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Familial myelodysplastic syndrome/acute leukemia syndromes: a review and utility for translational investigations

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Abstract

The familial myelodysplastic (MDS)/acute leukemia (AL) predisposition syndromes are inherited disorders that lead to significantly increased lifetime risks of MDS and AL development. At present, four recognized syndromes have Clinical Laboratory Improvement Amendments–certified testing for their respective germline mutations: telomere biology disorders due to mutation of *TERC* or *TERT*, familial AML with mutated *CEBPA*, familial MDS/AML with mutated *GATA2*, and familial platelet disorder with propensity to myeloid malignancy. These disorders are heterogeneous with regard to their causative genetic mutations, clinical presentation, and progression to MDS/AL. However, as a group, they all share the unique requirement for a high index of clinical suspicion to allow appropriate genetic counseling, genetic testing and mutation-specific clinical management. In addition, translational investigations of individuals and families with these syndromes provide a rare opportunity to understand key pathways underlying susceptibility and progression to MDS/AL and allow the possibility of novel strategies for the prevention and treatment of both familial and sporadic forms of MDS/AL.

Keywords

familial; *RUNX1*; *CEBPA*; *GATA2*; leukemia; myelodysplastic syndrome

Introduction

Myelodysplastic syndrome (MDS) and acute leukemias (AL), including both acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), are generally not thought of as having a strong hereditary component. However, the recent recognition of an increasing number of inherited MDS/AL predisposition syndromes, which affect both clinical care and our understanding of leukemogenesis, make awareness of familial forms of these diseases essential. The most established among these inherited syndromes are the disorders that have additional phenotypic findings and often present in childhood, such as the inherited bone marrow failure syndromes (e.g., Fanconi anemia, Shwachman–Diamond syndrome, and dyskeratosis congenita) and Down syndrome. However, in the last decade, an increasing number of disorders with predisposition to MDS/AL as the most common presenting feature, collectively termed the familial MDS/AL predisposition syndromes, have been recognized. Among them are the monogenic inherited disorders: familial AML with mutated *CEBPA*, familial MDS/AML with *GATA2* mutation, and familial platelet disorder (FPD),

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which is caused by monoallelic mutations in *RUNX1*. For all three of these disorders, MDS and AML are the predominant hematopoietic malignancies, but the description of cases of ALL in individuals in each syndrome require awareness in those with ALL as well.[1–4] In addition, novel presentations of the autosomal dominant forms of the telomere biology disorders (TBDs) specifically due to mutations in *TERT* or *TERC* can appear similar to the familial MDS/AL predisposition syndromes and are included in this category.[5,6]

The discovery and subsequent investigation of individuals with these disorders allow several opportunities for improvements in clinical care and research. First, the traditional thinking that inherited forms of MDS/AL are solely pediatric disorders is no longer appropriate, as many individuals present in adulthood. Second, these disorders directly affect the clinical care of the patient and others within the family, especially related HLA-matched individuals who are often considered as allogeneic hematopoietic stem cell transplantation donors. As such, all clinicians caring for MDS/AL patients must be aware of these disorders. Third, given the increasing use of gene sequencing both in research and in the clinical setting, more cases of these syndromes, as well as novel syndromes, are being recognized. Thus, they may be more common than previously appreciated. Fourth, research studies examining individuals with these inherited disorders provide a unique opportunity to study the many diverse pathways now clearly involved in leukemogenesis. They also allow detailed investigations into the multi-step process of leukemogenesis from a predisposing single-gene mutation to development of overt malignancy. Finally, because the genes involved in several of the familial forms of MDS/AL are also commonly somatically mutated in sporadic leukemia and MDS, findings from the study of familial disease have the potential to affect the prevention and treatment of all MDS/AL.

Here we review the known and emerging familial MDS/AL predisposition syndromes (Table 1) and highlight the utility of translational research investigating individuals with these syndromes.

The known familial MDS/AL predisposition syndromes

Inherited bone marrow failure syndromes

The inherited bone marrow failure (IBMF) syndromes are a well-described group of disorders typically presenting in childhood with characteristic physical features along with bone marrow failure and a predisposition to MDS/AL and other cancers. Although a review of these disorders is outside the scope of this article, one should be aware that some of these disorders can be diagnosed in adulthood with MDS/AL as the presenting feature. In general, this is due to subtle presentations without the usual physical features.[7–9] For example, about 25% of patients with Fanconi anemia (FA), the most common IBMF syndrome, lack the characteristic physical features such as short stature and radial-ray anomalies.[7,8] In addition, individuals with FA without congenital anomalies may be less likely to develop the characteristic bone marrow failure in early childhood.[10] Thus, with a 600- to 800-fold increased risk of MDS/AML, development of a hematopoietic malignancy may be the first presentation of FA.[7,8,10] An increased awareness of this possibility and increased screening of adults has resulted in a growing number of individuals diagnosed in adulthood, notably up to nearly age 50.[7,8]

The TBDs are also among the IBMF syndromes with increasingly recognized subtle clinical presentations. The TBDs are a group of disorders caused by mutations in nine different genes that result in abnormal telomere maintenance through dysfunction of the ribonucleotide- and protein-containing telomerase complex. Without adequate telomerase function, dividing cells, such as hematopoietic stem cells, lose telomere length with each cell division and eventually develop critically short telomeres that cause chromosomal

instability and trigger apoptosis.[5,6,11,12] Mutations affecting the telomerase complex were first identified in the gene *DKC1* in individuals with dyskeratosis congenita (DC). DC is the classically recognized X-linked recessive TBD that presents with the diagnostic triad of nail dystrophy, abnormal reticular skin pigmentation, and oral leukoplakia, along with bone marrow failure and a predisposition to malignancy.[5,6,13]

At least two genes involved in the TBDs, *TERC*, which encodes the telomerase RNA component, and *TERT*, encoding the telomerase reverse transcriptase component, cause clinical presentations that completely lack characteristic mucocutaneous findings. These TBDs present similarly to the other autosomal dominant familial MDS/AL predisposition syndromes detailed in this review and will be discussed in more detail here.[5,6,14,15] The most recently described gene implicated in TBDs, *RTEL1*, causes the severe TBD variant, Hoyeraal–Hreidarsson syndrome when two abnormal copies of the gene are inherited. Although no cases of an autosomal dominant familial MDS/AL presentation have been reported in individuals who inherit a single abnormal copy of *RTEL1*, the observation of short telomeres in some such individuals suggests that this may be possible.[12]

Those who inherit a single abnormal copy of *TERT* or *TERC* have an autosomal dominant TBD with variable clinical manifestations and incomplete penetrance.[16–18] Affected individuals within a single pedigree range from those who are completely normal or have only subtle blood count abnormalities such as an elevated MCV to those with early-onset aplastic anemia (AA), MDS, or AML. Individuals may also have isolated idiopathic pulmonary fibrosis or hepatic cirrhosis, early-onset anogenital or head and neck cancer, or combinations of these manifestations.[16–18] Other families have been identified in the setting of allogeneic stem cell transplantation, in which a sibling donor failed to mobilize stem cells and/or had baseline subtle blood count abnormalities before donating stem cells for a relative with a hematopoietic malignancy.[18,19] The frequency of presentations of *TERC* or *TERT* mutations similar to the autosomal dominant familial MDS/AL predisposition syndromes remains to be determined, but in one small series of 20 families with an MDS/AL predisposition who did not meet phenotypic criteria for DC, four families were found to carry either of the mutations.[6] This finding highlights the importance of considering *TERC* and *TERT* in diagnostic testing of families with more than one case of MDS/AL and/or individuals with subtle blood count abnormalities, failure to mobilize stem cells, or the other organ system manifestations referenced above.

In addition to the variable clinical presentations, age at onset also varies and demonstrates anticipation, in which each generation is affected at an earlier age.[17, 20] All of these features may be explained by differences in baseline telomere length. Each generation inherits shorter telomeres and those with the shortest telomeres are affected at earlier ages and with more severe phenotypes.[5,17] Awareness of anticipation is important because a child inheriting a *TERC* or *TERT* mutation could present with clinical manifestations before a parent who carries the same mutation.

Familial AML with mutated CEBPA

Familial AML with mutated *CEBPA* is a familial MDS/AL predisposition syndrome with autosomal dominant inheritance and near complete penetrance for AML development.[21,22] Age of onset of leukemia is variable, with reports in the literature ranging from age 2 to 59 years.[2,15,22] Diagnosis is challenging, as AML is the main feature and no additional preceding blood count abnormalities or physical features are known. Thus, a family history of AML and/or development of AML with biallelic *CEBPA* mutations are key findings to alert the clinician to this possible diagnosis.

The causative CCAAT/enhancer binding protein alpha gene, *CEBPA*, is located on chromosome band 19q13.1 and encodes a protein belonging to the basic region leucine zipper family of transcription factors important to myeloid development.[23,24] Mutations in this single-exon gene affect the production of its two main protein products: the full-length p42 protein, which mediates contact with the promoters of gene targets, dimerization, and protein–protein interactions; and the shorter p30 protein, which lacks the first transactivation domain but retains the ability to dimerize.[24] Most individuals with this syndrome inherit a frameshift mutation located in the 5′ region of the gene, resulting in dominant-negative effects due to production of the p30 protein and the lack of the p42 protein product.[21,22] Over time, individuals acquire additional genetic changes that cooperate to lead to the development of overt AML. For most, a 3′ mutation of the second, previously normal allele of *CEBPA* appears to be a key cooperating mutation.[2,22,25] *GATA2* mutations also appear to contribute, occurring in three of three families examined to date.[26]

Notably, mutations in *CEBPA* are also commonly seen in sporadic cases of AML. They occur in roughly 10% of cases and portend a favorable prognosis when biallelic mutations are present.[23,27] This has resulted in routine sequencing of *CEBPA* in sporadic AML for both research and clinical care and has allowed estimates of the possible prevalence of familial AML with mutated *CEBPA*.[23] Two small series found that 7–11% of individuals with AML featuring a *CEBPA* mutation at diagnosis carry a germline *CEBPA* mutation.[23,25] Germline mutations were more common in those with biallelic *CEBPA* mutations. Thus, given that the overall prevalence of *CEBPA* mutations in AML is roughly 10%, up to 1% of cases of sporadic AML could be attributed to familial AML with *CEBPA* mutation.[23,25]

Patients with sporadic AML with biallelic *CEBPA* mutations and those with familial AML with *CEBPA* mutations share a similar AML phenotype. The typical features include aberrant CD7 expression, a normal karyotype, and frequent Auer rods.[22] Both groups of patients also appear to respond well to standard induction chemotherapy and have a favorable prognosis.[22] However, those with the familial syndrome are prone to the development of future leukemias, making consideration of allogeneic stem cell transplantation for definitive cure necessary among familial cases. Allogeneic stem cell transplantation would not usually be recommended for those with sporadic AML with biallelic *CEBPA* mutations. This consideration, as well as the implications of leukemia risk for additional family members, makes recognition of familial AML with mutated *CEBPA* essential.

Familial MDS/AML with mutated GATA2

Familial MDS/AML with mutated *GATA2* was initially described among pedigrees of previously healthy individuals with an autosomal dominant inheritance pattern of MDS/AL.[4] Simultaneously, however, mutations in the same gene, *GATA2*, were identified as the cause of two additional syndromes, Emberger syndrome and MonoMac syndrome. Emberger syndrome and MonoMAC syndrome feature a predisposition to MDS/AL along with other organ system manifestations. These include primary lymphedema and immunodeficiency in the former and monocytopenia, NK cell, B cell, and macrophage deficiencies, predisposition to atypical infections, and pulmonary alveolar proteinosis in the later.[28–30] More recently, *GATA2* mutations have been identified in individuals presenting with apparent mild congenital neutropenia who were negative for mutations in the other known congenital neutropenia genes.[31]

Genetically, all of these syndromes are due to mutations that disrupt the same gene, *GATA2*. This gene encodes a GATA transcription-factor family zinc-finger transcription factor with critical roles in normal hematopoietic development and lymphoendothelial valve development.[32–34] Interestingly, the mutations observed among families with different

clinical syndromes occur at the same sites, suggesting no genotype–phenotype correlations.[35] For example, the predominant clinical manifestation of separate pedigrees carrying mutations at the hotspot p.T354M have included those with familial MDS/AL alone and others with MonoMac syndrome.[35] Therefore, among individuals with a family history of MDS/AL, a detailed medical and family history looking for even subtle associated organ-system manifestations, such as the presence of warts, could provide clues to the diagnosis.

Among those with a familial MDS/AL presentation, the age at onset of MDS/AL has ranged from age 10–48.[4,36] Earlier age at onset has been reported in those with syndromic presentations.[31] One case of ALL and another of a T cell non-Hodgkin lymphoma have been reported in individuals with this syndrome, suggesting that additional hematopoietic malignancies may be possible.[3,4]

The rate of transformation to MDS/AL remains to be determined, but appears high with transformation occurring during follow-up in six of 14 cases in one series.[31] In addition, transformation appears to be rapid, with varying MDS and AML phenotypes and variable cytogenetic abnormalities.[4,37] The most commonly associated cytogenetic finding is monosomy 7, but additional acquired mutations such as those in *ASXL1* may also contribute.[37] The prognosis after MDS/AL development appears to be poor, with the best outcomes reported among those undergoing allogeneic hematopoietic stem cell transplantation.[37,38]

Familial platelet disorder with propensity to myeloid malignancy (FPD)

FPD is the best characterized of the familial MDS/AL predisposition syndromes, with greater than 30 families described in the literature.[14] The classic phenotypic presentation of this autosomal dominant disorder includes both quantitative and qualitative platelet defects as well as an increased lifetime risk of developing MDS/AL.[5,39] However, some patients do not demonstrate thrombocytopenia or the aspirin-like platelet dysfunction, and thus, the absence of these findings does not rule out the diagnosis.[40] The lifetime risk of MDS/AL in mutation carriers approaches 40%, with an average age of onset of 33 years (range 6–76 years).[5,15] Interestingly, anticipation also appears to occur in many of the reported pedigrees with FPD, requiring one to keep in mind that a child may present before older generations. Four cases of T cell ALL have also been reported and appear to be a part of the spectrum of hematopoietic malignancies in FPD.[1]

FPD is caused by monoallelic mutations in *RUNX1*. This gene encodes the DNA-binding subunit of the core binding factor (CBF) transcription complex, a key complex required for normal hematopoiesis.[5,39] The causative mutations in *RUNX1* in FPD occur throughout the gene, including missense, nonsense, frameshift, insertion, deletion, and a recently reported congenital translocation disrupting the gene. Some of these mutations appear to act via haploinsufficiency and have dominant-negative effects.[40–42]

Progression to MDS/AL requires second-hit mutations, which may help account for the variable penetrance of MDS/AL in FPD as well as the varying phenotypes of MDS/AL that develop. Acquisition of a mutation on the second, previously normal copy of *RUNX1* upon progression to MDS/AL appears to be a common second hit, but is not required.[40,43] Recently, descriptions of additional acquired abnormalities such as a *CBL* mutation in an individual with FPD at the time of chronic myelomonocytic leukemia development and a mutation of *ASXL1* along with loss of *NF1* in a case of T cell ALL in FPD support these hypotheses.[44,45] Finally, because *RUNX1* mutations have been found in up to 32% of sporadic cases of MDS/AML, translational investigations of mechanisms of leukemogenesis in FPD offers the potential to benefit individuals with FPD as well as those with *de novo* acute leukemias.[36,46]

Emerging familial MDS/AL syndromes

The recognition of the above syndromes has made progress in identifying the causes of familial MDS/AL for a substantial portion of patients. However, additional families without abnormalities in these known genes remain, suggesting that additional loci are likely.[4,6] Widespread use of next-generation sequencing among similar pedigrees has led to the identification of additional candidate genes in single reports, including *SRP72* and *DIDO1*. Heterozygous mutations of *SRP72*, which encodes a component of the signal-recognition particle, were identified in two independent families with an autosomal dominant inheritance pattern of familial MDS or MDS and AA as well as congenital nerve deafness.[47] Heterozygous mutations of *DIDO1* were identified in a single family with three siblings affected by MDS featuring a deletion of chromosome band 20q.[48] Both of these findings remain to be confirmed in additional families.

Finally, mutations in a third potential candidate, *ANKRD26*, were initially identified as the cause of thrombocytopenia 2 (*THC2*), an autosomal dominant form of inherited thrombocytopenia.[49] Further phenotyping of families with *THC2* has identified a mild bleeding defect as well as a possible increased risk of acute and chronic leukemia.[50] Although the risk of hematopoietic malignancies requires confirmation, it is possible that *THC2* is a clinical phenocopy of FPD. Thus, at least on a research basis, *THC2* should be on the differential of familial MDS/AL predisposition syndromes especially in the setting of bleeding and/or thrombocytopenia. Finally, additional genetic studies as well as careful follow-up and phenotyping will undoubtedly identify additional familial MDS/AL predisposition syndromes.

Clinical management and screening

All of the familial MDS/AL predisposition syndromes have only recently been defined. Thus, the number of reported affected individuals with each syndrome as well as the length of their clinical follow-up, is limited. As such, guidelines for genetic testing and clinical management are based on expert opinion at this point.[15]

Key components of the clinical management of those with identified mutations in the aforementioned genes include specialized monitoring and/or referral for management of other organ system manifestations. For example, those with mutations in *TERT* or *TERC* require consideration of routine pulmonary function tests and head and neck/anogenital cancer screening. In addition, those with familial MDS/AL predisposition syndromes who develop marrow failure or hematopoietic malignancies require careful consideration of the timing and use of allogeneic stem cell transplantation, with particular attention to avoidance of using a stem cell donor who also carries the same genetic predisposition. Finally, diagnosing these syndromes allows avoidance of unnecessary treatments due to misdiagnosis (e.g., steroid treatment for ITP in those with FPD), and the opportunity to extend care to additional at-risk family members.

Widespread incorporation of a detailed medical and family history into the clinical care of every patient with unexplained cytopenias, AA, or MDS/AL—along with knowledge of these syndromes—will continue to identify an increasing number of individuals with these disorders. Any individual with a suggestive medical or family history should be referred to specialized providers able to assist in genetic counseling and genetic testing of the patient and his/her family. In addition, providers should encourage participation in research studies aimed at careful phenotyping, long-term follow-up, and translational investigations to aid in the understanding of both familial and sporadic hematopoietic malignancies.

Utility for translational investigations

Research has revealed the extensive molecular and genetic heterogeneity of bone marrow failure, MDS, and acute leukemia. In addition, most of these studies support a multi-step process in the development of these hematopoietic disorders. At present, the clinical outcomes of the majority of adult patients with MDS and AL treated with currently available therapies is less than ideal, creating a need for novel approaches for the prevention and treatment of these diseases.

As discussed above, the familial MDS/AL predisposition syndromes have already provided additional insight into the heterogeneous pathways involved in MDS/AL. Notably, several of the genes implicated in familial disease, such as *CEBPA*, *GATA2*, and *RUNX1*, are also mutated in sporadic disease. Thus, individuals who carry inherited, well-defined mutations in one of these genes and develop hematopoietic malignances provide a human models of these diseases. Further investigations of these populations have the potential to more clearly define the mechanisms and multi-step processes driving leukemogenesis.

Given the rarity of families with these identified syndromes at present, these investigations require a network of collaboration, which we and several other investigators have begun to establish. The aims of this collaboration are (1) to provide an organized framework for the identification and detailed clinical phenotyping of individuals with familial MDS/AL; (2) to provide a mechanism for long-term follow-up of those with defined and undefined familial MDS/AL predisposition syndromes to delineate evidence-based prevention and management strategies; (3) to identify the underlying genetic cause of those with undefined MDS/AL predisposition; and (4) to perform detailed longitudinal genetic and molecular investigations of those with each syndrome to more clearly define the mechanisms underlying the presenting phenotypes and those driving progression to leukemogenesis. We expect that these investigations will provide key insights to allow novel treatment and prevention approaches for those with both familial and sporadic MDS/AL. We invite any interested investigators to join the collaboration.

Conclusions

The known monogenic disorders responsible for an inherited susceptibility to MDS/AL include the telomere biology disorders due to mutations in *TERC* or *TERT*, familial AML with mutated *CEBPA*, familial MDS/AML with *GATA2* mutation, and familial platelet disorder with propensity to myeloid malignancy. Recent research into these entities has resulted in the recognition that inherited forms of MDS/AL are more common than initially appreciated and can frequently present in adulthood, rather than solely in childhood. Ongoing research into the familial MDS/AL predisposition syndromes aims to further characterize the clinical phenotype and ideal management strategy of those with familial disease. It also aims to elucidate the molecular mechanisms underlying each phenotype and the multi-step process leading from a predisposition to hematopoietic malignancy to the development of overt MDS/AL. These efforts will ultimately provide a deeper understanding of bone marrow failure and leukemogenesis that will allow future methods of prevention as well as improved treatments for those with both familial and sporadic forms of these diseases.

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Table 1

The known familial MDS/AL predisposition syndromes

Name of syndrome	Causative gene(s)	Pattern of inheritance	Characteristic hematopoietic malignancies	Other hematopoietic abnormalities	Susceptibility to other malignancies	Other associated syndromes/phenotypic findings	Initial diagnosis in childhood or adulthood	CLIA-approved testing available	Recommended diagnostic clinical test	References
Familial platelet disorder with propensity to myeloid malignancies (OMIM 601399)	*RUNX1*	AD	MDS/AML/T-cell ALL	Lifelong thrombocytopenia (mild-moderate); Bleeding propensity due to aspirin-like platelet dysfunction	None	None	Both	Yes	Full gene sequencing and rearrangement testing of *RUNX1*	1, 4, 12, 38
Familial AML with mutated *CEBPA* (OMIM 116897)	*CEBPA*	AD	AML	Eosinophilia	None	None	Both	Yes	Full gene sequencing of *CEBPA*	18–20, 24
Familial MDS/AML with mutated *GATA2* (OMIM 137295)	*GATA2*	AD	MDS/AML	None**	None	Emberger Syndrome: primary lymphedema, immunodeficiency, cutaneous warts, sensorineural deafness MonoMAC syndrome: pulmonary alveolar proteinosis, monocytopenia, NK cell, dendritic cell, and B cell lymphopenia, disseminated atypical mycobacterial/viral/fungal infections	Both	Yes	Full gene sequencing and rearrangement testing of *GATA2*	26–29
Telomere biology disorders due to mutation in *TERC* or *TERT* (OMIM 127550)	*TERC* *TERT*	AD AD*	MDS/AML	Macrocytosis Mild to moderate single or multiple cytopenias Aplastic anemia	Squamous cell carcinomas of the head/neck and anogenital regions	Autosomal dominant TBD: Idiopathic pulmonary fibrosis, idiopathic hepatic cirrhosis Autosomal recessive or X-linked recessive TBD: nail dystrophy, oral leukoplakia, skin hypo- or hyperpigmentation, premature gray hair, dental caries, hepatic cirrhosis, pulmonary fibrosis; Severe AR forms: cerebellar hypoplasia, immunodeficiency, developmental delay	Both	Yes	Initial diagnostic test: Telomere length studies of lymphocyte subsets via FlowFISH; If abnormal: Full gene sequencing of *TERT* and *TERC*	5, 14–16

* Also has an autosomal recessive form with a more severe clinical presentation including mucocutaneous findings.

** The described families with familial MDS/AML with mutated *GATA2* did not have preceding hematopoietic abnormalities, but given the overlap with Emberger and MonoMAC syndromes as well as identification of *GATA2* mutations among those with congenital neutropenia, it is likely possible to find some of the hematopoietic deficits described in these syndromes also featuring *GATA2* mutations such as neutropenia, monocytopenia, NK cell, dendritic cell, and B cell deficiencies.

AD, autosomal dominant.