MAYO CLINIC

Hereditary Predisposition to Hematopoietic Neoplasms: When Bloodline Matters for Blood Cancers

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Abstract

With the advent of precision genomics, hereditary predisposition to hematopoietic neoplasms—collectively known as hereditary predisposition syndromes (HPS)—are being increasingly recognized in clinical practice. Familial clustering was first observed in patients with leukemia, which led to the identification of several germline variants, such as *RUNX1*, *CEBPA*, *GATA2, ANKRD26*, *DDX41*, and *ETV6*, among others, now established as HPS, with tendency to develop myeloid neoplasms. However, evidence for hereditary predisposition is also apparent in lymphoid and plasma–cell neoplasms, with recent discoveries of germline variants in genes such as *IKZF1*, *SH2B3*, *PAX5* (familial acute lymphoblastic leukemia), and *KDM1A/LSD1* (familial multiple myeloma). Specific inherited bone marrow failure syndromes—such as *GATA2* haploinsufficiency syndromes, short telomere syndromes, Shwachman-Diamond syndrome, Diamond-Blackfan anemia, severe congenital neutropenia, and familial thrombocytopenias—also have an increased predisposition to develop myeloid neoplasms, whereas inherited immune deficiency syndromes, such as ataxia-telangiectasia, Bloom syndrome, Wiskott Aldrich syndrome, and Bruton agammaglobulinemia, are associated with an increased risk for lymphoid neoplasms. Timely recognition of HPS is critical to ensure safe choice of donors and/or conditioning-regimen intensity for allogeneic hematopoietic stem-cell transplantation and to enable direction of appropriate genomics-driven personalized therapies. The purpose of this review is to provide a comprehensive overview of HPS and serve as a useful reference for clinicians to recognize relevant signs and symptoms among patients to enable timely screening and referrals to pursue germline assessment. In addition, we also discuss our institutional approach toward identification of HPS and offer a stepwise diagnostic and management algorithm.

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As genetic sequencing approaches are increasingly being integrated in clinical oncology and hematology, a number of germline genetic variants are being discovered in patients with cancer and their family members, also known as hereditary predisposition syndromes (HPS). For hematopoietic malignancies, familial clustering was first identified in several families with chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML).[1-4] Since then, several putative germline variants have been associated with myeloid neoplasms such as *RUNX1*[5] (for expansion of gene symbols, go to www.genenames.org), *CEBPA*,[6] *GATA2*,[7] *ANKRD26*,[8,9] *DDX41*,[10] *ETV6*,[11] *TERC/TERT*,[12] and *SRP72*,[13] along with those (such as *TP53*[14]) implicated in established cancer predisposition syndromes. In recognition of these discoveries, the latest iteration of the World Health Organization (WHO) classification of hematopoietic neoplasms now includes a separate category for myeloid neoplasms with a germline predisposition.[15] However, hereditary predisposition toward hematopoietic neoplasia is not only limited to those with a myeloid lineage cell of origin but also includes lymphoid and plasma-cell cancers, with recent discoveries of pathogenic variants in genes *KDM1A/LSD1*[16] and *DIS3*,[17] among others. In light of these new findings, clinicians should

have a high index of clinical suspicion in recognizing these entities, especially in patients with whom a typical family history or classical disease-associated signs and symptoms may be noticeably absent. Recognizing a germline predisposition has important clinical implications for both the patients (donor and/or conditioning regimen selection for allogeneic hematopoietic stem cell transplantation [HCT] and directing appropriate therapies) and their family members (screening and genetic counseling).

In this review, we discuss hematopoietic neoplasms with a hereditary predisposition and provide an overview of a personalized management approach followed at the Mayo Clinic Center for Individualized Medicine Precision Medicine Clinic (IRB# 16-004173 and NCT#02958462), where patients with high indices of clinical suspicion for hereditary predisposition syndrome (HPS) undergo a stepwise approach, starting with counseling, targeted sequencing (targeted exome) (Supplemental Table 1 [available online at http://www,mayoclinicproceedings.org]) and, if negative, whole exome sequencing to identify candidate gene variants followed by confirmation on germline tissue or sequencing affected/unaffected family members.

ARTICLE HIGHLIGHTS

- Among hematopoietic neoplasms, hereditary predisposition is being increasingly recognized in clinical practice.
- It is important for clinicians to recognize the subtle clinical signs and symptoms to diagnose and manage patients expeditiously.
- Identifying a hereditary predisposition can have significant therapeutic implications for patients with hematopoietic neoplasms.

MYELOID NEOPLASMS

Among hereditary hematopoietic neoplasms, hereditary myeloid malignancy syndromes (HMMS) are the best characterized, both clinically and genomically.[18] Despite considerable overlap—based on the presence or absence of characteristic syndromic features—these disorders can grouped as follows:

Familial Thrombocytopenia With Predisposition to Myeloid Malignancies

Initial linkage analysis studies among families with AML and familial platelet disorders revealed clustering at chromosome 21q22.1-22.2 loci,[19] which led to the identification of germline *RUNX1* haploinsufficiency (also called RUNX1-familial predisposition syndrome).[5] Other disorders include autosomal dominant variants in the 5' untranslated region of *ANKRD26* gene, which is associated with increased risk of myelodysplastic syndrome (MDS)/AML[8,9] and germline missense pathogenic variants in the *ETV6* gene, which increases predisposition to a heterogeneous group of hematologic malignancies (multiple myeloma [MM], pre—B-cell acute lymphoblastic leukemia (ALL), MDS, chronic myelomonocytic leukemia (CMML), and biphenotypic acute leukemia).[8,9,11,20] Additional details are mentioned in Table 1.[20,21]

Syndromic Familial Myeloid HPS. Syndromic association of lymphedema and MDS/AML, known as Emberger syndrome, was found to result from alterations in *GATA2* gene, which normally encodes a critical transcription factor essential for vascular development and hematopoietic stem-cell differentiation. Similarly, patients with monocytopenia and mycobacterial infections (MonoMAC) syndrome, and those with dendritic cell, monocyte, B and natural killer lymphoid deficiency, were found to harbor heterozygous variants in *GATA2*. Collectively, perturbations in the *GATA2* gene are now categorized as "*GATA2* haploinsufficiency syndrome," and afflicted individuals are unified by a characteristic phenotypic variability and an increased tendency toward developing MDS and/or AML.[7] Inherited defects in the nucleotide excision repair pathway are also associated with HPS. Patients with xeroderma pigmentosum, characterized by defects in nucleotide excision repair (*XPC* delTG germline variants) were found to have an increased predisposition toward developing Tp53/complex

TABLE 1. Hematological Disorders and Neoplasms With a Germline Predisposition and Associated Gene Mutations and/or Chromosomal Abnormalities*

Genes involved	Chromosomal location	Gene function	Associated neoplasms and hematologic disorders	Ref.
Myeloid neoplasms and bone marrow-failure syndromes				
CEBPA	19q13.11	Enhancer/transcription factor	AML	6
DDX41	5q35.3	RNA helicase function	MDS	10
SRP72	4q12	Endoplasmic reticulum function	MPN	22
MBD4	3q21.3	Binding and protection of methylated DNA		23
SAMD9/9L	7q21.2	DNA repair		24–26
RECQL4	8q24.3	DNA helicase (unwinding of DNA)		27–29
PTPN11	12q24.13	Regulation of RAS/MAPK signaling pathway	CMML, JMML, Noonan syndrome	30
CBL	11q23.3	RAS pathway regulation	JMML	31,32
RUNX1	21q22.12	Transcription factor	Familial thrombocytopenia	5
ETV6	12p13.2	Transcription factor		11
ANKRD26	10p12.1	Protein-protein interactions		8,9
MECOM	3q26.2	Transcriptional regulator		33
RBM8A (5'UTR, 1st intron)	1q21.1	Cellular protein production		20
C-MPL	1p34.2	Cell proliferation		21,34
ELANE	19p13.3	Neutrophil elastase production	Severe congenital neutropenia	35
HAX1	1q21.3	Regulation of apoptosis		36
WAS	Xp11.23	Maintaining cellular structural framework		37
CSF3R	1p34.3	Granulocyte maturation and function		38
GATA2	3q21.3	Zinc-finger transcription factor	*GATA2* haploinsufficiency syndrome	7
TERT	5p15.33	Catalytic subunit of telomerase	Short telomere syndromes	12,33,39–41
TERC	3q26.2	Telomerase RNA component		
RTEL1	20q13.33	DNA helicase (telomere protection)		
POT1	7q31.22	Telomere maintenance		
FANCA	16q24.3	DNA repair	Fanconi anemia	42
FANCB	Xp22.31			
FANCC	9q22.3			
FANCD1/BRCA2	13q12.3			
FANCE	6p21.3			
FANCF	11p15			
FANCG	9p13			
FANCI	15q25-26			
FANCJ	17q22.3			
FANCL	2p16.1			
FANCM	14q21.3			
FANCN	16p12.1			
SBDS	7q11.21	RNA processing	Shwachman-Diamond syndrome	43
DNAJC21	5p13.2	Co-chaperone for HSP70, RNA biogenesis		44,45
EFL1	15q25.2			46

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TABLE 1. Continued

Genes involved	Chromosomal location	Gene function	Associated neoplasms and hematologic disorders	Ref.
SBDS, continued				
RPS19	19q13.2	Ribosome assembly and function (all *RPS* and *RPL* genes)	Diamond-Blackfan anemia	42,47,48
RPS24	10q22.3			
RPS17	15q25.2			
RPL5	1p22.1			
RPL11	1p36.11			
RPL35A	3q29			
GATA1	Xp11.23	Erythroid transcription factor	Familial MPN Down's syndrome (with associated AML, ALL, TMD)	48–52
TSR2	Xp11.22	Ribosomal maturation factor		53
ATG2B/GSKIP	14q32.2	Cell differentiation		54,55
Trisomy 21	-	-		56
Lymphoid neoplasms and immune deficiency syndromes				
IKZF1	7p12.2	Transcription factor	ALL	57
PAX5	9p13.2	Transcription factor	NHL	58
SH2B3	12q24.12	Cell signaling and transduction	HL/NHL	59,60
TP53	17p13.1	Tumor suppressor	CLL	14,61
ATM	11q22.3	Cell division and DNA repair	Ataxia telangiectasia	62
BLM	15q26.1	DNA helicase	Bloom syndrome	62
PTPN11	12q24.13	Regulation of RAS/MAPK signaling pathway	Leopard/Noonan syndrome	62
NF1	17q11.2	Encodes neurofibromin	Neurofibromatosis (type 1)	62
NBS1	8q21.3	DNA repair	Nijmegen Breakage syndrome	62
WAS	Xp11.23	Maintaining cellular structural framework	Wiskott-Aldrich syndrome	62
BTK	Xq22.1	Development and maturation of B cells	Bruton agammaglobulinemia	62
FAS	10q23.31	Cell signaling and apoptosis	Autoimmune lymphoproliferative syndrome	62
FASLG	1q24.3	Induction of apoptosis		
CASP10	2q33.1	Execution-phase of apoptosis		
KLHDC8B (also 5'UTR region)	3p21.31	Protein-protein interactions	Hodgkin lymphoma	63
Plasma cell neoplasms				
KDM1A/LSD1	1p36.12	Histone demethylation	MM, MGUS, WM	16
DIS3	13q22.1	RNA processing		17
Cancer predisposition syndromes				
TP53	17p13.1	Tumor suppression	Li-Fraumeni syndrome	14
MSH2	2p21-p16.3	DNA mismatch repair	Lynch syndrome	64
MLH1	3p22.2			
MSH6	2p16.3			
PMS2	7p22.1			

*Owing to the large number of genes, only a select few have been incorporated in the table.

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphoblastic leukemia; CMML = chronic myelomonocytic leukemia; HL = Hodgkin lymphoma; JMML = juvenile myelomonocytic leukemia; MDS = myelodysplastic syndromes; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; MPN = myeloproliferative neoplasm; NHL = non-Hodgkin lymphoma; TMD = transient myeloproliferative disorder; WM = Waldenstrom macroglobulinemia.

karyotype MDS and AML.[61] In 2016, a new syndrome of myelodysplasia, infection, growth restriction, adrenal hypoplasia, genital abnormalities, and enteropathy (also known as MIRAGE syndrome) was identified among 11 patients and found to be caused by germline-activating heterozygous variants in the *SAMD9* gene. Similarly, missense variants

in a paralog of SAMD9, known as *SAMD9L*, were found to be associated with ataxia-pancytopenia syndrome. Biologically, both these genes have a role in endosomal fusion, and SAMD9 regulates growth factor signal transduction.[24] It is interesting that loss of chromosome 7 was the most common genetic event heralding the onset of MDS, likely as an adaptation mechanism to the growth-restrictive effects from mutant SAMD9 protein.[25,26] Heterozygous variants in DNA helicase genes—in particular, *RECQL4*—have been associated with AML.[27] Germline variants in this gene have been implicated in causing a defined syndrome characterized by dermatosis, short stature, juvenile cataracts, skeletal abnormalities, radial ray defects, premature aging, and predisposition to malignancies such as osteosarcoma, lymphoma, and AML, also known as Rothmund-Thomson syndrome.[28,29]

Genomic signatures that define the predisposing clinical syndromes can sometimes point toward the type of myeloid neoplasms that may develop later. Specific examples include germline variants activating the *RAS-MAP* kinase pathway in genes, *PTPN11* (Noonan syndrome) and *CBL*, which increase predisposition to develop myeloid neoplasms primarily genomically dominated by RAS pathway variants (juvenile myelomonocytic leukemia [JMML], CMML)[30–32] (Table 1).

Familial Predisposition to Myeloproliferative Neoplasms

Evidence of a familial predisposition for myeloproliferative neoplasms (MPNs) was apparent when single nucleotide polymorphisms within the *JAK2* (46/1 haplotype) gene were shown to predispose to MPN.[65-69] Subsequently, in 4 genetically related families, germline duplication of a 700-kilo base containing region of chromosome 14q32 containing 5 protein coding genes—*TCL1A*, *ATG2B*, *GSKIP*, *BDKRB1*, and *BDKRB2*—were found to cooperate with acquired *JAK2*, *MPL*, and *CALR* mutations in inducing disease by conferring a fitness advantage to cells carrying these mutations and resulting in a highly penetrant MPN phenotype.[54] Substantive correlative studies narrowed down the pathogenicity to *ATG2B* and *GSKIP* genes; however, this conclusion has been contested by the report of a family with germline duplication of chromosome 14q32 without involving the *ATG2B* and *GSKIP* genes.[55] Other germline variants shown to predispose to development of MPNs include *RBBP6*[70] and *SH2B3*.[71] Single nucleotide polymorphisms in *TERT*, *SH2B3*, *MECOM*, *HBS1L*, *MYB*, *TET2*, *ATM*, *CHEK2*, *LINC-PINT*, and *GF1B* genes have also been associated in families with MPN clustering.[33,39,60,71,72] However, it is also relevant to note that despite familial clustering of MPNs, a clear predisposition gene cannot be found, highlighting limitations of current technology and knowledge.

Nonsyndromic Familial Myeloid Predisposition Syndromes

This group of HMMS do not present with any characteristic syndrome or clinical features. Germline variant in the gene, *CEBPA*, which encodes CEBPAα, has been associated with MDS/AML.[6] This was followed by the discovery that patients with germline pathogenic variants in the DEAD/H-box helicase gene, *DDX41* gene, were predisposed to somatic *DDX41* variants as a second hit, with the consequent development of high-risk MDS/AML.[10] In addition, *DDX41* expression was found to be haploinsufficient in patients with deletion 5q involving the *DDX41* locus and associated with responses to lenalidomide, highlighting important therapeutic implications.[10,73] Similarly, biallelic germline pathogenic variants in *ERCC6L2* have been shown to increase predisposition to AML,[74] and exome and single-nucleotide polymorphism haplotype analysis have also identified *SRP72* pathogenic variant in a family with aplastic anemia (AA) and MDS.[22] Recently, germline pathogenic variants in the *MBD4* gene, which functions to repair spontaneous deamination-induced methylation damage via the base excision pathway, were found to be associated with early-onset AML, through acquisition of mutant driver

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genes, most notably *DNMT3A*.[23] Additional details are in Table 1.

Inherited Bone Marrow-Failure Syndromes With Predisposition to Myeloid Neoplasms

Beyond these specific genomically defined HMMS, patients with inherited bone marrow failure also have an increased cumulative incidence of MDS and AML.[42] Complementation groups of Fanconi anemia have a well-established association with MDS/AML,[75] which is characterized by presence of a specific pattern of unbalanced chromosomal translocations and partial chromosome arm duplications or deletions (including a cryptic RUNX1/AML1 fusion) and virtual absence of classical *de novo* translocations such as t(8;21), t(15;17) and *MLL*.[76] Biallelic germline pathogenic variants in the 22 *FANC* genes (except *FANCB* and *FANCR*) are associated with AML.[77]

Inherited bone marrow-failure syndromes grouped by gene variants affecting telomere structure and function, also known as short telomere syndrome (STS), display a wide spectrum of phenotypic diversity (premature graying of hair, idiopathic pulmonary fibrosis, immune dysregulation, and/or cryptogenic cirrhosis) and are characterized by increased predisposition toward MDS/AML.[40,41,78-80] Specifically among STS genes, thus far only *TERT*, *TERC*, and *RTEL1* have been associated with myeloid neoplasms.[12,40,80,81] Germline variants in the *POT1* gene, which is part of the Shelterin complex and functions to protect the structural integrity of telomeres, is also associated with increased incidence of several cancers such as familial CLL, colorectal carcinoma, angiosarcoma, glioma, and malignant melanoma, also called "long telomere syndromes," owing to a pathological mechanism of telomere maintenance and elongation.[82-85]

As iterated before, *GATA2* haploinsufficiency syndrome is now considered a genomically defined germline bone marrow-failure syndrome, with an increased predisposition to develop myeloid leukemias.[86,87] Specific morphologic, immunophenotypic, and cytogenetic features distinguish *GATA2*-related bone marrow failure from idiopathic AA, such as presence of greater overall cellularity, increased atypical megakaryocytes, reduced monocytes, mature B and NK cells, increased atypical plasma cells (in a subset of *GATA2* patients), and abnormal cytogenetics (in >50% *GATA2* patients) with common abnormalities including trisomy 8, monosomy 7, and deletion 7q.[88] Specific genotypic correlations are observed in germline *GATA2*-related AML such as predominance of pathogenic variants in the second zinc finger domain of *GATA2* and acquisition of somatic "second-hit" variants in *ASXL1* and *FLT3L* genes heralding the development of AML.[87,89,90] Mechanistic cooperation of *GATA2* gene with the aforementioned somatic variants needs further exploration. Shwachman-Diamond syndrome is an autosomal recessive inherited bone marrow-failure syndrome (IBMFS) caused by pathogenic variants in the *SBDS* gene (>90% patients) affecting ribosome biogenesis and clinically characterized by skeletal and neurodevelopmental abnormalities, exocrine pancreatic insufficiency, and bone marrow failure with increased predisposition toward development of MDS and/or AML.[91] Specific chromosomal abnormalities include interstitial deletion of long arm of chromosome 20 and isochromosome of long arm of chromosome 7.[92,93] Clonal interstitial deletion of the long arm of chromosome 20 is thought to confer a better prognosis and is genomically characterized by the loss of *EIF6*.[92] In a small proportion of patients, biallelic variants in 2 other genes, *DNAJC21* and *EFL1*, may also cause a Shwachman-Diamond syndrome-like condition.[44–46]

Diamond-Blackfan anemia (DBA) is an IBMFS classified as a ribosomal disorder characterized by red cell aplasia, congenital abnormalities (craniofacial anomalies such as cute snub nose and wide-spaced eyes and upper-extremity anomalies such as radial abnormalities including hypoplastic thumbs, genitourinary and cardiac anomalies such as atrial and/or ventricular septal defect and coarctation of aorta), and increased predisposition toward developing MDS/AML and osteogenic sarcoma.[42,47] In approximately 70% cases with a DBA phenotype, causative variants include *RPS19*,

RPS24, *RPS17*, *RPL5*, *RPL11*, and *RPL35A*, all inherited in an autosomal dominant pattern and with an impact on ribosomal biogenesis.[42,48] Of note, among this group of HPS, there are specific genotype-phenotype correlations such as association of craniofacial abnormalities with *RPL5* (which binds with *TCOF1*).[47] Typical laboratory clues to identification of DBA include presentation of anemia before the first birthday, reticulocytopenia, macrocytosis, increased fetal hemoglobin levels, and elevation of erythrocyte adenosine deaminase enzyme (to be assessed before red blood cell transfusion dependence).[47] In a large DBA registry, the incidence of AML/MDS was reported to be approximately 1% (6 of 608 patients) after a prolonged follow-up.[49] However, mechanistic biology of clonal evolution in this disease is still not clear. DBA-like phenotype can also occur as a consequence of loss of function *GATA1* variants,[50–52,94] biallelic *ADA2* variants resulting in a deficiency of adenosine deaminase-2,[95] and *TSR2* variants, also associated with mandibulofacial dysostosis.[53]

Severe congenital neutropenia (SCN) is a heterogeneous group of disorders responsible for neutropenia at or near birth, only a fraction of which are due to inherited or germline variants. Based on the presence or absence of specific clinical features, they can grouped into the following categories:

SCN without extrahematopoietic abnormalities or primary immunodeficiency. This group includes patients with SCN and pathogenic variants in the *ELANE* gene,[35] which encodes for neutrophil elastase and is inherited as an autosomal dominant disorder, and those with germline variants in the G-CSF receptor (*CSF3R*, which may also result in nonresponsiveness to granulocyte growth factor therapy).[96,97]

SCN without extrahematopoietic abnormalities but with primary immunodeficiency. This group includes SCN patients with loss-of-function *CXCR2* and gain-of-function *CXCR4* variants (associated with warts; hypogammaglobulinemia, immunodeficiency; and myelokathexis syndrome, also known as WHIM syndrome),[98] Wiskott Aldrich Syndrome (X-linked disorder associated with microthrombocytopenia, eczema, and recurrent infections),[99] *CD40LG* (decreased IgM response), *GFI1* germline variants (also associated with lymphopenia),[100] and *STK4* (T- and B-cell deficiency) gene abonormalities.[101]

SCN with extrahematopoietic abnormalities. Patients with SCN and variants in genes, *HAX1* (neurologic manifestations such as developmental delay and seizures),[36] *G6PC3* (Dursun syndrome characterized by prominent superficial venous pattern, urogenital and congenital cardiac defects, intermittent thrombocytopenia, and pulmonary hypertension),[102] *TAZ* (Barth syndrome, manifesting as short stature, cardiac and skeletal myopathy),[103] *LYST* (Chédiak-Hegashi syndrome, manifesting as hypopigmentation, neuropathy, immunodeficiency, and hemophagocytic lymphohistiocytosis), *AP3B1* (Type 2 Hermansky-Pudlak syndrome), and *AP14* (albinism),[104] *SBDS* (aforementioned Shwachman Diamond syndrome),[43] *C16orf57* (Clericuzio poikiloderma),[105] *SLC37A4* (glycogen storage defect causing hypoglycemia, glycogen overload in liver), *VPS13B* (Cohen syndrome, manifesting as intellectual deficiency, microcephaly, facial abnormalities, joint laxity, hypotonia, truncal obesity, chorioretinal dystrophy, and myopia),[106] *VPS45* (nephromegaly, splenomegaly, primary myelofibrosis of infancy, neurological abnormalities),[107] *TCIRG1* (prominent hemangiomas),[108] *JAGN1* (short stature, bone and teeth defects),[109] *CLPB* (3-methyglutaco-nic aciduria type VII),[110] *TCN2* (vitamin B12 deficiency),[111] *EIF2AK3* (diabetes mellitus, skeletal dysplasia, stunted growth),[112] *DNM2* (Charcot-Marie Tooth disease presenting as limb weakness and atrophy),[113] *RAB27A* (hypopigmentation, immunodeficiency, and hemophagocytic lymphohistiocytosis, also known as type 2 Griscelli syndrome),[114] *CTSC* (hyperkeratosis and periodontitis),[115] and *LAMTOR2* and *RAB27A* (skin manifestations)[116,117] belong in this group.

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Although more than 100 pathogenic variants have been associated with SCN, in approximately 25% patients, no causative variant is found. Further, literature on a definitive association with increased predisposition to develop MDS/AML is only available for a handful of SCN genes: namely, *ELANE*, *HAX1*, *WAS*, and *CSF3R*.[37] Classic bone marrow findings include maturation arrest at the promyelocyte/myelocyte stage of development, with atypical nuclei and cytoplasmic vacuolization. A large registry report of 374 well-characterized patients with SCN on long-term (10 years) granulyte-colony stimulating factor (G-CSF) therapy suggested an annual risk of MDS/AML to be about 2.3% per year, and after 15 years on G-CSF therapy, rate of death from sepsis was approximately 10%, whereas MDS/AML was approximately 22%.[118] Some reports imply that acquisition of G-CSF receptor variants signal the onset of MDS/AML in these patients.[38,119]

Thrombocytopenia absent radii (TAR) syndrome and congenital amegakaryocytic thrombocytopenia (CAMT) are 2 important hereditary causes of thrombocytopenia. TAR syndrome is a rare congenital disorder characterized by bilateral radius aplasia and thrombocytopenia and caused by a chromosome 1 microdeletion including the *RBM8A* gene or a single nucleotide polymorphism within the 5'-UTR or first intron of the *RMB8A* gene.[20] CAMT is caused by alterations in the gene for the thrombopoietin receptor, c-Mpl, resulting in high levels of serum thrombopoietin.[34] There have only been a few case reports of CAMT and TAR that have evolved to AML.[42]

LYMPHOID NEOPLASMS

Clinical studies including twin, case-control, cohort, and registry-based studies have shown that first-degree relatives of patients with CLL, non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL) have ~8.5, 1.7, and 3.1 times the rate of developing the same lymphoid malignancy.[120] Following these clinical observations, Genome-Wide Association Studies have identified several genetic susceptibilities for these cancers[121-127] but definite familial predisposition is only attributed to select genes (Table 1).

Inherited pathogenic variant of lymphoid transcription factor, *PAX5* (also called BSAP), accompanied by loss of heterozygosity and retention of a mutant allele at chromosome 9p13, was shown to be associated with familial B-ALL.[58] Similarly, germline homozygous variants in a negative regulator of cytokine signaling, SH2 adaptor protein 3 (*SH2B3*) and a lymphoid transcription factor, IKAROS (*IKZF1*) are associated with B-ALL.[57,59] As mentioned earlier, the *POT1* gene, part of the shelterin complex of telomeres, has been associated with familial CLL (among other cancers).[83] Reciprocal translocation and 5'-UTR polymorphisms in the gene-encoding midbody kelch protein (*KLHDC8B*) have been associated classical and nodular lymphocyte predominant Hodgkin lymphoma.[63,128]

Specific inherited immune deficiency syndromes—such as ataxia telangiectasia (ATM), Bloom syndrome (BLM), Wiskott Aldrich syndrome (WAS), Nijmegen Breakage syndrome (NBS1), cartilage hair hypoplasia (RMRP), adenosine deaminase 1 deficiency (ADA1), Bruton agammaglobulinemia (BTK), and many others—are also associated with an increased risk of B- and T-cell lymphomas.[62] Cartilage hair hypoplasia is especially unique as it has some degree of phenotypic overlap with dyskeratosis congenita (DKC), is associated with critically shortened lymphocyte telomere length secondary to a perturbed telomere homeostasis, significant immunodeficiency and predisposition to lymphoid neoplasms.[129,130] Among B-cell lymphomas in patients with primary immunodeficiency and immune dysregulatory disorders, a meta-analysis has shown a frequency of 37% for unspecified NHL, 15% for diffuse large B-cell lymphoma, 13% for HL, 5% for HL and marginal zone lymphoma, 4% for Burkitt lymphoma, and 0.4% for diffuse histiocytic lymphoma, respectively.[62] Although the biological mechanism for neoplastic transformation is unclear, an intrinsic susceptibility to DNA damage and excess antigenic stimulation

due to repeated infections in the setting of impaired immune checkpoints and antitumor surveillance could explain the increased predisposition for cancer in these disorders. Cellular pathway involving DNA double-strand break repair, which uses nonhomologous end joining and homology-directed recombination, is of particular relevance in the context of monogenic immune system defects and predisposition to hematopoietic neoplasms.[62] Specific associations are highlighted in Table 1 and reviewed extensively elsewhere.[62] It is important to note that several monogenic DNA repair defects associated with cancer susceptibility have been classified as XCIND (X-ray susceptibility, cancer, immunodeficiency, and neurologic defects), which also includes the aforementioned syndromes such as ataxia telangiectasia and Nijmegen breakage syndrome.[131-134]

CLONAL PLASMA CELL DISORDERS/ DYSPROTEINEMIAS

Similar to lymphoid neoplasms, familial clusters of monoclonal gammopathy of undetermined significance, MM, and Waldenstrom macroglobulinemia have been noted in population studies. In 2018, *KDM1A/LSD1* was identified as the first inherited autosomal dominant gene, with an increased predisposition to develop MM. It encodes for a tumor-suppressor protein, which acts as an epigenetic transcriptional repressor by demethylating histone H3 on lysine 4 and regulates hematopoietic stem cell renewal.[16] Recently, exome sequencing has identified variants in the *DIS3* gene in 2 families with MM.[17]

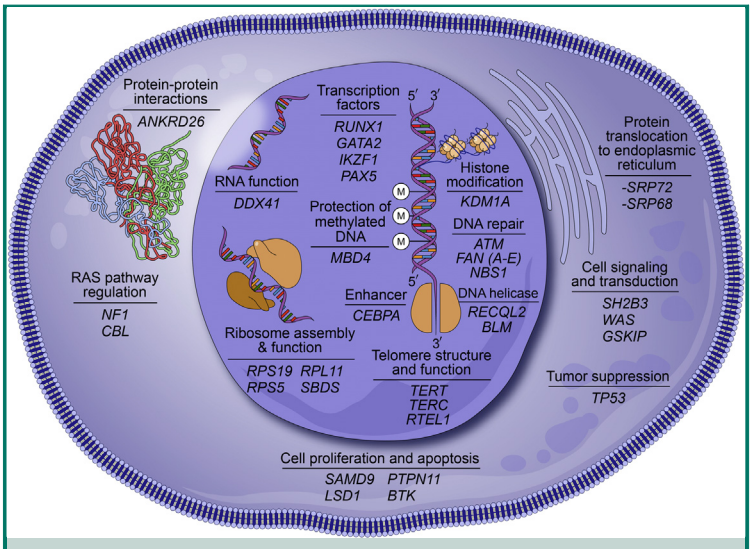

FIGURE 1. Figure showing cellular functions of putative pathogenic germline variants implicated in hereditary predisposition syndrome associated with hematopoietic neoplasms. Of note, only a few examples of involved genes are shown in the Figure. Please refer to the text for a comprehensive list of genes involved.

GENERAL CANCER PREDISPOSITION SYNDROMES

Besides specific genomic variants associated with either myeloid, lymphoid, or plasma-cell neoplasms, established cancer predisposition syndromes, such as Li-Fraumeni, Lynch, and Down syndrome, also have increased predisposition toward developing hematopoietic neoplasms along with other cancers (Table 1). Approximately 70% of families of Li-Fraumeni syndrome harbor germline variants in the *TP53* gene and develop early onset (age of onset $\leq$ 45 years) cancers such as soft tissue and osteosarcomas, adrenal cortical carcinoma, pancreatic, pediatric, and breast cancers, and leukemia, among others.[135,136] Lynch syndrome is genetically characterized by defects in the mismatch repair genes: namely, *MSH1*, *MLH1*, and *MHS6*.[137] Although hematopoietic malignancies are not traditionally included in the diagnostic criteria for this syndrome, leukemia (AML and CLL), MM and NHL have been associated predominantly with *MSH2*-related defect in mismatch repair.[64,138] Down syndrome is genomically characterized by the presence of trisomy 21 and truncating variants in the *GATA1* gene, which predispose to the development of transient abnormal myelopoiesis, solid tumors such as retinoblastomas; testicular germ-cell tumors; lymphomas and leukemias, particularly acute megakaryocytic leukemia and B-cell ALL.[42] Recently, an oncogenic hotspot gain-of-function variant in myeloid cytokine receptor gene, *CSF2RB*, was shown to cooperate with acquired variants in cohesion complex and epigenetic regulators and drive

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TABLE 2. Table Highlights Clinical Cues (Other Than Malignancies) That Can Alert Clinicians to Diagnose Patients With Specific Hereditary Predisposition Syndromes

Syndrome	Clinical features
General cues	Young age of onset of cytopenias (age ≤ 40 years), persistent unexplained cytopenias (≥3 months), prolonged period of cytopenia before diagnosis of a hematopoietic malignancy, elevated fetal hemoglobin level, unexplained macrocytosis and/or hypocellularity on bone marrow evaluation, unexplained monocytopenia, reticulocytopenia or opportunistic infections, positive family history of a hereditary predisposition syndrome in one or more first- or second- degree relative
Short telomere syndromes	Premature greying of hair (age ≤ 30 years), oral leukoplakia, idiopathic pulmonary fibrosis, cryptogenic cirrhosis, unexplained cytopenias and/or immunodeficiency
Fanconi anemia	Short stature, microcephaly, development delay, urogenital abnormalities, cutaneous warts, café-au-lait skin lesions
GATA2 haploinsufficiency	Lymphedema, monocytopenia, recurrent nontuberculous mycobacterial, fungal and viral infections, pulmonary alveolar proteinosis, anogenital warts
Diamond-Blackfan anemia	Early-onset macrocytic anemia, craniofacial, genitourinary and cardiac abnormalities, normocellular bone marrow with erythroid hypoplasia.
Shwachman-Diamond syndrome	Skeletal and neurodevelopmental abnormalities, exocrine pancreatic insufficiency
Thrombocytopenia-absent radii syndrome	Thrombocytopenia, bilateral radius hypoplasia
Severe congenital neutropenia	*Varied phenotype and depends on genetic association.* Common associations include immunodeficiency, skeletal defects, stunted growth, skin hypopigmentation, recurrent infections, neurological defects

leukemic transformation from transient abnormal myelopoiesis in these patients.[56] Detailed discussions of these syndromes are beyond the scope of this review and interested readers are referred to Garber et al.[137] Figure 1 provides a mechanistic overview of cellular functions disrupted by common HPS-associated germline variants.

CLINICAL IMPORTANCE OF HPS IDENTIFICATION

Although precision genomics has improved the speed and accuracy of diagnosis for patients with HPS, its impact on therapy is also becoming increasingly relevant. As allogeneic HCT remains an integral part of management of bone marrow failure and malignancy in HPS, exclusion of variants in related sibling and/or haploidentical donors is critical to prevent post-HCT donor-derived malignancies.[139] Transplant-related morbidity and mortality is higher in patients with underlying HPS due to increased chemotherapy and radiation-therapy sensitivity, particularly pertinent for chromosomal breakage disorders and short telomere syndromes.[140-142] This leads to an excessive risk of cytopenias, infections, and complications from graft-versus-host disease. Further, owing to the underlying inherent bone marrow dysfunction, immune dysregulation, and use of less intensive conditioning regimens in HPS, patients are at a higher (~10-20%) risk for graft failure.[143-145] Studies on alternate HCT-conditioning strategies (preferably without chemotherapy or radiation), appropriate donor selection (use of unrelated donors, exclusion of causative variant in related donors, alternate donor strategies such as cord blood) is necessary to pursue HCT safely in these patients.[146]

The benefit of genomic assessment is not limited to streamlining HCT management. At Mayo Clinic, our 2-year experience with a precision medicine clinic evaluating 68 patients with unexplained persistent (≥6 months) cytopenias (after exclusion of known infectious, autoimmune, toxic, and malignant causes; 29 [43%] with HPS) showed that genomic assessments resulted in an objective change in management in approximately 25% of tested patients.[147] Definition of a change in management included altered donor-selection strategy, conditioning regimen intensity, and/or initiation or discontinuation of a new drug and

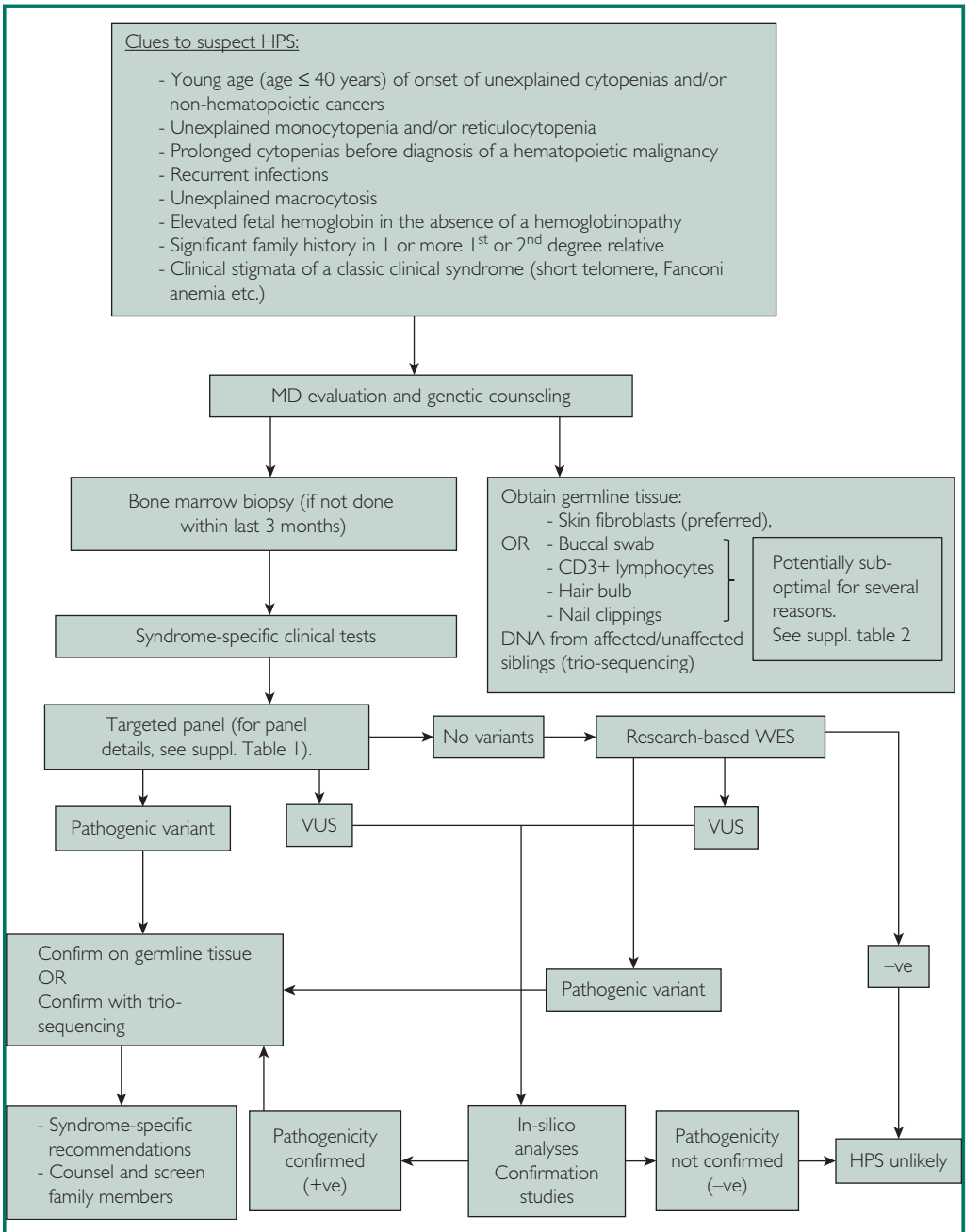

FIGURE 2. Figure showing a stepwise algorithmic approach toward identification and management of HPS at our institution. HPS = hereditary predisposition syndrome; VUS = variants of uncertain significance; WES = whole-exome sequencing.

was chosen as per a similar study published by Alder et al., assessing utility of a clinical test to measure telomere length (flow cytometry-fluorescence *in situ* hybridization) in the hospital setting.[148] However, diagnosis can be challenging even for patients affected with syndromic HPS, as was recently shown by a recent Center for International Blood and Marrow Transplant Research (CIBMTR) study.[149]

Genomically defined HPS and related IBFMS have specific interventions that are

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necessary both from therapeutic and supportive-care standpoints. Specific examples include use of danazol in short telomere syndromes[150] (although controversial other reports have raised questions whether danazol truly prevents telomere attrition[151,152]), azithromycin prophylaxis to prevent atypical mycobacterial infections in patients with *GATA2* haploinsufficiency syndromes,[153] use of granulocyte growth factor support for patients with severe congenital neutropenia,[154] and upcoming investigational strategies such as post-transcriptional modulation of *TERC* by inhibition of PAPD5 in dyskeratosis congenita[155] and gene therapy,[156] among others.

Finally, identification of HPS has important implications for screening family members. Owing to genetic phenomena such as incomplete penetrance and somatic reversion, relatives of affected individuals may carry the gene variant but may be clinically silent. Despite lack of early intervention strategies, it is important to offer them appropriate genetic counseling and testing.

OUR APPROACH TO DIAGNOSIS

At Mayo Clinic, we follow a stepwise approach for identification of HPS. Clinical cues that suggest the need for screening include a younger age (≤40 years) at onset of cytopenias or diagnosis of a hematopoietic neoplasm; unexplained macrocytosis; elevated fetal hemoglobin; significant personal or family history of either a similar hematopoietic neoplasm, generalized cancer predisposition syndrome, or a bone marrow-failure syndrome associated with HPS; and syndromic features associated with unique genetic abnormalities (HPV-driven warts and warts, lymphedema, and monocytopenia for GATA2 haploinsufficiency, and reticulocytopenia for DBA [Table 2]). These patients are referred to precision medicine clinics where patients are evaluated by physicians, undergo genetic counseling, and get consented for research-based precision genomics testing. After history and physical examination, a detailed family history is obtained. A bone marrow evaluation (aspirate and biopsy) is performed, if clinically indicated. Based on the suspected clinical syndrome, specific clinical tests (for example, flow cytometry-fluorescence *in situ* hybridization to measure telomere length, chromosomal breakage assays for Fanconi anemia), and custom-designed targeted panel is ordered (Supplemental Table 1). If a pathogenic variant is discovered, germline confirmation is carried out with either testing in affected/unaffected family members or germline tissue. Germline tissue options include skin fibroblasts, hair follicles, nail clippings, CD3+ T-cells, and buccal swabs, each with their own disadvantages (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). Nail clippings often give a lower DNA yield, T cells may not be ideal germline controls for all HPS, and buccal swabs may be contaminated with leukocytes. One report also claimed skin biopsy to be unsatisfactory owing to a high number of false positive results.[157] In our experience, skin fibroblasts offer reliable results and serve as our preferred germline control. If a variant of uncertain significance is found, a dedicated bioinformatics team assesses *in silico* predictions, sequence conservation through species, and presence or absence in various publicly available population databases. Cases are then discussed in a genomics tumor board, comprising clinicians, geneticists, bioinformaticians, and molecular biologists. Confirmation studies are then carried out after a consensus in a functional validation laboratory. If targeted panel testing results are negative, a research-based whole-exome sequencing data analysis is carried out, with a similar approach for pathogenic variants and variants of uncertain significance (Figure 2).

FUTURE DIRECTIONS

Genomic characterization of HPS has expanded our knowledge on the biological underpinnings of these unique disorders. Studying the mechanism of clonal evolution and neoplastic transformation in these patients are expected to yield novel insights into treatment strategies aimed at altering their natural history. Investigations into how these genetically deficient cells survive and allow clonal selection/proliferation

would guide drug development directed against specific therapeutic vulnerabilities. The advent of gene-editing technologies offers another therapeutic avenue.

CONCLUSIONS

Early recognition of hereditary predisposition to hematopoietic neoplasms is paramount to allow timely diagnosis and direct personalized management. A stepwise genomics approach enables an accurate diagnosis in a majority of patients and helps avoid contextually inadvertent treatments. Future areas of study include feasibility and applicability of such specialized multidisciplinary precision medicine clinics, innovative strategies for variant validation and transplant conditioning, and novel therapies to prevent clonal evolution and reverse genetic discrepancies in HPS.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AA** = aplastic anemia; **ALL** = acute lymphoblastic leukemia; **AML** = acute myeloid leukemia; **CAMT** = congenital amegakaryocytic thrombocytopenia; **CLL** = chronic lymphocytic leukemia; **CMML** = chronic myelomonocytic leukemia; **DBA** = Diamond-Blackfan anemia; **G-CSF** = granulocyte-colony stimulating factor; **HCT** = hematopoietic stem cell transplantation; **HL** = Hodgkin lymphoma; **HPS** = hereditary predisposition syndrome; **IBFMS** = inherited bone marrow failure syndrome; **MDS** = myelodysplastic syndrome; **MM** = multiple myeloma; **MPN** = myeloproliferative neoplasm; **NHL** = non-Hodgkin lymphoma; **SCN** = severe congenital neutropenia; **STS** = short telomere syndrome; **TAR** = thrombocytopenia absent radii; **WHO** = World Health Organization

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