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ONCOLOGY: Genetic Predisposition to Hematologic Malignancies

Prepared by the Association for Molecular Pathology
Training and Education Committee

Abbreviations

AA	Aplastic Anemia	BMF	Bone Marrow Failure	GOF	Gain Of Function	MPAL	Mixed-phenotype Acute Leukemia
AD	Autosomal Dominant	CHIP	Clonal Hematopoiesis of Indeterminate Potential	JMML	Juvenile Myelomonocytic Leukemia	NHL	Non-Hodgkin Lymphoma
ALL	Acute Lymphoblastic Leukemia	CLL	Chronic Lymphocytic Leukemia	LOF	Loss Of Function	PB	Peripheral Blood
AML	Acute Myeloid Leukemia	CML	Chronic Myelogenous Leukemia	MDS	Myelodysplastic Syndrome	PV	Polycythemia Vera
AR	Autosomal Recessive	CMML	Chronic Myelomonocytic Leukemia	MN	Myeloid Neoplasm	TAM	Transient Abnormal Myelopoiesis
BM	Bone Marrow	ET	Essential Thrombocythemia	MMR	Mismatch Repair		

Syndrome	Gene (cytoband) [mode of inheritance]	Type of neoplasm	Age of onset of hematologic complications	Mechanism and most common alterations	References
Myeloid neoplasms with germline predisposition and pre-existing platelet disorders/ Thrombocytopenia 2	*ANKRD26* (10p12.1) [AD]	Thrombocytopenia, MDS, AML, rarely CML, CMML, CLL	Median age of thrombocytopenia is 33 years (range 1-84).	*ANKRD26* (ankyrin repeat domain containing 26) is crucial for megakaryocytic differentiation. Pathogenic *ANKRD26* germline variants (mostly missense) result in AD predisposition to thrombocytopenia and MNs.	WHO (5th ed), 21467542, 35751752, 31069978
Myeloid neoplasms with germline predisposition due to duplications of *ATG2B* and *GSKIP*	*ATG2B* (14q32.2) [AD], *GSKIP* (14q32.2) [AD]	MPN, ET, PV, PMF, rarely AML, MDS, aCML and CMML	Adult onset of MN (40.2 years), median of 9.7 years for progression to AML	*ATG2B* (autophagy-related 2B) and *GSKIP* (GSK3B interacting protein) have a synergistic role in megakaryopoiesis. A ~700 kb germline duplication at 14q32 predisposes carriers to a highly penetrant AD form of MNs.	NCCN Guidelines for Myeloid Malignancies v2 2025, 26280900
CBL syndrome	*CBL* (11q23.3) [AD]	JMML	Range infancy to early childhood	Detection of germline heterozygous pathogenic variants in proto-oncogene CBL (mostly missense and splice-site) is one of diagnostic criteria for JMML. Many patients acquire CN-LOH 11q23, resulting in a homozygous *CBL* variant state.	WHO (5th ed), NCCN Guidelines for Pediatric AML 2025, 20543203
Familial AML with mutated *CEBPA*	*CEBPA* (19q13.11) [AD]	AML	Range 2 to 50 years old	Germline *CEBPA* variants mostly occur in the N-terminal region (frameshift or nonsense); somatic mutations affect the C-terminal bZIP domain (in-frame indels, missense or frameshift). Somatic mutations are unstable; >50% carriers of germline *CEBPA* experience recurrence showing new independent clones.	WHO (5th ed), NCCN Guidelines for Myeloid Malignancies v2 2025, 26162409, 27895058
DDX41-Associated Familial MDS and AML	*DDX41* (5q35.3) [AD]	MDS, AML, CMML, rarely NHL	Range late 30s to the early 80s	Patients with MNs with germline *DDX41* variants (founder mutation p.Met1? or other nonsense, frameshift, or splice-site changes) often acquire 2nd variant (p.R525H or other missense change in the helicase domain).	WHO (5th ed), NCCN Guidelines for Myeloid Malignancies v2 2025
Thrombocytopenia 5	*ETV6* (12p13.2) [AD]	Thrombocytopenia, MDS, AML, CMML, PV, AA, B-ALL, MPAL, MM	Range 2 to 82 years old.	Etv6 is a transcription factor. Missense mutations (well-known P214L, R369Q, R399C) have dominant-negative effects and result in defective maturation of megakaryocytes and predisposition to MNs.	WHO (5th ed), 28555414, 26522332, 25807284, 26102509
Familial MDS/AML with mutated *GATA2* (*GATA2* deficiency syndromes)	*GATA2* (3q21.3) [AD]	MDS, AML, CMML, aCML	Median age at diagnosis is 20 years. High penetrance.	First described as 4 syndromes (MonoMAC syndrome, dendritic cell, monocyte, B, and NK lymphoid deficiency (DCML) with vulnerability to viral infections, familial MDS/AML, and Emberger syndrome); now it is a single gene disorder. *GATA2* germline LOF variants can occur in coding and noncoding elements.	WHO (5th ed), NCCN Guidelines for Myeloid Malignancies v2 2024, 25359990, 21765025
Familial AML with mutated *MBD4* / AML in *MBD4*-Associated Neoplasia Syndrome (MANS)	*MBD4* (3q21.3) [AR]	MDS, rarely AML	Between 33 and 49 years	*MBD4* (methyl-CpG binding domain 4) plays a role in stability of the MMR complex and epigenetic control. *MBD4* LOF mutations/deletions result in genomic instability, acquisition of a pathogenic driver mutations in *DNMT3A*, accelerating the CHIP phenotype and early-onset AML.	NCI-MBD4-Associated Neoplasia Syndrome (PDQ®)–Health Professional Version
MECOM-associated syndrome	*MECOM* (3q26.2) [AD]	Amegakaryocytic thrombocytopenia, congenital thrombocytopenia, BMF, AA, MDS	Varying from *in utero* to late adulthood	Germline *MECOM* variants (deletions, missense, nonsense, frameshift, or splice site variants) lead to a wide spectrum of clinical manifestations, including severe BMF with or without skeletal abnormalities or radioulnar synostosis (RUS)	NCCN, MDS Guidelines, v2.2025, 26581901, 29097497

Syndrome	Gene (cytoband) [mode of inheritance]	Type of neoplasm	Age of onset of hematologic complications	Mechanism and most common alterations	References
Myeloid neoplasms with germline predisposition and pre-existing platelet disorders	*RUNX1* (21q22) [AD}	Mainly MDS, AML, rarely T-lymphoblastic leukemia/lymphoma or B-cell neoplasms	Any age	*RUNX1* encodes a major transcription factor for core factor beta (CBFB). Germline mutations occur predominantly in RUNT domain and transactivation domain. Lifetime risk of MN at ~20~65%.	WHO (5th ed), 31648317, 32165484, 33075818, 29365323
MIRAGE syndrome/ Myelodysplasia and leukemia syndrome with monosomy 7 (MLSM7)/ Ataxia pancytopenia (ATXPC) syndrome	*SAMD9* (7q21.2) [AD], *SAMD9L* (7q21.2) [AD]	MDS, AML, ATXPC syndrome, MLSM7, Refractory cytopenia of childhood (RCC), Transient monosomy 7 in children, *SAMD9L*-associated autoinflammatory disease (SAAD), Inherited AA, BMF	GOF mutations - pediatric MDS (median age 9.6 years (range, 0.2-17.6)); LOF mutations - adult onset MDS. Incomplete penetrance.	*SAMD9* (sterile alpha motif domain-containing protein 9) and *SAMD9L (*a paralog) are crucial for cell proliferation. Heterozygous germline GOF *SAMD9/9L* variants result in multisystem syndromes with variable manifestations, including BMF, monosomy 7, and high risk of MDS in pediatric patients, whereas LOF variants are recurrent in the older population.	WHO (5th ed), 33038986, 29146900, 27182967, 28346228 28202457 28487541, 30046003
Familial aplastic anemia / MDS with *SRP72* mutation	*SRP72* (4q12) [AD]	MDS, AA, Familial leukemia, BMF	Childhood to adult onset. Variable penetrance.	*SRP72* encodes a component of the signal recognition particle (SRP) crucial for protein transport to the endoplasmic reticulum. Heterozygous germline variants (such as T355Kfs*19 and R207H) were described in patients with AD BMF, AA, and familial MDS.	WHO (5th ed); PMIDs: 22541560, 30951445, 34518161
Fanconi anemia (FA)	*FANCA* (16q24.3) [AR], *FANCB* (Xp22.2), *FANCC* (9q22.32) [AR], etc.	BMF, AA, MDS, AML	Early childhood	FA is caused by biallelic germline pathogenic variants in one of more than 22 FANC genes, most commonly *FANCA*, *FANCC*, and *FANCG*, involved in DNA repair. FA patients are at risk of progressive BMF, hematologic neoplasms.	WHO (5th ed), NCCN Guidelines for Myeloid Malignancies v2 2025
Shwachman-Diamond syndrome (SDS)	*SBDS* (7q11.21) [AR], *DNAJC21* (5p13.2) [AR], *EFL1* (5q25.2) [AR], *SRP54* (14q13.2) [AD]	BMF, MDS, AML	Median age for BMF is 1.7 years (range, 0.4-39.5), progression to MDS at 12.3 years (range, 0.5-45.0) and AML at 28.4 years (range, 14.4-47.3).	Biallelic pathogenic variants in *SBDS* (mostly ex 2; hot-spots c.258+2T>C and c.183_183TA>CT) are detected in ~90% of SDS patients. Pathogenic bi-allelic variants in *DNAJC21* and *EFL1*, and heterozygous pathogenic variants in *SRP54*, are responsible for SDS or SDS-like phenotypes. SDS patients are at risk of MDS or AML. Sequencing of *SBDS* is complicated due to the presence of the highly homologous pseudogene *SBDSP*.	22491737, 31879230, 37226705, 34758064, 28062395, 12496757, 12496757, 15776428
Short telomere syndromes	*TERC* (3q26.2) [AD], *TERT* (5p15.33) [AD], *RTEL1* (20q13.13) [AD], *PARN* (16p13.12) [AR/DR], etc.	BMF, AA, MDS, AML	Childhood /adolescence. Carriers may present with adult-onset BMF or MDS. Anticipation and variable penetrance.	Heterozygous LOF and hypomorphic missense variants result in impaired expression of *TERC* (telomerase RNA component) or *TERT* (telomerase reverse transcriptase) and progressive telomere shortening, leading to BMF and predisposition to MDS/AML.	WHO (5th ed); NCCN Guidelines for Myeloid Malignancies v2 2025
Wiskott Aldrich syndrome (WAS)	*WAS* (Xp11.23)	EBV-associated NHL, ALL, AML, rarely MDS and Hodgkin lymphoma	Infancy to early childhood	*WAS* is crucial for actin cytoskeleton remodeling in hematopoietic cells. Affected males present with microthrombocytopenia, eczema, recurrent infections, and neutropenia and are at risk of hematologic neoplasms.	WHO (5th ed), NCCN Guidelines for Myeloid Malignancies v2 2025
Ataxia Telangiectasia (AT)	*ATM* (11q22.3) [AR]	Lymphoid malignancies	Median age of development of hematologic malignancy is at 9-12.5 years	AT is an AR multisystem disorder caused by biallelic pathogenic variants of *ATM*, with increased risk (10-25% prevalence) of hematological malignancies and breast cancer. *ATM* encodes a protein kinase involved in double-strand DNA break repair.	38917355, 14695997, 7792600, 25488969
Li-Fraumeni syndrome (LFS)	*TP53* (17p13.1) [AD]	BMF, hypodiploid ALL, AML, MDS, lymphomas, various solid tumors	Childhood onset	Classic tumor spectrum includes adrenocortical carcinoma, CNS tumors, premenopausal breast cancer, and hematologic complications (BMF and pediatric hypodiploid B-ALL). AML and MDS have been reported as complications post-cytotoxic exposure.	30709875, 26014290, 34709361
Down syndrome (DS)	Trisomy 21	Transient abnormal myelopoiesis (TAM), myeloid leukemia associated with DS (ML-DS), DS-associated ALL DS-ALL)	Within 7 days of birth (TAM), the median age of onset of ML-DS is 1.6 years, B-ALL at 4~5 years.	TAM is seen in 25-30% of DS patients, with clinical presentation in 10% (splenomegaly, skin rash, etc.). Somatic mutations in exon 2/3 of *GATA1* have been implicated in the pathogenesis of TMD and ML-DS.	WHO (5th ed); NCCN Pediatric AML Guidelines, v1.2025, 37895004

This card includes only common biomarkers and is not exhaustive.

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