosomal dominant
3436	*ERCC4*	16p13.12	Fanconi anemia, complementation group Q	23623389	Autosomal recessive

			Xeroderma pigmentosum, type F/Cockayne syndrome	8797827	Autosomal recessive
3495	*ETV6*	12p13.2	Thrombocytopenia 5	25581430	Autosomal dominant
3527	*EZH2*	7q36.1	Weaver syndrome	22177091	Autosomal dominant
3582	*FANCA*	16q24.3	Fanconi anemia, complementation group A	8755924	Autosomal recessive
3583	*FANCB*	Xp22.2	Fanconi anemia, complementation group B	15502827	X-linked recessive
3584	*FANCC*	9q22.32	Fanconi anemia, complementation group C	1574115	Autosomal recessive
3585	*FANCD2*	3p25.3	Fanconi anemia, complementation group D2	1303234	Autosomal recessive
3586	*FANCE*	6p21.31	Fanconi anemia, complementation group E	11001585	Autosomal recessive
3588	*FANCG*	9p13.3	Fanconi anemia, complementation group G	9806548	Autosomal recessive
25568	*FANCI*	15q26.1	Fanconi anemia, complementation group I	17452773	Autosomal recessive
20748	*FANCL*	2p16.1	Fanconi anemia, complementation group L	12973351	Autosomal recessive
23168	*FANCM*	14q21.2	Familial cancer of breast	28837162	
24861	*G6PC3*	17q21.31	Severe congenital neutropenia	19118303	Autosomal recessive
95661	*GATA1*	Xp11.23	Familial dyserythropoietic anaemia and thrombocytopenia	10700180]	X-linked recessive
			Diamond–Blackfan Anemia	24453067	
4171	*GATA2*	3q21.3	Familial myelodysplastic syndrome and acute myeloid leukemia	21892162	Autosomal dominant

4237	*GFI1*	1p22.1	Severe congenital neutropenia	12778173	Autosomal dominant
16915	*HAX1*	1q21.3	Severe congenital neutropenia	17187068	Autosomal recessive
5173	*HRAS*	11p15.5	Costello syndrome	16170316	Autosomal dominant
6407	*KRAS*	12p12.1	Noonan syndrome	16474405	Autosomal dominant
6601	*LIG4*	13q33.3	LIG4 syndrome	11779494	Autosomal recessive
7029	*MET*	7q31.2	Papillary renal cell carcinoma	9140397	
7127	*MLH1*	3p22.2	Hereditary non-polyposis colon cancer	7903889	
7325	*MSH2*	2p21-p16	Hereditary nonpolyposis colon cancer, type1	8252616	Autosomal dominant
7329	*MSH6*	2p16.3	Hereditary nonpolyposis colon cancer, type5	7604266	Autosomal dominant
7527	*MUTYH*	1p34.1	Familial adenomatous polyposis 2	12393807	Autosomal recessive
7652	*NBN*	8q21.3	Nijmegen breakage syndrome	9590180	Autosomal recessive
7765	*NF1*	17q11.2	Neurofibromatosis, type 1	2127432	Autosomal dominant
			Juvenile myelomonocytic leukemia	9639526	Autosomal dominant
14377	*NHP2*	5q35.3	Dyskeratosis congenital-2	18523010	Autosomal recessive
14378	*NOP10*	15q14	Dyskeratosis congenital-1	17507419	Autosomal recessive
26144	*PALB2*	16p12.2	Fanconi Anemia, Complementation Group N	17200672	
			Familial cancer of breast	17200668	Autosomal dominant
8619	*PAX5*	9p13.2	B-cell acute lymphoblastic leukemia-3	24013638	

9122	*PMS2*	7p22.1	Hereditary nonpolyposis colorectal cancer, type 4	8072530	
9413	*PRKDC*	8q11.21	Immunodeficiency 26	19075392	Autosomal recessive
9588	*PTEN*	10q23.31	Cowden syndrome 1	17526800	Autosomal dominant
9644	*PTPN11*	12q24.13	Noonan syndrome	11704759	Autosomal dominant
9820	*RAD51C*	17q22	Fanconi anemia, complementation group O	20400963	Autosomal recessive
			Familial Breast-Ovarian Cancer	20400964	
9884	*RB1*	13q14.2	Retinoblastoma	2895471	Autosomal dominant
10031	*RMRP*	9p13.3	Cartilage-hair hypoplasia	11207361	Autosomal recessive
10360	*RPL5*	1p22.1	Diamond-Blackfan anemia 6	19061985	Autosomal dominant
10440	*RPS7*	2p25.3	Diamond-Blackfan anemia 8	19061985	Autosomal dominant
10298	*RPS10*	Xq28	X-linked syndromic mental retardation-35	25316788	X-linked recessive
10301	*RPL11*	1p36.11	Diamond-Blackfan anemia 7	19061985	Autosomal dominant
10397	*RPS17*	15q25.2	Diamond-Blackfan anemia 4	17647292	Autosomal dominant
10402	*RPS19*	17q12	Diamond-Blackfan anemia 1	9988267	Autosomal dominant
10411	*RPS24*	10q22.3	Diamond-blackfan anemia 3	17186470	Autosomal dominant
10414	*RPS26*	12q13.2	Diamond-Blackfan anemia 10	20116044	Autosomal dominant
10345	*RPL35A*	3q29	Diamond-Blackfan anemia 5	18535205	Autosomal dominant
15888	*RTEL1*	20q13.33	Autosomal recessive dyskeratosis congenita-5	23453664	Autosomal recessive

			Autosomal dominant dyskeratosis congenita-4	23329068	Autosomal dominant
10471	*RUNX1*	21q22.12	Familial platelet disorder with associated myeloid malignancy	11830488	Autosomal dominant
11100	*SAMARCA4*	19p13.2	rhabdoid tumor predisposition syndrome-2	20137775	Autosomal dominant
1348	*SAMD9*	7q21.2	MIRAGE syndrome	27182967	Autosomal dominant
			Inherited predisposition to myeloid malignancies	29535429	Autosomal dominant
19440	*SBDS*	7q11.21	Shwachman-Diamond syndrome	12496757	Autosomal recessive
15573	*SETBP1*	18q12.3	Schinzel-Giedion midface retraction syndrome	20436468	Autosomal dominant
4061	*SLC37A4*	11q23.3	Glycogen storage disease	9675154	Autosomal recessive
23845	*SLX4*	16p13.3	Fanconi anemia, complementation group P	21240277	Autosomal recessive
6770	*SMAD4*	18q21.2	Juvenile polyposis syndrome	9545410	Autosomal dominant
11103	*SMARCB1*	22q11.23	Rhabdoid tumor predisposition syndrome 1	10521299	Autosomal dominant
11187	*SOS1*	2p22.1	Noonan syndrome 4	17143285	Autosomal dominant
11303	*SRP72*	4q12	Bone marrow failure syndrome 1	22541560	Autosomal dominant
11389	*STK11*	19p13.3	Peutz-Jeghers syndrome	9425897	Autosomal dominant
11727	*TERC*	3q26.2	Autosomal dominant dyskeratosis congenita-1	11574891	Autosomal dominant
11730	*TERT*	5p15.33	Autosomal dominant dyskeratosis congenita-2	16247010	Autosomal dominant

			Autosomal recessive dyskeratosis congenita-4	17785587	Autosomal recessive
11824	*TINF2*	14q12	Autosomal dominant dyskeratosis congenita-3	18252230	Autosomal dominant
11998	*TP53*	17p13.3	Li-Fraumeni syndrome	19556618	Autosomal dominant
25792	*USB1*	16q21	Poikiloderma with neutropenia	20004881	Autosomal recessive
12687	*VHL*	3p25.3	von Hippel-Lindau syndrome	8493574	Autosomal dominant
2183	*VPS13B*	8q22.2	Cohen syndrome	12730828	Autosomal recessive
12731	*WAS*	Xp11.23	Severe congenital neutropenia	19006568	X-linked recessive
25522	*WRAP53*	17p13.1	Autosomal recessive dyskeratosis congenita-3	21205863	Autosomal recessive
12796	*WT1*	11p13	Wilms tumor, type 1	15150775	Autosomal dominant

국문 초록

서론: 소아 급성골수구성백혈병은 성인에서와 달리 유전성 소인 돌연변이 여부가 질병의 발생에 큰 역할을 한다. 유전성 소인 돌연변이가 있는 급성골수구성백혈병 환자는 치료가 달라질 수 있고, 유전 상담이 필요할 수 있어, 그 중요성이 점차 커지고 있다. 본 연구에서는 한국인 소아 급성 골수구성백혈병 환자에서 유전성 소인의 빈도를 추정하고자 하였다.

방법: 소아 급성골수구성백혈병으로 진단받은 17 명의 환자를 대상으로 시행된 후향적 연구이다. 17 개의 초진 골수 흡인 검체 및 짝지어진 16 개의 관해 당시 골수 흡인 검체와 타액 검체 1 개가 수집되었다. 총 34 개의 검체를 대상으로 염색체, 형광동소보합법 및 507 개의 유전자로 구성된 패널을 이용해 차세대 염기서열 분석을 시행하였다.

결과: 11 명의 환자에서 총 18 개의 유전성 소인 돌연변이가 발견되었다. 2 명의 환자에서 3 가지의 병적일 것으로 예상되는 변이 및 9 명의 환자에서 임상적 의의가 불분명한 변이 15 개가 발견되었다. 한편, 총 17 명의 환자에서 12 명은 체세포 돌연변이가 있었고, 10 명은 유전자 융합이 있었다.

결론: 한국인 소아 급성 골수구성백혈병환자에서 유전성 소인 돌연변이의 빈도는 약 11.8%로 추정된다. 따라서 향후 소아 급성골수구성백혈병 환자에 대한 검사 시 유전성 소인 돌연변이 분석도 필수적으로 시행되어야 할 것이다.

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주요어: 유전성 소인 돌연변이, 소아 급성골수구성백혈병, 유전성 질병 소인, 체세포 돌연변이, 차세대 염기서열 분석
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