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Genetic Predisposition to Myelodysplastic Syndrome in Clinical Practice

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INTRODUCTION

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders that typically affect older adults (median age, 76 years[1]) but do occur less commonly in children and young adults. There is increasing recognition of an inherited predisposition to MDS as well as acute myeloid leukemia (AML) in both children and older individuals. Specific syndromes and gene mutations are infrequent but, collectively, inherited predisposition to myeloid malignancy represents a significant proportion of these diagnoses, with at least 5% of cases having a germline cause[2,3] and with a prevalence up to 10% to 15% in certain patient cohorts.[4–8] Germline predisposition to MDS can occur as a part of a syndrome or multisystem disorder or as a seemingly sporadic disease. The timely diagnosis of an underlying genetic predisposition is critical because it has broad implications for treatment, transplant considerations, long-term surveillance, and family counseling. It is more common for pediatric providers to consider these phenotypes, and thus increasing awareness for adult providers is becoming more important as clinicians realize that these disorders can present in older patients too. This article highlights the current state of knowledge for germline genetic causes of MDS (in children and adults); in addition, it provides a framework for the diagnosis and management of genetic predisposition to MDS/AML in the clinic for patients of all ages.

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DISCLOSURE

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GERMLINE MYELODYSPLASTIC SYNDROME PREDISPOSITION SYNDROMES

Because of the increasing recognition of germline predisposition to MDS/AML and the impact on clinical care, germline predisposition to myeloid neoplasm was incorporated into the World Health Organization classification, and diagnostic recommendations were added to the most recent National Comprehensive Cancer Network (NCCN) practice guidelines.[9,10] NCCN guidelines provide relevant guidance on how to test patients but are lacking in explanations to clinicians for identification of appropriate candidates for testing. As such, some institutions have developed their own approach to the diagnosis and management of hereditary myeloid malignancies,[6,11–13] and consensus guidelines for surveillance and management exist for several specific MDS predisposition syndromes.[14–16] Common to all of these approaches is the appreciation that patients can have a germline predisposition to MDS with the absence of other syndromic features on history and physical and without a family history. Atypical or cryptic cases of the classic pediatric bone marrow failure (BMF) syndromes can become apparent only in adulthood, and MDS or AML can be the first presenting feature of these syndromes.

The major hereditary MDS/AML syndromes to date are summarized in Table 1 with references to large case series detailing comprehensive features of each syndrome that have been published since the genetic diagnosis was established. The syndromes can be divided into the following categories:

1. Myeloid neoplasms with germline predisposition without a preexisting disorder or organ dysfunction (*CEBPA*, *DDX41*)
2. Myeloid neoplasms with germline predisposition and preexisting platelet disorders (*RUNX1*, *ANKRD26*, *ETV6*)
3. Myeloid neoplasms with germline predisposition and other organ dysfunction (*GATA2*, short telomere syndromes, other inherited BMF syndromes)
4. Traditional hereditary cancer predisposition syndromes (now understood to include hematologic malignancies in addition to solid tumors)

INDICATIONS FOR GENETIC TESTING

Certain clinical and laboratory features enrich for populations with inherited predisposition, and those populations warrant comprehensive screening for germline mutations as outlined later. However, limiting testing to only these high-risk patients could overlook a diagnosis in those older patients, nonsyndromic patients, or patients without family history who present with what seems to be de novo MDS but who carry a genetic predisposition.

Germline genetic testing is recommended in:

- Young-onset MDS, before 50 years of age; a proportion have negative family history and no other suggestive features

- MDS with any clinical or pathologic feature of a BMF syndrome (including lifelong history of cytopenias, even if MDS diagnosis made at a later age)
- Familial cases with MDS, acute leukemia, aplastic anemia, unexplained cytopenias, or bleeding history in 2 or more relatives (first or second degree)
- Individuals or families with MDS/AML clustering with extrahematopoietic manifestations characteristic of the BMF syndromes (see Table 1)
- Personal history of MDS and multiple primary malignancies and/or strong family history of cancers at early ages
- Individuals with mutations in genes known to be associated with hereditary MDS/AML found on somatic tumor testing (discussed later)

Consider germline genetic testing in:

- Hypoplastic MDS at any age (without paroxysmal nocturnal hemoglobinuria [PNH] clone)
- Personal history of thrombocytopenia (diagnosed as autoimmune) not responsive to standard therapies
- Patients with chemotherapy toxicity more severe than experienced by most patients
- Related donor with unexplained cytopenias or poor peripheral blood stem cell mobilization; donor-derived malignancy after related donor hematopoietic stem cell transplant (HSCT)
- Certain patients with therapy-related myeloid malignancies may be more likely to harbor germline variants in predisposition genes

EVALUATION FOR GERMLINE PREDISPOSITION TO MYELODYSPLASTIC SYNDROME

Standard diagnostic criteria for MDS apply to patients with germline predisposition and all the conventional diagnostic evaluations should be done. The underlying germline predisposition may not be evident on usual evaluations, so a high index of suspicion and dedicated work-up are needed. Mutations in some of the genes known to cause hereditary myeloid malignancy, such as *CEBPA*, *RUNX1*, or *TP53*, can also arise somatically in the clonal MDS/AML population. Clinically theses scenarios can lack clarity without further evaluation. Published guidelines now include consideration of additional molecular and genetic testing specifically for hereditary hematologic malignancies.[10] Patients should receive both pretest and posttest counseling according to standard genetic testing clinical practice guidelines.[17,18]

Bone Marrow Studies

MDS arising from an underlying marrow failure state can have distinguishing syndrome-specific features[19–21] or can appear to be sporadic MDS. A marrow evaluation is imperative

in all cases. In the case of a hypocellular or patchy marrow in which MDS is suspected, increased cluster of differentiation (CD) 34 count, which can be quantified by flow cytometry of bone marrow aspirates or immunohistochemistry on the core biopsy, favors hypoplastic MDS rather than aplastic anemia.[22,23] Cytogenetics may also not grow or be nondiagnostic, and in that case fluorescence in situ hybridization (FISH) studies can be added to evaluate for the common aberrations.[13,24] In patients with noninformative or nondiagnostic cytogenetics, in cases in which this information may change management, single nucleotide polymorphism (SNP) microarrays could be considered as an alternative karyotyping tool to detect most cytogenetic aberrations.[25–27] In patients with cytopenias and suspicion of an inherited syndrome, repeat marrow examinations may be necessary to establish the diagnosis of MDS because of hypocellular or patchy marrows and background dysplasia. This testing can be done at the time of clinical changes with the interval between marrows informed by the severity of cytopenias.

Tiered Approached to Genetic Testing

The authors' practice is to use a stepwise approach to the genetic evaluation of patients with MDS (Fig. 1). The tiered methodology allows for attention to detail, managing appropriate patient-centered issues, and parallel testing (of potential donor) if appropriate or necessary; there must also be acknowledgment of both the financial and emotional cost of these pathways at the bedside. In patients in whom there is a presumed higher risk for a genetic predisposition to MDS or features suspicious for these diagnoses, initial screening is done from the peripheral blood if applicable. Notably these tests include flow cytometry for a PNH clone,[28] especially if hypoplastic; telomere length measurement by CLIA (Clinical Laboratory Improvement Amendments)-certified flow cytometry and FISH (flowFISH)[29]; and chromosome breakage with diepoxybutane (DEB).[30] Polymerase chain reaction–based quantification of telomere length is not a reliable measure and should not be used in clinical settings.[29,31] The results of these initial tests help to further guide appropriate germline genetic testing.

The benefit of this approach is that these tests can be readily done from peripheral blood, are less expensive, and have a shorter turnaround time than most next-generation sequencing (NGS) platforms. This process quickly identifies patients at risk for short telomere syndromes and Fanconi anemia who are at high risk for increased toxicity from certain therapies, and the finding of a PNH clone, suggesting an acquired disorder, precludes the need for further genetic testing.[32] A tiered approach also allows for expectation management and reassurance to patients and families when possible. However, it can be less efficient, even if it is resource conscious. Further, it is important to facilitate appropriate work-up for both the patients and any related potential donors. Related donors should be screened in a targeted fashion if a predisposition syndrome is identified in the recipient. This screening is relevant for fully matched siblings or haploidentical siblings, children, or parental donors. If the choice has been made a priori to use an unrelated donor, then the added stress of a familial work-up can be deferred or delayed until the patient has been treated.

Germline Source of DNA

It is critical at the bedside to evaluate the proper genetic material to document a germline disorder. Mutations in some of the genes known to cause hereditary myeloid malignancy can occur somatically. Thus, a germline source of DNA is imperative to distinguish acquired from inherited mutations. In addition, chromosomal aberrations and, in rare cases, revertant somatic mosaicism can obscure allele frequencies and may cause the genetic diagnosis to be missed if sequencing is only done from the peripheral blood.[33–38]

The preferred source of germline material for sequencing is DNA derived from skin fibroblasts cultured in a CLIA-certified laboratory.[39] Some sequencing laboratories require up to 5 μg of DNA for complete testing, which is difficult to obtain from other tissue sources (ie, hair roots and nail clippings[40]). Fibroblasts are usually obtained from a 3-mm skin punch biopsy, which can be done at the bedside even in very young patients or thrombocytopenic patients. Because of the time required to culture fibroblasts (3–6 weeks), a skin biopsy should be obtained as early as clinically feasible in the diagnostic evaluation. Saliva, buccal swab, and DNA from a skin biopsy directly yield sufficient DNA but can be contaminated with circulating cells.[41] In clinical situations in which a genetic diagnosis is needed urgently, these sources can be used initially with confirmatory testing done on cultured fibroblasts.[11]

Germline Next-Generation Sequencing Approaches

In the work-up of MDS, especially in adult hematology/oncology clinics, the use of NGS testing most often refers to targeted panels of somatic mutations known to be associated with myeloid malignancies.[42] These panels are distinct from alternative panels specific to germline mutations. Because of the phenotypic overlap of syndromes and nonclassic presentations, a comprehensive panel-based approach inclusive of the many genes implicated in genetic predisposition to MDS/AML is imperative.

Attention to the details of the testing ordered is vital because, without specific knowledge of the results obtained, false reassurance could come from a negative test that does not cover the relevant genetic markers for the inherited syndrome; this may require specific consultation with the genetic counselors as well as molecular pathologists before testing or at the time of interpretation of the results. The use of NGS methodology to detect point mutations in addition to copy number changes including large deletions/duplications is key.[4,43] It is also important that the NGS panel is specifically designed to capture certain noncoding regions that are known to be involved in disorders that predispose to MDS: the promoter in the 5′ untranslated region (UTR) of *ANKRD26* (most families, reviewed by Godley[43]) and the enhancer region deep in intron 4 of *GATA2* (NM_032638, accounting for at least 10% of families[8,44]). Capture of the UTR of *ANRKD26* is variable on standard clinical whole-exome sequencing, and variants deep in the middle of the large *GATA2* intron 4 are likely to be missed unless specifically targeted. Furthermore, somatic prognostic panels for MDS/AML, many of which include *GATA2*, do not capture these intronic variants nor report known pathogenic synonymous variants. There are several clinically available genetic testing panels for hereditary MDS/AML, and testing methodology, genes included and

interpretation expertise, in addition to turnaround time and cost, should be assessed prior to test selection.

Variants in Known Predisposition Genes Identified on Somatic Panels

As discussed earlier, it is recommended as standard of care to consider molecular testing for somatic mutations associated with MDS.[10] Increasingly these panels guide discussions of biology, prognosis, treatment pathways, and in rare instances targeted therapy on clinical trials. NGS of tumor samples using somatic panels may inadvertently identify patients at risk for germline predisposition to MDS/AML that were not otherwise appreciated to be high risk. Acquired pathogenic/likely pathogenic mutations in the same genes associated with genetic predisposition to MDS (*ANKRD26*, *CEBPA*, *DDX41*, *ETV6*, *GATA2*, *RUNX1*, or *TP53*) may be detected in more than 20% of patients tested with somatic myeloid malignancy panels.[45] Because of gross chromosomal rearrangements and more subtle gains and losses, the variant allele frequency of mutations in peripheral blood–derived DNA from patients with MDS is commonly unreliable, and deleterious variants identified on prognostic panels, especially in *DDX41* and *GATA2*,[45] should be investigated for germline origin regardless of allele frequency.[46] Ten percent of patients with biallelic *CEBPA* variants possess 1 of the 2 mutations in their germlines.[47,48] In genes such as *RUNX1* and *TP53*, the same variants can occur either in the germline or somatically in the MDS/AML clone. In these cases, the presence of a variant in the Catalogue Of Somatic Mutations In Cancer (COSMIC) database does not preclude it from being carried in the germline.[49,50] Variants in other pathways, such as telomerase and telomere maintenance genes, are rarely found in sequenced MDS/AML samples.[51] Germline confirmatory testing should be done in these cases to assess whether the somatically detected variant is really in the germline. In contrast, it is noteworthy that the absence of pathogenic variants on somatic panels does not exclude a germline predisposition and should not be used as a substitute for dedicated germline testing.

Interpretation of Somatic Gene Variants with Germline Allele Frequencies

In general, variants with allele frequencies between 40% and 60% could be germline, as opposed to acquired, in the malignant population. When these occur in genes known to be associated with an MDS predisposition syndrome, as described earlier and in Table 1, further consideration is warranted. When the variant occurs in genes known only to have a somatic role in MDS/AML, the clinician should be cautious before ascribing too much significance to it. It is possible that the variant could still be somatic and the allele frequency explained by the disease burden at the time of testing, or it could be a germline benign polymorphism. These potentially germline and inheritable variants should be approached carefully so as to ensure proper counseling but also avoidance of undue testing burden.

Interpretation of Germline Variants of Unknown Significance

When reviewing the results of somatic panel testing, it is possible for mutations that have a germline association to receive annotation. How these are codified and interpreted may vary by report. Interpretation of dedicated germline sequencing should be done according to guidelines for variant classification from the American College of Medical Genetics and Genomics, which recommends identified variants be assigned 1 of 5 categories: pathogenic,

likely pathogenic, uncertain significance, likely benign, and benign.[52] In patients referred to the laboratory in an academic center for panel-based testing of hereditary MDS/AML, a pathogenic or likely pathogenic variant established the diagnosis in 15–20% of patients, but more than one-third of the patients carried variants of uncertain significance (VUSs) in known genes.[4] VUSs pose a challenge to clinicians and patients; thus, consultation with a geneticist may be indicated. Extreme caution must be taken when basing treatment decisions on the presence of a VUS so as to avoid ascribing a disorder to a nonpathogenic mutation. All individuals carry numerous heterozygous nonsynonymous coding variants in their germlines, many of which are common in the general population and likely benign polymorphisms.[53] Determining the frequency of germline VUSs in the general population is useful in assessing their potential pathogenicity.[54] In a rare mendelian disorder such as these myeloid diseases and syndromes, an allele frequency in the general population that is greater than expected for the disorder is less likely to be driving the disease. However, this assumption is less reliable in diseases with later onset in life.[52,55,56] Functional studies, such as telomere length measurement or chromosome breakage, if not previously done, can aid in assessing the pathogenicity of VUSs where applicable. Use of genomic tumor boards or multidisciplinary groups with germline expertise, in practice at some institutions to assess VUSs, can aid in variant interpretation before clinical decisions are made.[57] Variant pathogenicity should also be reevaluated as new cohorts are sequenced and new evidence is accrued. For example, *TERT* variants A202T, H412Y, and A1046T were at one time thought to be pathogenic, but evidence now suggests these are common polymorphisms.[6,58,59] Additional assessments of variants, such as segregation of VUSs in asymptomatic relatives and in vitro functional studies, should be done on a research basis.

CLONAL HEMATOPOIESIS IN GERMLINE MYELODYSPLASTIC SYNDROMES

The mechanisms by which these germline predisposition syndromes are leukemogenic are not fully understood. There are a few recurrent chromosomal aberrations and somatic mutations that are important to highlight. These mutations can be seen recurrently within MDS/AML arising from a single syndrome, such as somatic *TP53* mutations in Shwachman-Diamond, or shared across MDS arising from different syndromes, such as monosomy 7.

Recurrent Chromosomal Aberrations

The selective pressure of the failing marrow in several of the inherited BMF syndromes drives recurrent, nonrandom chromosomal aberrations,[13,24] which are not necessarily leukemogenic but can affect prognosis. There is an increased prevalence of monosomy 7 in genetically mediated MDS compared with de novo, most commonly reported to date in *SAMD9/9L* in younger children and *GATA2* in adolescents, but this can also be seen in the other syndromes. The loss of chromosome 7 or del(7q) in patients with *SAMD9/9L* mutations (located on chromosome 7q) deletes the mutant allele, alleviating the growth repression caused by the gain-of-function germline mutation. The outcome of this acquired monosomy 7 ranges from normalization of the karyotype and bone marrow (through duplication of the nonmutated allele) or progression to advanced MDS, thought to occur

through acquisition of additional somatic driver mutations. The functional role of monosomy 7 in GATA2-deficient BMF is less clear. Isochromosome 7q and del20q occur in Shwachman-Diamond syndrome,[60] and 1q+ and 3q26q29 amplifications are common in Fanconi anemia.[61–63] Recurrent changes may be found in other inherited BMF syndromes as more cases are systematically studied. Review of the literature, even for case reports at the time of identification of these changes in a single patient, will be important as additional knowledge emerges.

Clonal Evolution Through Acquired Mutations

Driver and cooperating mutations are important for the pathogenesis of both de novo MDS/AML and MDS arising from a germline predisposition. The understanding of these co-mutational patterns is rapidly evolving; these acquired mutations may explain some of the variable penetrance and expressivity seen within families. For this reason, it is vital in older patients with previously undiagnosed predisposition syndromes to have both somatic and germline testing if applicable. In addition, patients with therapy-related myeloid malignancies may be more likely to harbor germline variants in predisposition genes and should be considered for testing as well.[64]

In unaffected *RUNX1* carriers <50 years, 6 of 9 (67%) harbored detectable somatic mutations, and all of the patients with *RUNX1*-mediated MDS/AML (5 of 5) had somatic mutations, suggesting clonal hematopoiesis occurs before the development of overt MDS/AML in *RUNX1* carriers.[65] However, most of these mutations detected by exome sequencing occurred in genes different than those seen recurrently mutated in MDS. In patients with germline *GATA2* mutations who developed MDS/AML, three-quarters (22 of 29) harbored MDS-associated somatic mutations; recurrent mutations in *ASXL1* (40%, loss of function) and *STAG2* (28%) were most common.[66,67] In relatives also carrying *GATA2* mutations but without MDS, it was less common for those with essentially normal marrows to have somatic driver mutations (1 of 5 studied), whereas, in those with abnormal marrows, 5 of 7 had somatic mutations, including 3 with *ASXL1*, suggesting this may be an intermediate phenotype in transition to an MDS state.[67]

Acquired *TP53* mutations were seen in 7 of 7 young adults with biallelic SBDS mutations before HSCT for MDS.[2] Further, ultradeep sequencing of patients with Shwachman-Diamond without MDS/AML has also identified acquired *TP53* mutations in half (13 of 27 patients), although at exceptionally low allele frequencies (median 0.36%, range 0.05%–3.1%) of unclear clinical significance.[68] The role of these recurrent events in the transformation to MDS/AML is an active area of research. Application of these somatic findings to monitoring and prevention is not yet established. Furthermore, the lack of prospective observational data limits the clinical ability to incorporate the knowledge of somatic variants' presence for prognostication in predisposed patients before the development of MDS.

SURVEILLANCE AND MANAGEMENT

There are many bedside benefits of real-time diagnosis of a germline MDS predisposition disorder. Some germline MDS predisposition disorders are characterized by

extrahematopoietic manifestations, which can contribute to significant morbidity and for which screening can change management (see Table 1). Another important clinical advantage is insight into the natural history of the disorder. Most importantly, the added knowledge of a germline syndrome can alter or facilitate more appropriate therapy in affected individuals. Presumed lack of responsiveness to noncurative therapies for a germline disease likely prompts HSCT evaluation sooner from an unrelated donor. Recognition of the possibility of these diagnostic and treatment interactions is only the first step and then appropriate referrals with the use of resources can follow.[71]

Selection of Related Donors

Recognition of an inherited disorder is important before assessment and selection of a related donor. Unexplained cytopenias, recurrent/severe infections, or failure to mobilize stem cells in a donor may be caused by an underlying marrow failure syndrome and warrant additional investigation. However, completely asymptomatic related donors may still be carriers of the familial mutation because there can be significant heterogeneity for hematologic and extrahematopoietic manifestations within and across families carrying the same mutation. If a mutation has been identified in the recipient, potential related donors should be counseled and then offered targeted testing to screen for this mutation. Results of this testing are important both for decision on use as a donor as well as to identify the person's own potential predisposition and disease risk. These aspects should be explained clearly to the patient and related donor as the process is ongoing. Using a related donor carrying the familial mutation puts both the donor and recipient at risk for complication.[72,73]

If the personal or family history is suspicious for a germline MDS predisposition syndrome but no causative mutation can be identified, an attempt should be made to find a matched unrelated donor in hopes of avoidance of the conceivable risk of transplanting the causative mutation. If there is no HLA-matched unrelated donor or there is an urgent indication for HSCT, the potential risks and benefits should be discussed with both the recipient and the donor.[73] It is also possible to use second-degree relatives as haploidentical donors, so there may be less traditional options to find a suitable donor for potentially curative HSCT in these families as well.[74] Regardless, bone marrow studies and thorough hematologic evaluation in relatives under consideration for allograft donation is strongly encouraged.

Recipient Specific Implications

Diagnosis of a germline MDS predisposition disorder also has implications for timing of transplant, preparative regimens, and posttransplant care. Understanding the natural history of individual disorders is critical to making decisions at the bedside. Patients with Fanconi anemia and short telomere syndromes can experience increased toxicity from standard chemotherapy and radiation and need attenuated regimens; however, there is more published experience with HSCT for BMF than MDS.[75–77] Patients with short telomere syndromes post-HSCT continue to be at risk for additional short telomere manifestations as they age, which can occur at an earlier age in this setting. Patients with Fanconi anemia have an increased cancer risk post-HSCT.[69,78] Patients with germline *CEBPA* mutations are at risk of second primary AMLs, but prospective trials have not been done to assess the best timing for HSCT in this situation.

Familial Implications

Identification of a genetic predisposition to MDS has implications for both the immediate and extended family. This possibility should be discussed with the patients by genetic counselors or clinicians experienced in these issues before genetic testing is pursued. In children, parental testing to determine whether a variant is inherited or de novo should be obtained before screening asymptomatic siblings. Genetic testing of asymptomatic individuals, especially children, should only be undertaken after consultation of risks and benefits with a genetic counselor. This consultation can become more complicated with adult children of older patients with MDS, given that it is less expected in these ages to diagnose a germline condition. Dialogues surrounding the repercussions must be had transparently with all those involved.

EMERGING IDEAS

Discovery

The genetic cause for more than half of familial MDS/AML cases remains unsolved.[6,38,65,80] Further study of these families, especially of those who present as adults, has the potential to identify new mechanisms of disease in known genes (regulatory mutations, synonymous mutations) and identify new genes and pathways. This knowledge will aid in diagnosis, surveillance, and management, and also may provide insight into leukemogenic mechanisms for prevention and targeted therapy in both germline and somatic conditions.

Prevention and Treatment

Increasing use of targeted treatments in MDS/AML may apply to familial cases with sporadic mutations in these same pathways. Understanding of the pathogenesis in specific syndromes may also lead to targeted therapies that can be used for prevention of MDS/AML. It is hoped that additional investigation of genetic and epigenetic alterations in these patients will elucidate the mechanisms of reduced penetrance in some syndromes and also lead to prevention strategies. Acquisition of multiple somatic mutations in genes recurrently mutated in myeloid malignancy is high risk for transformation. No prospective trials exist to guide treatment decisions, but consideration of intervention should be discussed with the patient.

SUMMARY

Germline predisposition to MDS, even in adults, is more common than was previously recognized and important to diagnose in real time before treatment, and especially before HSCT. Individual syndromes may be rare but, collectively, represent a significant risk in both pediatric and adult patients. Awareness of the risk as well as methods of identification are increasingly important steps in providing high-quality care to all patients with MDS. Growing knowledge about this has the potential to lead to personalized treatment paradigms for these patients that also have broader implications for the more numerous patients with somatic mutations in similar pathways.

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KEY POINTS

- Inherited predisposition to myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) occurs in children as well as older adults.
- Analysis of the genetics of the disease is now standard of care in the evaluation of patients with MDS.
- Patients without syndromic features and negative family histories can still have a germline predisposition to MDS.
- Somatic tumor panels cannot replace dedicated genetic evaluations for germline mutations in the many genes implicated in genetic predisposition to MDS/AML.
- Diagnosis of an inherited predisposition has important implications for counseling and management.

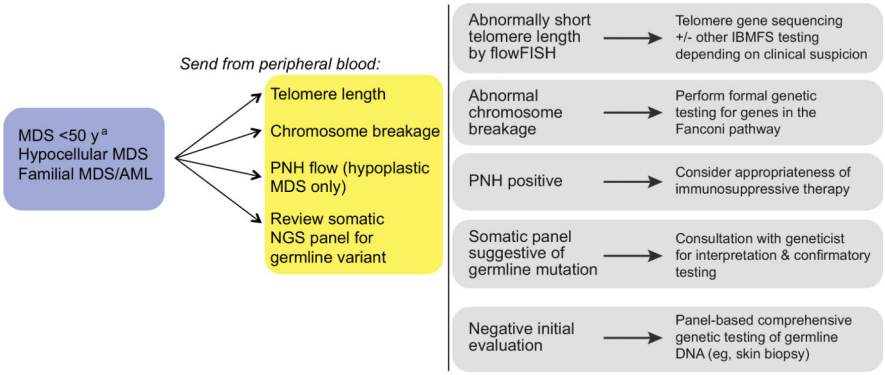

Fig. 1.

Screening and evaluation for genetic predisposition to MDS. flowFISH, flow cytometry and FISH; IBMFS, inherited bone marrow failure syndrome; NGS, next-generation sequencing.

[a] Limiting screening to patients less than 50 years old misses cases of inherited MDS/AML.

Table 1

Genes involved in predisposition to myelodysplastic syndrome/acute myeloid leukemia and important clinical features

Syndrome	Gene(s)	Inheritance Mutation Types	Age of MDS/AML Onset (range, y)	Hematologic Features	Extrahematopoietic Features	Other Cancers	Implications for Management	References
Myeloid Neoplasms with Germline Predisposition Without Preexisting Disorder or Organ Dysfunction								
Familial AML with CEBPA mutations	*CEBPA*	AD Missense, FS	Adult>Ped (range 1–62)	AML	—	—	Chemosensitive Risk of second primary AML	47,48,81–86
Familial MDS/AML with mutated DDX41	*DDX41*	AD Missense, FS, NS, CNV	Older adult (range 40–89)	MDS, AML, CML Lymphoma	Granulomatous and autoimmune disorders in a few families	—	—	70,87–91
Myeloid neoplasms with germline predisposition and preexisting platelet disorders								
ANKRD26-related thrombocytopenia	*ANKRD26*	AD UTR variants; coding NS, missense[a]	Adult (range 26–70)	MDS, AML, CML CMML, CLL Thrombocytopenia	—	—	Mild bleeding tendency	92–98
ETV6-related thrombocytopenia	*ETV6*	AD Missense, FS, NS	Ped-Adult (range 8–82)	B-ALL, MDS, AML, CMML, DLBCL Variable thrombocytopenia	Not shared across pedigrees (developmental delay, dysmorphisms, autoimmunities)	Colon, breast, meningioma	Mild to moderate bleeding tendency	99–106
Familial platelet disorder with propensity to AML	*RUNX1*	AD Missense, FS, NS, CNV, rearrangements	Adult>Ped (range 5–72)	MDS, AML, T-ALL, hairy cell leukemia, CMML Mild to moderate thrombocytopenia	Case report of co-occurring eczema	—	—	50,112–120
Myeloid neoplasms with germline predisposition and other organ dysfunction								
Germline SAMD9/ SAMD9L	*SAMD9* *SAMD9L*	AD Missense	Ped, rare adult (range 1–56)	AA, MDS, AML, CMML[a] Increased prevalence of monosomy 7	MIRAGE syndrome (*SAMD9*) Ataxia-Pancytopenia (*SAMD9L*)	—	—	7,37,38,121–124
Familial MDS/AML with GATA2 mutation	*GATA2*	AD Missense, NS, FS, splicing, regulatory, CNV	AYA (range 3–78)	AA, MDS, AML, CMML Increased prevalence of monosomy 7	Infection Lymphedema Pulmonary alveolar proteinosis Hearing loss	—	—	8,19,44,65,107–111

Syndrome	Gene(s)	Inheritance Mutation Types	Age of MDS/AML Onset (range, y)	Hematologic Features	Extrahematopoietic Features	Other Cancers	Implications for Management	References
Diamond-Blackfan anemia	*GATA1* *RPL5* *RPL11* *RPL15* *RPL23* *RPL26* *RPL27* *RPL31* *RPL35a* *RPL36* *RPS7* *RPS10* *RPS15* *RPS17* *RPS19* *RPS24* *RPS26* *RPS27* *RPS27A* *RPS28* *RPS29* *TSR2*	AD, X linked (*GATA1, TSR2*) Missense, FS, NS, splicing, CNV, 3′ UTR	Adult>Ped (range 2–57)	Red cell aplasia, MDS, AML	Growth retardation, congenital malformations	Osteosarcoma, colon, possibly others	—	69,125–128
Fanconi anemia	*FANCA* *FANCB* *FANCC* *FANCD1/BRCA2* *FANCD2* *FANCE* *FANCF* *FANCG* *FANCI* *FANCJ/BRIP1* *FANCL* *FANCM* *FANCN/PALB2* *FANCO/RAD51C* *FANCP/SLX4* *FANCQ/ERCC4* *FANCR/RAD51* *FANCS/BRCA1* *FANCT/UBE2T* *FANCU/XRCC2* *FANCV*	AR AD (*FANCR*) X linked (*FANCB*) Missense, FS, NS, splicing, CNV	AYA (range 1–57)	AA, MDS, AML ALL with *FANCD1*	Short stature, developmental delay, skeletal and renal abnormalities	SCC of head, neck and anogenital region	Require attenuated therapy, radiosensitive	61,69,129–132

Syndrome	Gene(s)	Inheritance Mutation Types	Age of MDS/AML Onset (range, y)	Hematologic Features	Extrahematopoietic Features	Other Cancers	Implications for Management	References
Short telomere syndromes	*ACD/TPP1* *CTC1* *DKC1* *NAF1* *NHP2* *NOP10* *PARN* *POT1* *RTEL1* *TR* *TERT* *TINF2* *WRAP53/TCAB1* *ZCCHC8*	AD, AR, X linked Missense, FS, NS, splicing, CNV *TR*: SNV, INDELs	Adult>Ped (range 2–77)	AA, MDS, AML	Mucocutaneous features, pulmonary fibrosis, liver disease, immunodeficiency, enteropathy, severe congenital anomalies in some	SCC of head, neck and anogenital region	Attenuated regimen, radiosensitive	69,79,80,133–144
Shwachman-Diamond	*SBDS* *DNAJC21* *EFL1*	AR Missense, FS, NS, splicing, CNV	AYA (range 2–53)	Neutropenia, MDS, AML	Exocrine pancreatic insufficiency, neurodevelopmental and skeletal abnormalities	—	—	2,38,69,145–147
Traditional Hereditary Cancer Predisposition Syndromes								
Li-Fraumeni	*TP53* *CHEK2*	AD Missense, FS, NS, splicing, intronic, CNV	Ped + adult (range 4–50)	ALL, MDS, AML, CML, lymphoma	—	Breast, sarcoma, CNS, adreno cortical carcinoma	—	6,148–152

Abbreviations: AA, aplastic anemia; AD, autosomal dominant; ALL, acute lymphoblastic leukemia; AR, autosomal recessive; AYA, adolescent and young adult population; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CNV, copy number variant; DLBCL, diffuse large B-cell lymphoma; FS, frameshift; MIRAGE, myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes and enteropathy; NS, nonsense; Ped, pediatric-onset disease; SCC, squamous cell carcinoma.

[a]Finding reported in a single family or case report.

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