Inherited Predisposition to Acute Myeloid Leukemia

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Germline testing for familial predisposition to myeloid malignancies is becoming more common with the recognition of multiple familial syndromes. Currently, Clinical Laboratory Improvement Amendments–approved testing exists for the following: familial platelet disorder with propensity to acute myeloid leukemia, caused by mutations in RUNX1; familial myelodysplastic syndrome/acute myeloid leukemia with mutated GATA2; familial acute myeloid leukemia with mutated CEBPA; and the inherited bone marrow failure syndromes, including dyskeratosis congenita, a disease of abnormal telomere maintenance. With the recognition of additional families with a genetic component to their myeloid diseases, new predisposition alleles are likely to be identified. Awareness of the existence of these syndromes will facilitate proper genetic counseling, appropriate testing, and clinical management of these cases.

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Familial cases of adult myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) are considered rare but are likely to be more common than currently appreciated. Understanding the recognized syndromes is critical for clinicians to have a high index of suspicion and offer appropriate genetic counseling and testing.1,2 Familial MDS/AML can be divided into 3 groups: those for which Clinical Laboratory Improvement Amendments (CLIA)-approved testing exists, those emerging from basic research and requiring validation in additional families and/or development of clinical testing, and those without an identified genetic basis. Examples of familial MDS/AML syndromes for which clinical testing is available include the following: familial platelet disorder with propensity to myeloid leukemia (FPD/AML), caused by mutations in RUNX1; familial MDS/AML with mutated GATA2; familial AML with mutated CEBPA; and the inherited bone marrow failure syndromes, including dyskeratosis congenita, a disease of abnormal telomere maintenance, and Fanconi anemia (FA). Clinical testing and management of patients with a suspected inherited predisposition to AML/MDS are complicated by the few clinical guidelines available for patients found to have a predisposing mutation.3,4 The present review focuses on the current understanding of the genetic basis and clinical presentation of known and emerging familial MDS/AML syndromes.

HOW TO RECOGNIZE AND MANAGE PATIENTS WITH A FAMILIAL MYELOID LEUKEMIA SYNDROME

To recognize which patients may have an inherited predisposition to myeloid disease, clinicians must take a complete family and bleeding history and be familiar with the characteristics of the recognized familial MDS/AML syndromes. Consultation with a certified genetic counselor familiar with inherited hematopoietic predisposition syndromes and documentation of a complete family history are integral to this assessment. Guidelines suggest that formal genetic counseling should be given to several classes of individuals: any patient with acute leukemia (AML or acute lymphoblastic leukemia [ALL]) or MDS with a first- or second-degree relative with AML, ALL, MDS, thrombocytopenia, a clinical bleeding propensity, macrocytosis, abnormal nails or skin pigmentation, or oral leukoplakia; any patient with a hematologic malignancy occurring at a young age (<45 years old) with a first-degree relative with any cancer occurring at a young age (<45 years old) or multiple first- and second-degree relatives with cancers (especially sarcoma, early-onset breast cancer [<50 years old], and brain tumors); or any healthy related stem cell donor (donating for a family member with a hematologic malignancy who requires an allogeneic stem cell transplantation [SCT]) who is found to have thrombocytopenia, a clinical bleeding propensity, macrocytosis, abnormal nails or skin pigmentation, or oral leukoplakia or who fails to mobilize stem cells well according to standard protocols.3,4

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Certain features of the history or laboratory values may increase the likelihood of a particular syndrome over others in individual cases, as highlighted in the following discussion. The assembly of a family pedigree aids in developing a differential diagnosis to determine the most likely genetic syndrome in the family, allowing construction of a genetic testing plan appropriate for the patient’s clinical situation. Patients under consideration for allogeneic stem cell transplantation (SCT) with a human histocompatibility leukocyte antigen (HLA)-matched relative warrant expedited genetic testing to rule out a familial MDS/AML predisposition syndrome; use of hematopoietic stem cells from a relative carrying the familial mutation can then be avoided. In these cases, testing of multiple genes at once, rather than sequential testing, is appropriate.

During pretest genetic counseling, the patient and his or her family should receive education on the principles of human genetics and details about what is known about the specific hereditary syndrome(s) being considered in the patient’s case. This information forms the basis of the informed consent process for genetic testing, ensuring that the patient understands the risks and benefits of genetic testing, the possible testing outcomes, alternatives to genetic testing, and the potential medical and psychological impact of test results on the patient and his or her family.

For all subjects who undergo genetic testing, a follow-up plan for disclosure of genetic test results, whether they are negative or positive, should be in place. Ideally, genetic testing results should be given in a face-to-face setting and should include post-test genetic counseling focused on educating the patient about the meaning of his or her test results, the implications of the results for the patient’s health or clinical management, and any additional testing. In the event of a positive genetic test result, it is important to discuss the implications of these results for other at-risk family members and to inform the patient of his or her duty to share this information with at-risk family members. Individual genetic counseling would also be recommended for these family members. Additional health implications should be discussed, such as the risk of non-hematologic malignancies associated with certain germline disorders, including telomere biology disorders or FA, as well as the implications on selection of treatment modality, including alternative treatment protocols. All mutation carriers should be counseled to avoid exposure to known bone marrow toxins (eg, smoking, heavy alcohol use). Other genetic issues, including risk of recurrence and preimplantation genetic testing for potential parents, should be addressed.

We recommend that all mutation carriers undergo a baseline bone marrow biopsy to assess for occult malignancy, as well as twice-annual physical examinations and complete blood cell count with differential testing. If there is a significant change from baseline, the complete blood cell count should be repeated 1 to 2 weeks later, and a bone marrow evaluation should be repeated if the change persists. If a mutation carrier develops a bone marrow malignancy, we recommend against using stem cells from any donor who also carries the familial MDS/AML predisposition mutation because poor engraftment, graft failure, and donor-derived leukemia can occur. Certain families have a clinical history consistent with a predisposition to MDS/AML but who do not carry a mutation in one of the familial MDS/AML predisposition genes for which CLIA-approved testing exists; for these families, the treating physician should weigh the strength of the confirmed family history as well as the availability of unrelated donors and the urgency of the transplant when deciding whether to use an HLA-matched related donor.

**KNOWN CAUSES OF FAMILIAL MYELOID MALIGNANCIES**

**Predisposition Associated With Thrombocytopenia and Platelet Dysfunction: Germline RUNX1 and ANKRD26 Mutations**

Germline mutations in two genes (RUNX1 and ANKRD26) are each associated with platelet abnormalities, both in platelet numbers and function, as well as predisposition to myeloid malignancies. In some cases, thrombocytopenia may be mild, with platelet counts between 100,000 and 149,000/μL; these levels often result in a lack of clinical recognition. Platelet aggregation studies also demonstrate abnormal platelet function, although these tests may be difficult to perform in the setting of thrombocytopenia, because they often require minimum platelet counts of 100,000/μL. Therefore, in patients and families who present with thrombocytopenia and myeloid malignancies, beginning analysis with these two genes is reasonable, although the current lack of a clinical test for ANKRD26 may hamper the widespread availability of this analysis.

**Familial Platelet Disorder With Propensity to AML (Germline RUNX1 Mutations; Online Mendelian Inheritance in Man #601399)**

**Background**

As described earlier, FPD/AML is characterized by platelet dysfunction, often causing clinical bleeding with minor trauma or surgical procedures as well as poor wound healing, mild to moderate thrombocytopenia, and a propensity to develop myeloid malignancies. The syndrome is caused by germline mutations in RUNXI, which encodes one subunit of a heterodimeric transcription factor that controls genes essential for hematopoiesis. Most individuals have a hemizygous mutation, but rarer gene rearrangements have also been described (Figure 1A). Within individual FPD/AML families, carriers of the same RUNXI mutation display heterogeneity in phenotype, with some family members having moderate thrombocytopenia/bleeding...
and/or myeloid malignancies, whereas others appear unaffected. Interestingly, when multiple members of the same family develop myeloid malignancies, they can develop MDS/AML of varying subtypes, suggesting that although every affected family member has the same germline mutation, different secondary genetic mutations can lead to distinct diseases. In addition to myeloid malignancies, families with FPD/AML are at risk for the development of T-cell ALLs; B-cell malignancies have also been described in RUNX1 mutation carriers, although very rarely.

Distinct FPD/AML families have varying risks of progression to myeloid malignancy (range, 11%-100%; median, 44%),\(^8,9,11-19\) which likely reflects the fact that each family carries unique mutations that disrupt different domains within the protein. Many types of germline RUNX1 mutations have been described (Figure 1), including frameshift and nonsense mutations throughout the gene and missense point mutations within the highly conserved RUNT homology domain at residues important for DNA binding or heterodimerization. Truncating mutations within the RUNT domain result in hypomorphic alleles, whereas at least one mutation that truncates the protein at the extreme C-terminus activates the baseline transcriptional activity of the protein when tested in vitro, despite resulting in the same clinical syndrome.\(^17\) Rarely, partial or whole-gene deletions as well as gene duplications have also been described (Figure 1B). For this reason, germline testing for subjects with suspected RUNX1 mutations should include tests capable of detecting gene deletions, duplications, and rearrangements, if standard sequencing techniques fail to identify a point mutation.\(^19-21\) Gene rearrangements can be detected through genomic arrays or multiplex ligation probe-dependent amplification analysis. Microdeletions of chromosome 21q22 (the genomic locus containing RUNX1) are associated with growth and developmental delay, dysmorphic features, congenital heart defects, and platelet abnormalities with predisposition to MDS/AML.\(^21-23\)

**Molecular Pathogenesis**

RUNX1 is known to act as a direct transcriptional activator of several proteins important for platelet function (PRKCQ, MYL9, and ALOX12) and as a transcriptional repressor of others, including MYH10\(^24-27\) and ANKKRD26.\(^28\) In addition, germline RUNX1 mutations were found in 23% (3 of 13) of families with excessive bleeding, mild thrombocytopenia, and platelet-dense granule secretion abnormalities.\(^29\) The prevalence of germline RUNX1

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**Figure 1.** Missense, nonsense, frameshift, duplication, and deletion mutations in RUNX1. (A) Protein schematic of RUNX1 isoform B (NP_001001890.1). Missense mutations are shown in grey/solid arrows; nonsense mutations in grey/dashed arrows; and frameshift, duplication, and deletion mutations in black. Superscripts used for the deletion mutations delineate those shown in greater detail in part B. Adapted from Owen et al.\(^30\) (B) Genomic structure of RUNX1 demonstrating locations of disease-causing deletions. ATG\(_1\), the first start codon, corresponds to full-length RUNX1 isoform C (NP_001116079.1), and ATG\(_2\), the second start codon, corresponds to RUNX1 isoform B (NP_001001890.1). The genomic location of RUNX1 is given at the top of the figure.
mutations in individuals/families presenting with predisposition to myeloid leukemias has not been determined. Despite this detailed knowledge regarding the role of RUNX1 in megakaryopoiesis, it is unclear how haploinsufficiency of RUNX1 leads to malignancies and whether the abnormalities in platelet number and function are related in any way to cancer predisposition in RUNX1 mutation carriers.

**Presentation**

The presence of qualitative and quantitative platelet defects in a family with multiple individuals who have developed myeloid leukemias, or less commonly, T-cell ALL or B-cell malignancies could suggest a germline RUNX1 mutation. However, the phenotypic variation that can be seen within and among families makes this syndrome particularly difficult to diagnose. For this reason, we recommend testing subjects for germline RUNX1 mutations if more than two individuals in the family have been diagnosed with a myeloid malignancy (particularly when at least one subject is thrombocytopenic).

**Management**

Because germline RUNX1 mutations do not predispose to a single type of myeloid disease, the management of a patient with a germline RUNX1 mutation and a bone marrow–derived malignancy is dictated by the nature of the leukemia. The diagnosis of an underlying germline mutation is critical when considering allogeneic SCT using a related donor for consolidation therapy, because transplant is the only way to rid the bone marrow of the underlying predisposing allele. In this case, clinical RUNX1 mutation testing in HLA-matched relatives must be performed in a timely manner, and if an appropriate related donor does not exist, an unrelated donor should be considered.

Managing RUNX1 mutation carriers who have not developed myeloid malignancies is very difficult, because clinical guidelines for these patients have only been discussed recently. Because FPD/AML displays strong anticipation (the phenomenon in which members of younger generations present with disease at earlier ages than those of previous generations), it is critical to provide close clinical follow-up for members of the youngest generations in the family. Generally, we recommend performing a baseline complete blood cell count with differential and a bone marrow biopsy, and screening all first-degree relatives to identify those who are HLA-identical before malignancy is diagnosed; this information will expedite the clinical management of the affected subject. Thereafter, we recommend twice yearly complete blood cell counts and repeating a bone marrow biopsy only if there is a significant change in the peripheral blood counts.

**Thrombocytopenia 2 (Germline ANKRD26 Mutations) (Online Mendelian Inheritance in Man #610855)**

**Background**

Thrombocytopenia 2 is an autosomal dominant thrombocytopenia with moderate thrombocytopenia, demonstrating normal mean platelet volumes; elevated thrombopoietin levels; variable aggregation defects in response to collagen, adenosine diphosphate, or ristocetin; and bone marrow examinations revealing dysmegakaryopoiesis with small megakaryocytes and hypolobulated nuclei. In > 20 families with thrombocytopenia 2, point mutations and one deletion mutation have been identified within a 22 base-pair region of the ANKRD26 5’ untranslated region (UTR) (Figure 2). One family has been described with a missense mutation (D158G) encoded within exon 2. Individuals with ANKRD26 mutations have a 30-fold increased risk of developing MDS/AML compared with expected levels.

**Molecular Pathogenesis**

ANKRD26 encodes for a protein with N-terminal ankyrin domains thought to mediate protein–protein interactions. However, ANKRD26 mutations are unusual in that most

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**Figure 2.** Mutations within ANKRD26. Schematic diagram of the ANKRD26 gene, showing the promoter with mutations within the 5’ untranslated region and one reported missense mutation encoded by exon 2. One deletion mutation has been described within the promoter, indicated by the box and grey highlighting. The genomic location of ANKRD26 is given at the top of the figure.
have been described within the 5′ UTR of the gene,31,32,34 with only one family to date having a point mutation within the coding region.55 The 5′ UTR mutations disrupt the assembly of RUNX1 and FLI1 on the ANKRD26 promoter, in which they act as transcriptional repressors, resulting in increased gene transcription and consequently increased signaling through the MPL pathway, leading to impaired pro-platelet formation by megakaryocytes.28 Inhibition of ERK rescues the pro-platelet defect in vitro, implicating the mitogen-activated protein kinase pathway in the thrombocytopenia 2 platelet defect. Furthermore, the platelets and megakaryocytes from subjects with ANKRD26 mutations contain elevated levels of ubiquitin/proteasome-rich particulate cytoplasmic structures, particulate structures identifiable by electron microscopy within the cytoplasm and found in several solid tumors, Helicobacter pylori–associated gastritis and related preneoplastic lesions, and in the neutrophils from patients with Shwachman-Diamond syndrome.36 The link between the presence of particulate cytoplasmic structures, platelet dysfunction, and predisposition to myeloid malignancies is not yet clear.

Presentation

Patients with ANKRD26 mutations are recognized by their familial inheritance of thrombocytopenia in combination with increased risk of hematologic malignancies. Currently, there is no CLIA-approved test for these mutations.

Management

The presentation of a patient with long-standing thrombocytopenia should prompt a consideration for a germline mutation. Often these patients have been given a diagnosis of autoimmune-based idiopathic thrombocytopenic purpura. However, when patients present with chronic thrombocytopenia and any family history of bleeding and/or MDS/AML, strong consideration should be given to the presence of a RUNX1 or ANKRD26 mutation. If either is confirmed, the patient and at-risk family members should receive genetic counseling, appropriate screening, and a discussion of management options and the risks of developing myeloid malignancy. As discussed, the specific management of a hematologic malignancy follows the malignant diagnosis.

PREDISPOSITION ASSOCIATED WITH LYMPHEDEMA—MONOCYTE AND IMMUNE DYSFUNCTION: GERMLINE GATA2 MUTATIONS

Familial MDS/AML With Mutated GATA2 (Online Mendelian Inheritance in Man #137295)

Background

Individuals with germline mutations in GATA2 (Figure 3) exhibit phenotypic heterogeneity, which can be grouped into several described syndromes: familial MDS/AML, MonoMAC syndrome, and Embberger syndrome. Interestingly, an inherited GATA2 mutation has been described in at least one case with phenotypic features that combine those found in both MonoMAC and Embberger syndromes.37 All of these syndromes lead to an overall increased risk of developing MDS/AML, with ~70% of subjects with germline GATA2 mutations developing MDS/AML.38

Molecular Pathogenesis

GATA2 encodes a zinc finger transcription factor critical for normal hematopoiesis39,40 and lymphatic vascular development.41 Using a targeted sequencing approach, 29% of patients with a germline GATA2 mutation had an acquired ASXL1 mutation identified within the hematopoietic malignancy, suggesting cooperativity between these two genes.38,43 ASXL1 encodes a polycomb-associated protein that co-localizes with ETS (E-twenty six) transcription factors and influences histone modifications.44–46

Presentation

Familial MDS/AML With GATA2 Mutations. Among the ~200 individuals described to date with germline GATA2 mutations, all show a highly penetrant autosomal dominant inheritance pattern of early-onset MDS/AML, with poor outcomes, especially when combined with ASXL1 mutations.42,47 The MDS that arises in GATA2 mutation carriers is often hypocellular with increased reticulin fibrosis, and progression to AML is often associated with the acquisition of an ASXL1 mutation.42,48 Monosomy 7 is often observed along with trisomy 8 and trisomy 21.

MonoMAC Syndrome. The MonoMAC syndrome comprises severe monocytopenia and infections with nontuberculous Mycobacteria, typically Mycobacterium avium complex (MAC). Patients exhibit natural killer–cell and B-cell lymphocytopenia and severely decreased circulating and tissue dendritic cells as well as a predisposition to MDS/AML or chronic myelomonocytic leukemia.39 They develop disseminated viral and opportunistic fungal infections as well as pulmonary alveolar proteinosis. In these patients, the infectious and pulmonary features of MonoMAC syndrome tend to predate the development of bone marrow malignancy and are thought to arise from tissue macrophage dysfunction mediated by GATA2 deficiency.

Patients with MonoMAC syndrome display a significantly younger average age of onset compared with de novo MDS patients (33 vs 70-80 years), with characteristic bone marrow features including hypopcellularity, significant fibrosis, and multilineage dysplasia.50 Common cytogenetic abnormalities include monosomy 7, trisomy 8, and trisomy 1q.
Emberger Syndrome. Emberger syndrome is defined by primary lymphedema of the lower extremities and genitals, with myelodysplasia progressing to AML. Additional clinical features may include a low CD4/CD8 T-cell ratio, cutaneous warts, and sensorineural deafness. When inherited, Emberger syndrome occurs in an autosomal dominant fashion with incomplete penetrance. One series identified eight independent \( \text{GATA2} \) variants in 14 subjects with Emberger syndrome.\(^\text{51}\) The cytogenetic abnormalities seen in these subjects also include monosomy 7, and their MDS often rapidly transforms to AML.

**Diagnosis**

Clinical sequencing testing of the entire coding region of \( \text{GATA2} \) is available. Given the existence of pure familial MDS/AML with mutated \( \text{GATA2} \), this test should be considered in all patients being evaluated for a familial predisposition to myeloid malignancy.

**Management**

Management of a subject’s bone marrow malignancy is typically similar to that presenting sporadically, although special consideration for the use of allogeneic SCT should be entertained when considering familial predisposition syndromes.

**PREDISPOSITION ASSOCIATED WITH A FAVORABLE PROGNOSIS: GERMLINE \( \text{CEBPA} \) MUTATIONS**

Familial AML With Mutated \( \text{CEBPA} \) (Online Mendelian Inheritance in Man #116897)

**Background**

Familial AML with mutated \( \text{CEBPA} \) (Figure 4) is inherited in an autosomal dominant fashion and displays complete or near-complete penetrance for development of AML.\(^\text{30,52,53}\) Generally of favorable prognosis.\(^\text{54}\) Notably, \( \text{CEBPA} \) is also mutated sporadically in AML, but the familial form is associated with biallelic \( \text{CEBPA} \) mutations, most commonly with the germline mutation found within the 5’ end of the gene, accompanied by acquisition of a second 3’ mutation in the leukemia. However, germline 3’ \( \text{CEBPA} \) mutations have also been identified.\(^\text{55,56}\) Because \( \text{CEBPA} \) mutations confer prognostic information, \( \text{CEBPA} \)
mutation testing is becoming routine in the diagnosis of leukemia, and patients found to have biallelic CEBPA mutations within their leukemic cells should be tested for germline mutations.57,58

**Molecular Pathogenesis**

CEBPA encodes a master hematopoietic transcription factor that acts as a critical regulator of granulocyte and monocyte differentiation.59 CEBPA activity is disrupted by a variety of mechanisms in AML, including via gene repression occurring as a consequence of promoter methylation and the action of leukemia-specific translocation fusion proteins.

Genetic testing of the single exon comprising CEBPA is available clinically, and no germline mutations causing familial AML with mutated CEBPA have been reported outside the coding region.

**Presentation**

Although germline CEBPA mutations confer no specific genotype– phenotype relationships, the familial and sporadic forms of the disease share similar pathologic features, including normal cytogenetic analysis, a predominance of FAB subtypes M1 and M2, the presence of numerous Auer rods, and aberrant CD7 expression in leukemic blasts. AMLs with a germline CEBPA mutation and a normal karyotype have an overall favorable prognosis, with survival rates in the 50% to 65% range, compared with survival rates of 25% to 40% in normal-karyotype AML without germline CEBPA mutations.60–63 Approximately 9% of AML patients, and 15% to 18% of AML patients with normal karyotype, have either a germline or (more commonly) somatic CEBPA mutation.53 In one series, 18 of 187 consecutive patients presenting with AML were found to have CEBPA mutations, two of which were germline. Both of the patients with germline CEBPA mutations also had a family history of AML.64 This study provides the best estimate of the prevalence of germline CEBPA mutations in AML: 1% (2 of 187) of all AML cases, and 11% (2 of 18) of those with CEBPA mutations. Monozygotic twins with germline CEBPA mutations have also been reported.65

**Management**

Management of cases of familial AML with mutated CEBPA may include allogeneic SCT, because it is the only treatment capable of replacing the mutated allele within the bone marrow.66 However, given the relative favorable prognosis of familial CEBPA AML, the risks of this procedure must be considered on an individual basis. Of note, patients with familial CEBPA-mutated AML may be at increased risk of developing additional malignant clones after initial treatment, as evidenced by the appearance of clones with acquired CEBPA mutations distinct from those found in the original leukemia.64 Therefore, both longer and more frequent post-cure surveillance may be appropriate in patients with the familial form of disease.

Because penetrance is nearly complete, genetic counseling is critical for these patients. Although thus far all reported patients have had an affected parent, either the identification of a de novo mutation in a proband or the early unrelated death of a parent could potentially confound diagnosis.

**Telomere Biology Disorders and Inherited Bone Marrow Failure Syndromes**

**Background**

Within the spectrum of inherited bone marrow failure syndromes, the telomere biology disorders (TBDs) are associated with abnormal telomere maintenance and predisposition to MDS/AML.67 DC is the prototypical example of a TBD, with its classic triad of nail dystrophy, abnormal reticular skin pigmentation, and oral leukoplakia.68 Patients with DC have a high risk of MDS/AML, with an observed/expected ratio of 2663 (95% confidence interval, 858–6215) and a mean age of onset of 35 years.69 Because the genetic causes and clinical presentations of TBDs are heterogeneous, not all patients with a TBD demonstrate the classic features, and patients may present initially with bone marrow failure, MDS, or pulmonary fibrosis.70,71 Bone marrow failure is the leading cause of death in affected patients.58
**Molecular Pathogenesis**

TBDs result from mutations in at least 10 genes with three inheritance patterns. X-linked recessive DC (Online Mendelian Inheritance in Man [OMIM] #305000) is associated with mutations in *DKC1*. Autosomal recessive DC (OMIM #224230) results from mutations in *NOP10*, *TERT*, *NPH2*, *TCAB1* (also known as *WRAP53*), *C1orf57*, or *RTEL1*. Autosomal dominant DC (OMIM #127550) results from mutations in *TERT*, *TERC* (Figure 5), *TINF2*, or *RTEL1*. Heterozygous mutations in the telomerase reverse transcriptase *TERT* and RNA component—encoding gene *TERC* may present as familial MDS/AML predisposition syndromes. Of note, biallelic mutations in *TERT* resulting in autosomal recessive DC are generally more severe than monoallelic *TERT* mutations seen in autosomal dominant DC, with the presence of mucocutaneous features of the disease and greatly reduced telomeric repeat amplification protocol activity, a measurement of telomerase activity. Mutations in *TINF2*, which encodes the shelterin component TIN2, lead to extremely short telomeres and often present as de novo mutations, leading to severe DC or other genetic syndromes, with high penetrance and an early age of onset. Recently, mutations in *RTEL1*, a gene encoding a telomere-associated elongation helicase, were identified in two families with Hoyeraal-Hreidarsson syndrome, a clinically severe form of DC that includes cerebellar hypoplasia, immunodeficiency, enteropathy, and intrauterine growth retardation.

**Presentation**

TBDs affect tissues in which telomere maintenance is important, leading to a variety of disorders throughout the

![Diagram](image-url)
body, including idiopathic pulmonary fibrosis, seen in 20% of patients; extensive dental caries, 17%; esophageal stricture, 17%; premature hair loss or greying, 16%; and liver disease, 7% (including a predisposition to cirrhosis). In addition, defects in telomere stability predispose to malignancies: MDS/AML and a variety of solid tumors, including head and neck squamous cell carcinoma, skin squamous cell carcinoma, and anorectal, stomach, lung, esophageal, and colon cancer.

Although X-linked recessive DC, autosomal recessive DC, and TINF2 mutations often present with severe phenotypes at young ages, autosomal dominant DC caused by TERT and TERC mutations often present later in life without the classic mucocutaneous symptoms. Instead, bone marrow failure is a common presenting symptom. Patients with TERT and TERC mutations present with variable onset and disease progression, and their pedigrees show variable penetrance. Carriers of the same TERT or TERC mutation may exhibit few symptoms, with only slight macrocytosis or thrombocytopenia before the onset of aplastic anemia. Both TERT and TERC mutations are associated with anticipation, with progressively shorter telomeres with successive generations. Members of older generations often demonstrate mild disease, whereas younger patients experience more severe disease manifestations, such as aplastic anemia or MDS/AML. The combination of aplastic anemia and idiopathic pulmonary fibrosis in patients with the absence of classic mucocutaneous features is highly specific for a TBD.

**Diagnosis**

TBDs are best diagnosed by using telomere length testing, which correlates with disease severity. Telomere length testing is performed most effectively after separation of specific leukocyte subsets by flow cytometry followed by fluorescence in situ hybridization for human telomeres. Age-adjusted telomere lengths below the first percentile are diagnostic for a TBD. The clinical diagnosis of DC is based on the presence of at least two of four major features of the disease, which include the classic triad and bone marrow failure as well as at least two multisystem features of the disease, including: epiphora (overflow of tears), learning difficulties/developmental delay/mental retardation, pulmonary disease, short stature, extensive dental caries, esophageal stricture, premature hair greying or loss, hyperhidrosis (excessive sweating), or malignancy. Some centers conduct telomere length testing when only one major feature is present to account for the heterogeneity in clinical presentations. DC mutation testing is available clinically, but only ~60% of patients with demonstrably very short telomeres will test positive for a mutation in one of the nine known predisposition genes.

**Management**

Due to the phenomenon of anticipation, younger generations may present with more severe disease at earlier ages and should be screened appropriately for signs of disease. Oxymetholone treatment may improve hematopoietic function in some patients through upregulation of telomerase. SCT is the only definitive cure for patients with a TBD. Diagnosis of a TBD as the cause of bone marrow failure or malignancy is extremely important before HSCT, because patients with a TBD are at much greater risk for complications associated with conventional myeloablative conditioning regimens, including an increased risk of pulmonary complications and veno-occlusive disease. For this reason, low-intensity conditioning has been recommended, although this treatment has resulted in posttransplant complications. To date, outcomes after fludarabine-based non-myeloablative conditioning regimens have demonstrated reduced pulmonary and vascular complications and increased survival in patients who underwent allogeneic SCTs.

**Fanconi Anemia**

FA is an autosomal or X-linked recessive inherited bone marrow failure syndrome associated with growth retardation, organ malformation, and a predisposition to malignancy (in particular AML, but also other solid tumors). Common congenital abnormalities include short stature, abnormal skin pigmentation, radial ray defects, and abnormalities of various organs, including arms, head, eyes, ears, and kidneys. Importantly, 25% to 40% of patients lack physical abnormalities associated with the disease. Although the median age of diagnosis is 6.5 years for boys and 8 years for girls, the disease is diagnosed throughout pediatric and adult age groups. The median age of onset of bone marrow failure is seven years. Median survival for patients with FA is 24 years, with a cumulative incidence of 90% of bone marrow failure by age 40 years. At least 20% of patients with FA develop malignancy, with AML being the most common diagnosis. Recognition of FA is essential, because SCT offers the only cure for the condition.

**Molecular Pathogenesis**

Fifteen genes are known to be associated with FA. FANCA mutations are most prevalent, and FANCB is located on the X-chromosome and therefore confers an autosomal recessive inheritance pattern. FA genes function in repairing DNA crosslinks associated with the FA/BRCA pathway. FANCD1 is identical to BRCA2, with homozygous mutations resulting in FA and heterozygous mutations leading to an increased susceptibility to breast, ovarian, and pancreatic cancer. Within the MDS/AML that develops in patients with FA, certain chromosomal abnormalities are commonly found, including +3q (41%), –7/7q (17%), and –11q (14%). Cryptic rearrangements of RUNXI, including translocations and deletions, as well as point mutations are
also seen in ~21% of patients with FA. The +1q abnormality was seen in the bone marrow biopsy specimens of FA patients, regardless of whether they had myeloid malignancies.

**Presentation**

Patients with FA are typically diagnosed during childhood when they present with aplastic anemia or classic physical findings.\(^{92,93}\) However, up to 30% of patients may not present with any physical findings, emphasizing the clinical heterogeneity of FA, which can delay diagnosis. Because certain groups have particular phenotypic presentations, the FA complementation group subtype is useful in patient management. For example, FANCA-mutated patients demonstrate milder disease with later onset of bone marrow failure, whereas FANCG generally results in more severe hematologic disease.\(^{104}\)

**Diagnosis**

Although the clinical presentation and genetic causes are highly variable, in general, FA results in hypersensitivity to DNA-damaging agents, which can be tested in vitro. Typically, patient lymphocytes derived from peripheral blood are stimulated with diepoxybutane or mitomycin C.\(^{92,93}\) After mitotic arrest, the cells are put onto slides and scored for the number of chromosomal breaks. FA is diagnosed when there is an increased number of chromosomal breaks. If results of the chromosomal breakage test from peripheral blood are normal but there is a strong clinical suspicion of FA, the test can then be repeated by using skin fibroblasts. Clinicians should be aware of the phenomenon of somatic reversion, in which some or all hematopoietic lineages undergo a second mutation within the affected FA gene, resulting in restoration of partial or full activity of the encoded protein. Such an event will make the peripheral blood lymphocytes score falsely normal on the chromosome breakage test. Somatic reversion does not occur in other cell lineages, however, and the chromosome breakage test can therefore be repeated from skin fibroblasts, where it may score positive. CLIA-approved genetic testing for mutations within the FA genes is available but is complicated by numerous factors, including the large number of genes, their large sizes, and the many possible mutations within each gene, including large insertions and deletions.

**EMERGING TOPICS IN FAMILIAL MDS/AML**

**Recognition of Additional Predisposition Alleles**

In the author’s clinical experience, when individuals present with what appears to be familial predisposition to myeloid malignancies, most test negative for the known gene mutations. This outcome likely indicates that additional predisposition alleles have yet to be discovered. One additional predisposition gene that has been identified in only two families to date is **SRP72**.

**Familial Aplastic Anemia/MDS With SRP72 Mutation (OMIM #602122)**

**Background**

A mutation in **SRP72** was identified in a family with autosomal dominant inheritance of bone marrow failure and congenital neural deafness by using whole-exome sequencing.\(^{105}\) The family pedigree consisted of three siblings with aplastic anemia and deafness, and a mother with MDS. An additional sibling with normal hearing had normal blood counts. Bone marrow examination revealed a normal karyotype in each of the affected subjects. Subsequent screening of 96 additional patients with bone marrow failure identified one additional family with an **SRP72** mutation in which both the index case and her mother had MDS. In this second family, however, neither of the affected subjects had hearing loss, although the index case had presented with possible labyrinthitis.

To date, only these two pedigrees have been identified with **SRP72** mutations and aplastic anemia/MDS (Figure 6). Thus, it is difficult to describe a particular phenotype associated with this mutation. However, just as the phenotypes of patients with **GATA2** mutations became more apparent as more patients are identified, the phenotypic associations with **SRP72** mutations, including an association with hearing loss or other audi vestibular abnormalities, may become evident. As with other familial bone marrow failure syndromes, attention to possible inheritance of seemingly unrelated abnormalities will be important to elucidate the phenotype.

**Molecular Pathogenesis**

**SRP72** encodes one of six protein subunits of the signal recognition particle (SRP), part of the cellular apparatus responsible for nascent protein processing and trafficking. **SRP72** binds SRP68, and together they assemble onto chromatin to activate transcription and are regulated by PRMT1 and PRMT5. Interestingly, methylation of histone H4 at the third arginine in the histone tail (H4R3me) blocks binding of SRP68/72 to chromatin.\(^{106}\) Currently, it is unclear how germline mutations in **SRP72** alter protein function.

**Presentation**

Because only two families with **SRP72** mutations have been identified to date, it is difficult to describe a consistent clinical presentation, but bone marrow failure may precede the development of a myeloid bone marrow malignancy. Whether congenital neural deafness is a common associated finding is also unclear at this time. Commercial testing for **SRP72** mutations is not yet available.
Management

As with the other syndromes, initial management of the myeloid malignancy depends on the specific malignancy. However, if planned therapy includes an allogeneic SCT using a related donor, subsequent consideration should be given to the use of a nonmutated donor.

Identification of Germline Predisposition by Next-Generation Sequencing

The rapidly expanding application of next-generation sequencing presents opportunities and challenges in adapting this technology to the identification of individuals with a germline predisposition of cancer. Technical aspects of whole-exome sequencing can result in missing information, including poor coverage of DNA regions with high G/C content and/or failure to capture certain exons. Facilities need to have excellent quality control, and careful discussions between the clinical laboratory and the clinical staff must occur to confirm that all members are aware of the phenotype of a particular subject/family to ensure that appropriate genes are covered adequately.

Depending on the type of bioinformatic analysis that is performed on tumor tissue, it is possible to identify germline mutations when analyzing an individual’s primary tumor, because every cell in that person’s body will contain the germline mutation. This analysis can provide a convenient means to identify germline carriers. For example, the current standard for molecular analysis in the case of a patient presenting with AML includes mutational analysis of CEBPA.107 Because ~10% of AML patients found to have biallelic CEBPA mutations within their leukemic cells acquire one of those mutated alleles as a germline mutation, any AML patient found to have biallelic CEBPA mutations should undergo genetic counseling and molecular testing of germline tissue (as described earlier). This scenario may become more common as next-generation sequencing of leukemias is performed more frequently. The American College of Medical Genetics and Genomics recommends the disclosure of certain genetic information when clinical genetic sequencing is performed, including 24 genes that confer germline cancer predisposition.108,109

Barriers That Limit Identification of Germline Carriers

Several barriers exist that may limit the identification of new predisposition genes:

- Lack of appreciation by treating hematologists/oncologists for the existence of these predisposition syndromes. Because families with germline predisposition to myeloid diseases are rare, many physicians are not aware of these disorders or of the expanding list of predisposition alleles. In addition, because these conditions are considered rare, physicians may have the impression that they are unlikely to diagnose them in any one particular subject or family. Lack of knowledge about these disorders may extend to the genetic counseling community, in which genetic predisposition to breast, ovarian, endocrine, and gastrointestinal malignancies may be emphasized during training.
Lack of easy availability of testing. Currently, no single panel test is available commercially that allows assessment of all of the known MDS/AML predisposition alleles simultaneously, although these are under development. Whether these panels are eventually replaced by next-generation sequencing, as discussed earlier, is unclear at the moment.

Sample source can be a difficult issue. When genetic testing is sent for patients with MDS/AML, it is important to remember that blood is an affected tissue, and many of the genes mutated in the germline are also found mutated somatically, confounding the interpretation of genetic testing on blood or bone marrow samples. Therefore, if peripheral blood is the source used for testing, it may not be possible to assess germline status. For this reason, skin fibroblasts are the preferred source for germline analysis. In practice, a skin biopsy is easily performed with minimal local anesthetic and a punch biopsy or a small shaving of skin collected at the site of the skin incision during a bone marrow biopsy. Skin fibroblasts can be grown in vitro in a CLIA-approved laboratory, a process that can take several weeks depending on culture conditions and biopsy handling. This significant length of time is added to the turnaround time for germline testing and, in certain clinical settings, may not be acceptable in cases that require expedited results for patient management decisions. Unfortunately, not all clinical centers have the capacity to perform skin biopsies to allow testing of skin fibroblasts. In this situation, buccal swab or saliva samples may be preferred, because they can be obtained from patients immediately. However, both buccal swab and saliva samples contain up to 50% contaminating lymphocytes, which possibly confounds results.

Lack of availability of detailed family histories, including malignancy and bleeding histories. When patients present with life-threatening AML, many physicians feel that it is inappropriate or insensitive to take extensive family and/or bleeding histories at the time of presentation. As treatment progresses, physicians then forget to go back and obtain this information from patients and their family members. For this reason, the period of time in which relatives are being considered as allogeneic stem cell donors is a unique time to assess the likelihood of a predisposition syndrome. However, often by this period, there is clinical urgency in finding a related donor, and the length of time needed to perform genetic counseling, obtain appropriate tissue samples, and send sequential genetic testing precludes rapid determination of a familial predisposition syndrome and, if present, affected individuals within the family.

Lack of appreciation that family history is relevant to the medical care of adults. There is a bias among some physicians that inherited disorders affect patients in the pediatric age group exclusively and that family histories are therefore less important in adults. However, given that familial predisposition to myeloid malignancies often exhibit the phenomenon of anticipation, it is common to have members of younger generations presenting before those of older generations within a family. For this reason, lack of family history in parental/grandparental generations also does not preclude a genetic disorder.

Small family sizes in today's society limit the ability to detect genetic predisposition syndromes, because fewer family members are at risk for the familial disorder.

Opportunities for Translational Research

Given the rarity of families with germline mutations that predispose to myeloid malignancies, new gene discovery is likely to require the cooperative effort of groups worldwide to identify multiple families with mutations in common genes. Moreover, the members of families recognized to have a familial predisposition should be encouraged to participate in translational research studies to understand the associated clinical findings in these syndromes; phenotypic similarities among syndromes; and the genetic progression from germline mutation to overt malignancy, among others. Once a deeper understanding is obtained regarding secondary mutations that might be requisite events to the development of malignancy, it may then be possible to develop prevention strategies for at-risk individuals.

CONCLUSIONS

We encourage all physicians and nurses caring for patients with MDS/AML to familiarize themselves with the inherited predisposition syndromes so that detection of these families can occur at presentation of MDS/AML. Recognition of these syndromes is crucial for the proper clinical management of patients with an inherited susceptibility and for genetic screening of additional family members. These issues become especially important when planning an allogeneic SCT. We encourage all physicians who care for these patients to refer appropriate patients for genetic counseling, testing, and, potentially, research studies that could lead to the identification of additional predisposition alleles.

Although current CLIA-approved testing exists only for germline mutations in \textit{RUNX1}, \textit{CEBPA}, \textit{GATA2}, and the inherited bone marrow failure syndromes (including DC),
we look forward to the development of additional clinical tests to streamline germline predisposition testing. Currently, if physicians exhaust CLIA-approved genetic testing for a patient with a high suspicion for an inherited leukemia syndrome, further testing can only take place in the research setting. Patients may benefit from additional screening if experimental protocols are written to allow the disclosure of research-based, medically relevant information back to participating subjects. The incorporation of next-generation sequencing into clinical practice may change diagnostic testing, if full-exome, transcriptome, and/or genome sequencing become standard practice.110,111

REFERENCES

Inherited predisposition to AML


