Lessons From Pediatric MDS: Approaches to Germline Predisposition to Hematologic Malignancies

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Pediatric myelodysplastic syndromes (MDS) often raise concern for an underlying germline predisposition to hematologic malignancies, referred to as germline predisposition herein. With the availability of genetic testing, it is now clear that syndromic features may be lacking in patients with germline predisposition. Many genetic lesions underlying germline predisposition may also be mutated somatically in de novo MDS and leukemias, making it critical to distinguish their germline origin. The verification of a suspected germline predisposition informs therapeutic considerations, guides monitoring pre- and post-treatment, and allows for family counseling. Presentation of MDS due to germline predisposition is not limited to children and spans a wide age range. In fact, the risk of MDS may increase with age in many germline predisposition conditions and can present in adults who lack classical stigmata in their childhood. Furthermore, germline predisposition associated with DDX41 mutations presents with older adult-onset MDS. Although a higher proportion of pediatric patients with MDS will have a germline predisposition, the greater number of MDS diagnoses in adult patients may result in a larger overall number of those with an underlying germline predisposition. In this review, we present a framework for the evaluation of germline predisposition to MDS across all ages. We discuss characteristics of personal and family history, clinical exam and laboratory findings, and integration of genetic sequencing results to assist in the diagnostic evaluation. We address the implications of a diagnosis of germline predisposition for the individual, for their care after MDS therapy, and for family members. Studies on MDS with germline predisposition have provided unique insights into the pathogenesis of hematologic malignancies and mechanisms of somatic genetic rescue vs. disease progression. Increasing recognition in adult patients will inform medical management and may provide potential opportunities for the prevention or interception of malignancy.

Keywords: germline, inherited bone marrow failure syndromes, predisposition syndromes, myelodysplastic syndrome, hematologic malignancy
INTRODUCTION

Although historically considered in the context of pediatric myelodysplastic syndromes (MDS), genetic predisposition to hematologic malignancies, including MDS, is now recognized to manifest across the age spectrum (1–4). Germline etiology has been associated with up to 15% of MDS diagnoses (1, 2, 5, 6), a number that undoubtedly will increase with the availability of clinical genetic testing and our understanding of MDS pathobiology. Most germline MDS predisposition conditions were originally characterized in patients with severe early-onset presentations with specific syndromic features. However, the absence of classic physical features or family history of hematologic malignancies does not preclude consideration of germline predisposition, due to clinically cryptic phenotypes or de novo germline mutations.

MDS associated with germline predisposition is now classified separately in the 2016 World Health Organization system (7). Recognition of an underlying germline predisposition has broad implications for both patients and their families. As a hematopoietic stem cell transplantation is the curative therapy for many patients with MDS, donor choices will be influenced by the underlying genetics, which may affect other family members. Lastly, the diagnosis of germline MDS predisposition guides family counseling and family planning and allows appropriate monitoring of affected asymptomatic individuals to maintain health. We present here a framework for evaluating MDS that is applicable to both pediatric and adult patients.

PREDISPOSITION TO MDS AND OTHER HEMATOLOGIC MALIGNANCIES IS NOT RESTRICTED TO PEDIATRIC PATIENTS

Consider the following cases presenting to an adult clinic: (1) a 27-year-old sibling of a 19-year-old man with MDS is undergoing evaluation as a possible donor for a stem cell transplantation. This sibling is unexpectedly found to have macrocytic anemia and thrombocytopenia. A subsequent bone marrow evaluation reveals multilineage dysplasia with trisomy 8 consistent with MDS; (2) A 57-year-old woman with MDS reports that her 16-year-old sibling is unexpectedly found to have macrocytic anemia and thrombocytopenia. A subsequent bone marrow evaluation reveals multilineage dysplasia with trisomy 8 consistent with MDS; (2) A 16-year-old sibling of a 19-year-old man with MDS is undergoing evaluation as a possible donor for a stem cell transplantation. This sibling is unexpectedly found to have macrocytic anemia and thrombocytopenia. A subsequent bone marrow evaluation reveals multilineage dysplasia with trisomy 8 consistent with MDS.

A DIAGNOSTIC FRAMEWORK TO EVALUATE A SUSPECTED GERMLINE PREDISPOSITION TO MDS AND OTHER HEMATOLOGIC MALIGNANCIES

MDS may be the first presenting clinical feature of a germline predisposition condition. The diagnostic evaluation for a potential genetic predisposition condition integrates the history, laboratory tests, histopathological findings in the bone marrow, and genetic testing. Focusing on the syndromes that span pediatric and adult hematology, we will focus on clues to the diagnosis of germline predisposition. Since many of these syndromes have been described previously, we will not review them in detail here but refer the reader to these excellent references (17–19).

Clues in the Clinical Presentation

In general, the presenting signs and symptoms of MDS do not differ in patients with germline predisposition and include nonspecific clinical findings of fatigue, pallor, malaise, fevers, bleeding, increased bruising, weight loss, and anorexia. The marrow is often hypocellular in pediatric MDS or MDS in germline predisposition, in contrast to adult-onset MDS, which is more commonly hypercellular. Adult patients with hypocellular MDS have significantly more pronounced cytopenias at presentation compared to those presenting with normocellular or hypercellular marrows (20). It is yet unknown
Whether the small subset of hypocellular MDS in adults, between 10% and 20% of all MDS (21, 22), are more likely to be related to germline predisposition. For example, germline DDX11-related adult-onset MDS is associated with a hypocellular marrow (14, 16). The duration of specific clinical symptoms may allow insight into the chronicity of cytopenias. In patients with history of neutropenia in childhood and adolescence, information on the length and dose of granulocyte-colony stimulating factor (G-CSF) usage is helpful in the evaluation of a patient with new MDS, as it may suggest germline mutations associated with severe congenital neutropenia (SCN) due to germline ELANE mutations. Prolonged use, particularly with high doses, of G-CSF in SCN is associated with a 22% cumulative incidence of MDS or secondary AML after 15 years of therapy (23). The risk of MDS development is associated with a somatic acquisition of mutations in CSF3R, the receptor for G-CSF (24–26). A history of prior cytopenias or unexplained macrocytosis may also serve as a clinical clue for germline predisposition. Elevated hemoglobin F may be associated with inherited germline predisposition (27) but can also be elevated in MDS and, thus, should be interpreted with caution (28–30).

Past medical history of bleeding, easy bruising, or diagnosis of “chronic immune thrombocytopenia” is a feature associated with mutations in transcription factors important for megakaryopoiesis and platelet function, including RUNXI, ANKRD26, and ETV6 (31–33). Patients with germline mutations in these genes may have quantitative and/or qualitative platelet defects, manifesting with easy bruising, heavy menses in women, or other bleeding symptoms, which may be out of proportion to the platelet count. Amegakaryocytic thrombocytopenia, often with radioulnar synostosis, is associated with germline MECOM mutations, presenting as congenital bone marrow failure in early childhood (34, 35). In rare case reports, mutations in MECOM have been described in association with adult-onset MDS (36). A history of thrombosis has been reported in GATA2 deficiency, related to cerebrovascular accidents, deep vein thrombosis, pulmonary embolism, and portal vein thrombosis (9). Clinical features of GATA2 deficiency may include recurrent infections, atypical mycobacterial infections, warts, pulmonary alveolar proteinosis, or lymphedema. Although not with clear association to vascular dysfunction or immune deficiencies, premature labor and miscarriages have been described in GATA2 deficiency (9, 37) and other germline conditions (38–40).

**Personal History of Cancer**
Past medical history of malignancy should be investigated as part of the evaluation of germline predisposition (3). In RUNXI-FPD, cases of secondary malignancy with MDS after therapy for acute lymphoblastic leukemia (ALL) have been described, particularly in survivors of childhood T-cell ALL (10, 41, 42). A history of excessive toxicities with chemotherapy or radiation may also suggest a genetic predisposition such as Fanconi anemia (FA). A history of multiple malignancies should raise concern for possible germline predisposition. Solid organ cancers are associated with conditions such as FA [squamous cell carcinomas of head and neck, gastrointestinal (GI) and genital tract, and other solid organ cancers], TBD (head/neck and GI) (43), and Diamond–Blackfan anemia (DBA), particularly in adults (44). In the case of FA, patients may have subclinical mild cytopenias or normal blood counts in childhood, only to present with a solid organ cancer in adulthood, and experience severe protracted pancytopenia with chemotherapy or radiation (45). The diagnosis of a germline predisposition in a patient with a past medical history of malignancy guides subsequent cancer monitoring. This is particularly important in syndromes associated with mutations affecting genomic instability such as FA and Li-Fraumeni syndrome (LFS).

**Giveaways From the Past: Thinking Outside of the Hematopoietic System**
A detailed investigation of the past medical history of a patient with MDS may also identify non-hematologic clinical manifestations of germline predisposition (Table 1).

**Growth and Congenital Anomalies.** Many germline predisposition conditions are associated with a history of intrauterine growth retardation, failure to thrive in childhood, and short stature. Congenital malformations, including skeletal anomalies, abnormal digits, cardiac structural defects, and gastrointestinal (GI) or genitourinary (GU) abnormalities, are important to recognize, many of which may have been repaired in childhood. Such malformations may be part of early presentations of FA (99), TBD (100), DBA (101, 102), and other germline predisposition (Table 1). A history of hydrocele in infancy in patients with GATA2 deficiency may be one of the earliest manifestations of the lymphatic dysfunction of that syndrome that is often unrecognized.

**Immunologic Features.** Many predisposition conditions are associated with immunodeficiency, which may manifest with recurrent infections or immune dysregulation, or may be clinically asymptomatic but detected by laboratory testing for lymphocyte counts, lymphocyte subsets (T-, B-, and NK cells), and immunoglobulin levels. GATA2 deficiency syndrome, for instance, is associated with atypical mycobacterial infections and warts (genital and extragenital) due to the decreased natural killer and dendritic cells, as well as B-cell lymphopenia (9, 103). Immunodeficiency has also been described in TBD (104–107) and in germline TET2 deficiency (83), particularly in childhood for the latter. There may also be autoimmune or inflammatory manifestations of germline predisposition conditions that are actively being studied. These include thyroid disease [GATA2 deficiency (9)], eczema and allergies [RUNXI-FPD (10, 65)], psoriasis [RUNXI-FPD (10)], panniculitis, and lupus-like arthritis [GATA2 deficiency (103, 108)], and others listed in Table 1. Laboratory screening of immunological abnormalities is recommended below and should be considered in the workup of MDS patients.

**Beyond the Blood.** Given the multifaceted functional roles of the underlying genes in germline predisposition, it is not surprising to find tissues other than blood being affected in these conditions. Table 1 lists examples of non-hematologic manifestations of these conditions. A history of extremity edema, typically unilateral and sometimes diagnosed as hemihypertrophy, or genital edema (for example, hydrocele) may be related to germline GATA2 deficiency-associated
| Conditions with germline mutations associated with predisposition to MDS | Gene(s) | Inheritance | Hematologic malignancies reported | Pre-leukemia hematopoietic features | Immunologic features | Non-hematologic clinical features (may be entirely absent) | Somatic genetic rescue/reversion |
|---|---|---|---|---|---|---|---|
| Fanconi anemia | FANCA, FANCB, FANCC, FANCD1/BRCA2, FANCE, FANCF, FANCG, FANCI, FANCI/BRIP1, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51C, FANCP/SLX4, FANCO/ERCC4, FANCR/RAD51, FANCS/BRCA1, FANCT/UBE2T, FANCU/XRCC2, FANCV/REV7, FANCY/FAP100 | AR, AD (FANCR/RAD51) X-linked recessive (FANCB) | MDS, AML, T-ALL | Cytopenia(s), bone marrow failure | CVID, abnormal lymphopoenia | Reported (47–49) |
| Diamond-Blackfan anemia | GATA1 (50), RPL5, RPL11, RPL15, RPL18, RPL26, RPL27, RPL31, RPL35, RPL35A, RPS7, RPS10, RPS15A, RPS17, RPS19, RPS24, RPS26, RPS27, RPS28, RPS29, TSR2 (51), b | X-linked (TSR2) | MDS, AML, HL, NHL, ALL | Macrocytic anemia, reticulocytopenia, elevated fetal hemoglobin (HgF), elevated erythrocyte adenosine deaminase activity | Hypogammaglobulinemia, lymphopenia (52) | Short stature, failure to thrive, abnormal facies, normal radius, limb abnormalities, cardiac structural abnormalities, GI abnormalities, solid organ cancers (particularly soft tissue sarcomas) | Reported (53–55) |
| Shwachman-Diamond and related syndromes | SBDS, DNAJC21, EFT1, SRP54 | AR, AD (SRP54) (currently no reports in EFT1 or SRP54) | MDS, AML | Neutropenia, other cytopenias, bone marrow failure | Immune disorders (56), immunodeficiency (57) | Short stature, exocrine pancreatic insufficiency, skeletal dysplasias, thoracic dystrophy, osteopenia, transaminitis/hepatomegaly early in life, eczema, variable neurocognitive delays, inflammatory complications | Reported (58) |

(Continued)
| Conditions with germline mutations associated with predisposition to MDS<sup>a</sup> | Gene(s) | Inheritance | Hematologic malignancies reported | Pre-leukemia hematopoietic features | Immunologic features | Non-hematologic clinical features (may be entirely absent) | Somatic genetic rescue/reversion |
|---|---|---|---|---|---|---|---|
| Telomere biology disorders | ACD/TPP1, CTC1, DKC1, NAF1, NHP2/NOLA2, NOP10/NOLA3, PARN, RPA1<sup>(59)</sup>, RTEL1, STN1 TERC, TERT, TINF2, WRAP53/TCAB1, ZCCHC8 | AD (TERT, TERC, TINF2, RTEL1, ACD, PAR, NAF1, STN1), AR (TERT, NOP10, NHP2, WRAP53, CTC1, TERT, RTEL1, ACD, PARN), X-linked recessive (DKC1) | MDS, AML Monocytopenia, dendritic cell, B-cell and natural killer cell deficiency, chronic neutropenia, bone marrow failure | Bone marrow failure, aplastic anemia, macrocytosis, cytopenias | Lymphopenia, B-cell lymphopenia, hypogammaglobulinemia, and decreased T-cell function | Nail dysplasia, early greying, abnormal skin pigmentation, oral leukoplaikia, GI dysfunction, neuropsychiatric disorders, interstitial lung disease (adult presentation), emphysema (adult presentation), cryptogenic cirrhosis (adult presentation), Hoyeraal-Hreidarsson Syndrome (cerebellar hypoplasia in young children), Revesz syndrome (bilateral exudative retinopathy in young children, typically associated with TINF2) | Reported (59–62) |
| GATA2 deficiency syndrome | GATA2 | AD | MDS, AML, CML, CMML, JMML, B-ALL | Monocytopenia, dendritic cell, B-cell and natural killer cell deficiency, chronic neutropenia, bone marrow failure | Recurrent bacterial, fungal, and viral infections associated with immunodeficiencies; Mycobacterial infections, autoimmune features including thyroid issues, rheumatological features with Lupus-like arthritis, panniculitis | Lymphedema; sensorineural deafness; urogenital tract anomalies (e.g. hydrocele); pulmonary alveolar proteinosis; behavioral issues, neurologic issues, thrombosis, premature labor and miscarriage | Reported (64) |
| Severe congenital neutropenia | ELANE, G6PC3, GRF1, HAX1, SRPS4, CSRSP3, RUNX1-familial platelet disorder | AD (ELANE, GRF1, SRPS4), AR (HAX1, G6PC3, CSRSP3), AD | MDS, AML<sup>1</sup> (no reports in SRPS4, see below for germine CSRSP3) Neutropenia | | | osteopenia (ELANE), seizures and other neurologic disorders (HAX1), exocrine pancreatic insufficiency (SRPS4), congenital cardiac malformations and GU abnormalities (G6PC3), Dursun syndrome (familial primary pulmonary hypertension, leukopenia, and atrial septal defect, G6PC3) | None reported |
| RUNX1-familial platelet disorder | RUNX1 | AD | MDS, AML, T-ALL, T-NHL, CLL, HL, B-ALL | Thrombocytopenia, platelet function defect | Eczema, allergies, psoriasis, autoimmune disorders<sup>(65)</sup> | | Reported (66) |
| Thrombocytopenia 2 | ANKRD26 | AD | MDS, AML, CML, CLL, CMML | Thrombocytopenia, mild bleeding | | | None reported |
| Thrombocytopenia 5 | ETV6 | AD | MDS, AML, B-ALL, CML, CMML, PV | Thrombocytopenia, bleeding | | Rare case reports of solid organ cancers | None reported |

<sup>a</sup>Continued
| Conditions with germline mutations associated with predisposition to MDS<sup>a</sup> | Gene(s) | Inheritance | Hematologic malignancies reported | Pre-leukemia hematopoietic features | Immunologic features | Non-hematologic clinical features (may be entirely absent) | Somatic genetic rescue/reversion |
|---|---|---|---|---|---|---|---|
| DDX41-associated familial MDS/AML | DDX41 | AD | MDS, AML, CMML, lymphoma, MM | | | | None reported |
| Li-Fraumeni syndrome | TP53 | AD | MDS (often therapy-related), AML (often therapy-related), B-ALL (hypodiploid), T-ALL (early precursor), lymphoma MDS, AML | None | Solid organ cancer | | None reported |
| ERCC6L2 | ERCC6L2 | AR | MDS, AML (particularly AEL<sup>b</sup>) | None | | | None reported |
| Xeroderma pigmentosum | XPC | AR | MDS, AML, ALL (67, 68), B cell lymphoma (69) | | | Photosensitive skin, high frequency of skin tumors, microcephaly, diminished or absent deep tendon reflexes, progressive sensorineural hearing loss, progressive cognitive impairment | None reported |
| Bloom syndrome | BLM | AR | MDS, AML, lymphoma, ALL | Immunodeficiency | | Short stature, microcephaly, telangiectatic rash over face, nose, arms, sun-sensitive rash, pulmonary disease, high-pitched voice, hypogonadism | None reported |
| CEBPA | CEBPA | AD | AML | | | | None reported |

Germline predisposition syndromes typically associated with childhood myeloid neoplasms

| SAMD9 syndrome | SAMD9 | AD | MDS, AML | Bone marrow failure, pancytopenia, clonal hematopoiesis with monosomy 7 or acquired revertant mutations in SAMD9 | Immunodeficiency | Restriction of growth, adrenal hypoplasia, genital abnormalities, enteropathy | Reported (4, 5, 69) |
|---|---|---|---|---|---|---|---|
| SAMD9L syndrome<sup>a</sup> | SAMD9L<sup>b</sup> | AD | MDS, AML | Bone marrow failure, pancytopenia, clonal hematopoiesis with monosomy 7 or acquired revertant mutations in SAMD9L | B-cell immunodeficiency (typically associated with familial ataxia pancytopenia (ATXPC) syndrome related to SAMD9L)(70) | Cerebral calcifications (typically associated with familial ataxia pancytopenia (ATXPC) syndrome related to SAMD9L)(70), autoimmune inflammatory disease (71) | Reported (4, 72, 73) |
### Conditions with germline mutations associated with predisposition to MDS

| Gene(s) | Inheritance | Hematologic malignancies reported | Pre-leukemia hematopoietic features | Immunologic features | Non-hematologic clinical features (may be entirely absent) | Somatic genetic rescue/reversion |
|---------|-------------|----------------------------------|------------------------------------|----------------------|----------------------------------------------------------|---------------------------------|
| MECOM  | AD MDS     | Congenital bone marrow failure, amegakaryocytic thrombocytopenia | Immunodeficiency (34) | Limb dysmorphisms, including radioulnar synostosis, hearing impairment, cardiac abnormalities | None reported |
| NFI1, SPRED1 | AD MDS, JMML | | | | |
| WAS | X-linked MDS, AML | Monocytopenia, platelet function defect with bleeding | Immunodeficiency, T-cell lymphopenia and decreased function | | None reported |
| BRAF, KRAS, MAP2K1, NRAS, PTPN11, RA1, SOS1 | AD MDS, JMML, AML, MPN | | | Facial dysmorphism, short stature, cardiac, broad neck, thoracic, cryptorchidism, Noonan-like coagulopathy, solid organ tumors | None reported |
| CBL, SHOC2 | AD JMML (74) | | | impaired growth, developmental delay, cryptorchidism (CBL)(74), hair anomalies and skin pigmentation (SHOC2)(75) | None reported |
| MLH1, MSH2, MSH6, EPCAM, PMS2 | AR AML, ALL, lymphoma (76) | Decreased IgG and IgA (77) | | Gastrointestinal (colon), ovarian, uterine, CNS tumors and other solid organ cancers, cafe-au-lait macules, skin hyper- and hypopigmentation, pilomatrixomas, agenesis of the corpus callosum | |
| MPL | AR MDS (78) | Thrombocytopenia, bone marrow failure | | brain, ocular and orbital anomalies (strabismus, nystagmus), facial abnormalities (78) | None reported |
| TET2 | AD AML, CMMML, T-cell lymphoma (82) | Immunodeficiency (children) | | Absent radii, preservation of the thumb, other birth defects (hypoplastic ulnae, hypoplastic humeri, phocomelia, abnormal shoulders, bowed legs, hip dysplasias, abnormal knees), abnormal facies, renal malformations, gastroenteritis, | None reported |
| SPR72-associated familial aplasia and myelodysplasia | AD MDS, AML (84) | Bone marrow failure, aplastic anemia | | Sensorineural hearing loss | None reported |
| Conditions with germline mutations associated with predisposition to MDS* | Gene(s) | Inheritance | Hematologic malignancies reported | Pre-leukemia hematopoietic features | Immunologic features | Non-hematologic clinical features (may be entirely absent) | Somatic genetic rescue/reversion |
|---|---|---|---|---|---|---|---|
| CSF3R | CSF3R | AD | MDS, MM, ALL (85) | None reported | Overgrowth, developmental disorders, neuropsychiatric disorders | Reported (87) |
| Tatton-Brown-Rahman syndrome | DNMT3A | AD | Pre-leukemia hematopoietic features | Bone marrow failure | Immunodeficiency, particularly severe B-cell lymphopenia and reduced marrow B-cell progenitors | Reported (89) |
| MYSM1 deficiency | MYSM1 | AR | Myelodysplastic features in marrow (85) | Bone marrow failure | Midface hypoplasia, low-set ears, hypoplasia of the orbital floor, short neck, reduced cerebral volume on MRI, bony abnormalities, osteopenia, deep-set thumb, accessory papilla of the breast, gingiva hyperplasia, neurodevelopmental delay | Reported (89) |
| MBD4 deficiency | MBD4 | AR | AML with myelodysplastic features (89) | Clonal hematopoiesis | None reported |

*Data on individual gene associations with MDS are limited. Please note that the table does not provide a comprehensive list of all clinical features and the reader should referred to other excellent reviews.

Gain-of-function mutations in TP53 have been reported in two patients with pure red cell aplasia, growth retardation and other clinical features, however, there is limited information to classify TP53 as DBA-associated gene.

 Clinically significant infections seen in 3 patients of 107 total with large chromosomal deletions, encompassing RPL35A in 2 cases, and RPS19 in 1 case.

 A case report describes a somatic reversion event in a chromosomal region involving RPL4 in a patient with possible clinical features of DBA, although only a single timepoint of normocytic mild anemia and no further information on hematologic parameters (53).

 The del20q, a common chromosomal loss described in SDS which encompasses the EIF6 gene, has not been shown to cause functional reversion (53, 92–96), except in a single case series of 6 patients with mild effect on anemia (58). Loss of EIF6 does not confer clinically significant revertant phenotype, however, EIF6 mutant clones gain competitive fitness in SDS patients (97, 98).

 Biallelic hypomorphic mutations in CSF3R are associated with severe congenital neutropenia where no cases of MDS or AML have been reported. Heterozygous CSF3R germline mutations have been associated with single kindred with MDS, MM and ALL (85).

 Increased risk of MDS and AML has been reported in patients with severe congenital neutropenia who are on >8mcg/kg/day G-CSF therapy for a prolonged periods of time (23–26). However, cases before G-CSF use have also been reported.

 Acute erythroid leukemia is associated with a founder mutation in ERCC6L2, c.1457delT (p.Ile486ThrfsTer36), in a cohort from Finland (99).

 There are other genes associated with xeroderma pigmentosum but their association with myeloid neoplasms is not clear.

 Also previously known as MIRAGE syndrome (Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital problems, and Enteropathy)

 Also previously known as the Familial myelodysplastic syndrome/monosomy 7.

 SAMD9L has now been recognized to underlie three distinct syndromes which are familial ataxia pancytopenia (ATXPC) syndrome with clinical features of B-cell immunodeficiency and cerebral calcifications (70), familial myelodysplastic syndrome/monosomy 7 without neurological phenotype (72), and the SAMD9L-associated autoinflammatory disease (71).

 AD, autosomal dominant; AR, autosomal recessive; ALL, acute lymphoblastic leukemia; AEL, acute erythroid leukemia; AML, acute myeloid leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; MDS, myelodysplastic syndromes; CNS, central nervous system; GI, gastrointestinal; GU, genitourinary; CLL, chronic lymphocytic leukemia; CMML, chronic mono-myelocytic leukemia; PV, polycythemia vera; MM, multiple myeloma; MPN, myeloproliferative neoplasms.
lymphedema (9, 63). GATA2 is expressed in the lymphatic system (109, 110) and is thought to underlie various forms of lymphatic dysfunction, occasionally with atypical presentations such as swelling on the face or preauricular region (111). Adult-onset non-hematologic manifestations of TBD include a vast range of clinical findings (107). These include interstitial lung disease, particularly pulmonary fibrosis, and liver cirrhosis, often diagnosed and managed by various subspecialists. We inquire about hearing loss of any type and, if clinically indicated, pursue testing.

Examining the Family History: A Cautionary Tale of Phenotype Variability and Non-Hematopoietic Manifestations of Germline Predisposition

Family history provides important clues to an underlying germline predisposition; however, a negative family history does not rule out a genetic disorder. Attention should be paid to the hematologic and non-hematologic manifestations of germline predisposition conditions. Given the variable expressivity and penetrance of many of these conditions, with limited genotype–phenotype correlations described to date, clinical manifestations may vary or even be absent between different family members carrying the same genetic predisposition mutation. For example, studies in kindreds with GATA2 deficiency have reported that by age 40 years, 80% of affected individuals presented with either hematologic malignancies or infections (9, 103). However, the prevalence of clinical manifestations of germline predisposition should be interpreted with caution given potential confounding factors such as selection and ascertainment bias, and mechanisms of somatic genetic reversion discussed later.

A negative family history of MDS or other hematologic malignancies should not preclude consideration of an underlying germline genetic etiology of MDS. Silent clinical presentations have been described in a number of germline MDS syndromes. Disease manifestation may present at various ages within a kindred with the same germline genetic mutation (112). Disease anticipation has been described for some of these conditions, with clinical features being more severe and earlier in onset for each subsequent generation (113). Finally, the germline syndrome may be due to a de novo or recessive mutation. Table 1 lists many clinical features variably associated with germline predisposition, which can be used as a general guide; however, absence of these findings does not rule out a germline condition. As the inheritance of these conditions may be autosomal dominant or recessive, or X-linked (Table 1), in addition to the history of immediate family members (parents, grandparents, children, and siblings), querying the history of extended family members may also be illuminating.

It is important to inquire about family members with any cytopenias, need for transfusions, growth factor support, or splenectomy as possible therapy for thrombocytopenia. If there is a history of antecedent cytopenia, the type, duration, and severity of the cytopenia, prior diagnostic evaluation (such as bone marrow results), and responses to any prior treatments should be queried. Inquiring about clinical symptoms of bleeding, frequent infections, and chronic anemia will address any cellular dysfunction. For example, bleeding symptoms disproportionately severe relative to the platelet counts may be a clue to RUNX1-FPD or ANKRD26 mutations. A family history of recurrent infections of any type, but particularly viral (HPV caused warms in GATA2 deficiency), opportunistic infections [herpes zoster reactivation, primary CMV with retinitis/encephalitis, Pneumocystis jirovecii pneumonia, and Candida esophagitis in TBD (104, 107, 114)] or atypical bacterial (mycobacterial infections in GATA2 deficiency), may suggest the presence of concurrent immunodeficiency and should prompt a more careful laboratory evaluation.

We inquire about any family members with previous diagnoses of hematologic malignancies, such as MDS, myeloid or lymphoid leukemia, or lymphoma, and the age at which these diagnoses were made. A diagnosis of a malignancy at an unusually young age should be noted. Germline predisposition, such as those associated with mutations in hematopoietic transcription factors RUNX1, ANKRD26, GATA2, and ETV6, can present with different types of hematopoietic malignancies, including MDS, AML, T-cell ALL, B-cell ALL, and myeloproliferative neoplasms (MPNs). A family history of chemotherapy sensitivity or multiple malignancies also raise suspicion for a potential germline disorder. Solid organ or head and neck cancers may be presenting features of conditions such as FA, TBD, LFS, or DBA. A family history of clinical features associated with genetic predisposition should also raise suspicion.

Finally, a history of consanguinity in the family may raise the possibility of autosomal recessive syndromes. There are rare genetic associations with founder variants in germline predisposition, for example, North African XPC founder mutation associated with xeroderma pigmentosum subtype C (67, 68) and the ERCC6L2 mutation in the Finnish population (98). Thus, asking about ancestral origins may guide the differential diagnoses.

Telling Signs in the Physical Examination

The physical exam may provide additional clues to an underlying germline predisposition in the context of an MDS diagnosis; however, the lack of syndromic features (Table 1) does not rule out an underlying germline predisposition.

Short stature relative to predicted height is one of the most telling physical exam findings suggestive of a predisposition condition in an adult with MDS (Table 1). In a large study of MDS patients who underwent stem cell transplantation, among patients younger than 40 years of age, biallelic SBDS mutations were associated with significantly lower height percentile (2). Skin hypo- and hyperpigmentation are features of TBD and may also be present with FA, where café-au-lait spots are often observed. A careful oral exam, especially in patients with suspected TBD and FA, should be conducted. Suspicious oral lesions should be referred to an otolaryngologist for further evaluation. Patients with FA are at high risk for squamous cell carcinomas (99). Exam of extremities should note any type of thumb abnormalities found in FA (for example, hypoplasia or pouce flottant, “floating” thumb, with associated radius abnormalities), DBA (for example, small, large, or...
triphalangeal, finger-like, thumb), and MECOM-associated syndrome (radioulnar synostosis). Hand and forearm X-rays may be helpful to diagnose findings not readily apparent on exam if clinical suspicion is high.

**Laboratory Evaluation**

In addition to the complete blood count with differential and reticulocyte count at presentation, prior blood count reports are helpful to detect pre-existing cytopenias suggestive of a pre-existing disorder. Liver function tests are helpful in consideration of TBD and FA. To screen for immunological abnormalities, we typically test lymphocytes subsets for absolute counts of CD3⁺ T-cells, with CD4 and CD8 subpopulations, CD19⁺ or CD20⁺ B-cells, and CD16⁺ or CD56⁺ NK cells. We also screen for levels of IgG, IgA, and IgM immunoglobulins. Combined cytopenias and lymphocytopenias or lymphocyte dysfunction (low IgM or IgG levels) may flag a potential germline condition. B- or NK cell lymphocytopenias may be present in GATA2 deficiency, and abnormal Ig levels may be present in GATA2 deficiency and TBD. It should be noted that lymphocytopenia (low absolute lymphocyte count, ALC, of <1.2 × 10⁹/L) has been described in TBD. It should be noted that lymphocytopenia (low absolute lymphocyte count, ALC, of <1.2 × 10⁹/L) has been described in TBD. To screen for immunological abnormalities, we typically test lymphocytes subsets for absolute counts of CD3⁺ T-cells, with CD4 and CD8 subpopulations, CD19⁺ or CD20⁺ B-cells, and CD16⁺ or CD56⁺ NK cells. We also screen for levels of IgG, IgA, and IgM immunoglobulins. Combined cytopenias and lymphocytopenias or lymphocyte dysfunction (low IgM or IgG levels) may flag a potential germline condition. B- or NK cell lymphocytopenias may be present in GATA2 deficiency, and abnormal Ig levels may be present in GATA2 deficiency and TBD. It should be noted that lymphocytopenia (low absolute lymphocyte count, ALC, of <1.2 × 10⁹/L) has been described in MDS (115, 116). Here, again, a comparison of the ALC with previous values, if available, could be helpful to distinguish pre-existing abnormalities from those associated with MDS.

Chromosomal breakage testing for FA should be interpreted with caution in patients with MDS, particularly if peripheral blasts are present or if prior cytoreductive therapy has been administered. FA chromosome break test is typically performed on peripheral blood leukocytes exposed to clastogenic agents diepoxybutane (DEB) and mitomycin C (MMC). Increased chromosomal breaks and fusions with radial forms are observed in FA. FA chromosomal breakage testing in the blood may be non-diagnostic due to peripheral blood somatic mosaicism resulting in two distinct populations of cells, where one of the populations harbors the germline mutation, while the other has a somatic genetic rescue that corrects the hypersensitivity to DNA cross-linking agents (47, 48). Skin fibroblasts can help diagnose blood mosaicism. The FA chromosomal breakage tests can be affected by prior chemotherapy or radiation therapy, since the lymphocytes may manifest baseline chromosomal breakage, however, a further increase in chromosomal breakage with the addition of DEB or MMC would support the diagnosis of FA. In such cases, performing FA testing on skin fibroblasts may be helpful. The results of the FA chromosome breakage test should be interpreted with caution and with advice from experts in the field. The diagnosis of FA informs the therapeutic plan, particularly for stem cell transplantation conditioning regimen given the sensitivity to genotoxic agents, making this is a critical part of MDS evaluation.

The telomere length testing for TBD is available clinically using a flow-FISH assay (117); however, interpretation can be challenging in the context of MDS, particularly following prior cytoreductive therapy, which might result in secondary telomere shortening. In untreated MDS patients without excess blasts, telomere lengths less than the first percentile for age in at least three different lymphocyte subsets are highly suspicious for a primary disorder of telomere maintenance (118, 119). It should be stressed that this parameter, although highly predictive in children, is not as well defined in adults, where the telomere length may fall above the first percentile for age even with known underlying genetic mutations related to telomere biology (11). If telomere measurement is available only in a single lymphocyte subset and is less than the first percentile for age, this could be suggestive of an underlying TBD and should be correlated with personal or family history of clinical features of TBD and/or germline genetic lesions. Shortening of telomeres in the granulocytes is a non-specific finding and, in isolation, is insufficient to flag a TBD. The analysis of telomere length in patients with MDS needs further study. Flow-FISH telomere length measurement must be interpreted with caution in a patient with MDS, and the potential influence of excess blasts or other secondary hematologic stressors has not been defined for this assay. In the research setting, the telomere length in MDS measured using real-time quantitative polymerase chain reaction (qPCR) analysis has been described to be shorter than in healthy individuals and is independently related to outcome in MDS after stem cell transplantation (120). The telomere length should be integrated with the clinical context, personal or family history of any TBD-related manifestations, other laboratory findings suggestive of a genetic telomere disorder, and genetic testing (see below).

Additional focused laboratory testing may be considered if clinically indicated. Evaluation of pancreatic insufficiency in SDS or SDS-like syndromes includes a pancreatic isoamylase for anyone older than 3 years old. Abdominal imaging may be helpful to assess for pancreatic lipomatosis or an atretic/abnormal pancreas suggestive of SDS. If a prior history of significant idiopathic macrocytosis or non-immune red cell aplasia is identified, the measurement of erythrocyte adenosine deaminase may be considered for evaluation of DBA.

**Bone Marrow Evaluation and Cytogenetic Assessment**

One of the distinguishing features of pediatric MDS, and MDS associated with predisposition conditions, is hypocellularity of the marrow unlike adult-onset MDS, which is typically hypercellular. Up to 10%–15% of MDS in adults may be hypocellular with bone marrow cellularity of <30%, and it is not yet known if this indicates an association with a germline predisposition. Studies in adult patients have found that MDS with hypocellular marrows is observed in younger patients and is associated with severe cytopenias, when compared to MDS with normocellular or hypocellular marrows (21, 121).

Some germline predisposition conditions are associated with baseline dysplasia (122), which may be confused with MDS. Megakaryocyte dysmorphology is a frequent baseline finding in the absence of MDS in GATA2 deficiency (123), RUNX1-FPD (124), or other germline predisposition conditions (125, 126). Megakaryocyte immunostaining in the bone marrow with CD61 helps highlight atypical megakaryocytes, which may be difficult to identify with hematoxylin and eosin (H&E) stain. Baseline myeloid dysplasia with nuclear hypolobation (Pelger–Huët-like cells) and hypogranulation is often seen without MDS in patients...
with SDS (127). Baseline mild dysmorphology is also observed in FA, including megaloblastic erythroid precursors, Pelger–Huët-like neutrophils, and hypolobated megakaryocytes, and should be considered in the diagnostic pathology (126). In such cases, serial marrow exams showing progressively increasing dysplasia, high-risk cyogenetic findings (for example, monosomy 7 or deletion of 7q, complex cyogenetic abnormalities), certain patterns of high risk somatic clones [for example, rising mutant TP53 clone size in SDS (96)], or increased blasts would raise concern for MDS.

We routinely perform cyogenetic evaluation and FISH staining on all MDS marrows. Since the proportion of abnormal cells may be small particularly if the marrow is hypocellular, and/or these cells may have a relative disadvantage of growth and missed in cyogenetic testing, FISH testing may be helpful irrespective of cyogenetic findings (128). Complete or partial loss of chromosome 7 is the most common cyogenetic abnormality in pediatric MDS and is the most common cyogenetic abnormality observed in MDS associated with predisposition conditions (129, 130). Monosomy 7/deletion of 7q has been found in up to one-third of MDS and AML associated with FA, SDS, GATA2 deficiency, and SCN, and has been described in MDS associated with RUNX1-FPD, TBD, and ERCC6L2 (129). In a cohort of adolescent patients with monosomy 7 MDS, the prevalence of germline GATA2 deficiency was reported to be 72% (6). Isochromosome 7q [i(7)(q10)] or del(20q) are cyogenetic abnormalities found in SDS, but these clones have not been associated with progression to malignancy (91, 131). Other common cyogenetic abnormalities described with germline predisposition conditions include trisomy 8 with GATA2 deficiency (6) and gains of chromosomes 1q and 3q with FA (126).

**Genetic Testing for Germline Predisposition**

The availability of clinical next-generation sequencing (NGS) has revealed the complex landscape of germline mutations in myeloid neoplasms, including MDS. Many germline mutations underlying predisposition conditions are also often found as somatic mutations in myeloid leukemias and may first be picked up on a somatic mutation panel as part of the diagnostic evaluation for MDS. Distinguishing germline from somatic mutations, particularly in consideration of germline predisposition conditions in young patients, has added to the complexity of interpreting the NGS result and carries profound clinical implications discussed below.

Most genetic panels designed for somatic mutation analysis of myeloid malignancies target mutations recurrently found in adult hematologic malignancies. Commercial somatic and germline NGS panels differ with respect to what genes and gene regions are included. Analytic pipelines for germline versus somatic mutations are also distinct. Additionally, many of these somatic genetic panels can miss deletions or duplications in a gene (for example, in GATA2 deficiency and RUNX1-FPD) and changes in non-coding regions like promoter regions (ANKRD26) and introns (GATA2) that may underlie germline predisposition conditions. Indeed, a normal/negative somatic NGS panel does not rule out a germline genetic cause of an MDS diagnosis. In our practice, we utilize a somatic NGS panel of 88 genes to evaluate somatic MDS mutations (132), accompanied by a separate gene panel designed for genetic analysis of germline variants. The identification of variants in genes known to be mutated either somatically or in the germline, such as RUNX1, GATA2, and TP53, warrant further consideration regardless of variant allele frequency, which may be affected by confounding factors such as copy number variants, loss of heterozygosity, or somatic reversion. Approaches to distinguish germline from somatic mutations include examination of non-hematopoietic tissues such as skin fibroblasts and persistence of the variant at a constant appropriate variant allele fraction (VAF) in remission marrows after MDS-directed therapy. For example, we reported a case of an adolescent patient with RUNX1-FPD who presented with B-ALL, who had a personal and family history of mild bleeding symptoms. She was found with a RUNX1 variant on the NGS panel with a VAF of 52%, initially classified as a variant of unknown clinical significance (VUS). Remission marrow showed persistence of this variant at a similar VAF, which was confirmed to be a germline with fibroblast sequencing and positive testing of her father who had long-standing bleeding symptoms (133).

The designation of a VUS indicates lack of sufficient evidence to meet current American College of Medical Genetics (ACMG) requirements for pathogenic/likely pathogenic or benign/likely benign designation. Many germline variants classified as VUS have not been described in the literature or in publicly available databases gene variants such as ClinVar (https://www.ncbi.nlm.nih.gov/clinvar) or gnomAD (https://gnomad.broadinstitute.org). We work closely with experts in specific genes or diseases, and colleagues in genetic counseling to analyze these variants with the clinical history, laboratory evaluation, association of the variant within family pedigree phenotypes, variant allele frequencies in control populations, and gene-specific structural and functional data (134). There are ongoing research and collaborative expert panel recommendations such as Clinical Genome Consortium (ClinGen: https://clinicalgenome.org/) for the interpretation and classification of germline variants (135). For specific gene/disease pairs, such as for RUNX1, TP53, and others, guidelines are curated by a Myeloid Malignancy Variant Curation Expert Panel (MM-VCEP) and include additional functional assessment guidelines to enhance the accuracy of variant interpretation (136–138). Variant classification is a highly active area of research, and consultation with an expert in the field can be helpful.

Interpretation of the sequencing results may be confounded by somatic genetic rescue (SGR) (139). In a number of these syndromes, SGR results in the correction of the germline mutation in a single hematopoietic stem and progenitor cell, which then results in a selective growth of the wild-type corrected clone over time, with reduction in the relative presence of the germline mutant cells in the hematopoietic tissues (97). Examples of SGR or reversion reported in
Germline Predisposition

In adult patients with MDS, the diagnosis of a germline MDS predisposition will also inform the decision around SCT. A therapy with curative intent will often involve stem cell transplantation (SCT) where donor selection is a critical part of the workup. Attention to post-SCT monitoring is needed for a patient with germline SAMD/L/SAMD9L deficiency-related MDS who experience clinical signs of non-hematologic organ toxicity, which do not correct with SCT, such as GATA2 deficiency-related lymphatic dysfunction, or lung and liver disease in TBD. Attention to post-SCT monitoring is needed for a patient with germline predisposition conditions with an increased risk of solid tumors [for example, FA, LFS, GATA2 deficiency (103), and DBA (150)].

Considerations for Family Counseling

Diagnosis of germline predisposition conditions informs family counseling. In the current era of successful oncofertility programs, young patients undergoing MDS-directed therapy, including SCT, have an opportunity to consider family planning options after their treatment. At the appropriate time, genetic counselors are helpful to engage in discussions about prenatal counseling, preimplantation genetic testing, and other possibilities.

Testing of family members should be discussed to allow informed decision-making and to guide their health maintenance. Testing of siblings, particularly those who may be considered for stem cell donation, is often a first step in this process. Testing of all direct family members (parents, siblings, and children) of the affected patient and interested biologically related members of the extended family should be discussed together with a genetic counselor with expertise in these conditions.

The recognition of the underlying germline predisposition informs the approach to therapy in MDS. A therapy with curative intent will often involve stem cell transplantation (SCT) where donor selection is a critical part of the workup. Identification of a germline genetic predisposition allows evaluation of potential family member donors to avoid choosing an affected but clinically asymptomatic donor (145). If a pathogenic germline mutation is identified in the proband, targeted sequencing of the suspected germline variant should be evaluated in the potential family donor. As genetic testing of the donor is time sensitive, the sequencing platform that can most rapidly return test results should be utilized. If the workup of the patient reveals abnormal functional test results, for example, short telomeres concerning TBD, without identification of a specific gene mutation, then evaluation of the related donor for that functional test and a bone marrow examination to rule out any significant hematologic abnormalities should be considered. In adult patients with MDS, the diagnosis of a germline MDS predisposition will also inform the decision around SCT versus chemotherapy or other alternative therapeutic measures, as SCT will not only cure the disease at hand but also eliminate the future heightened risk of hematologic malignancy (146).

Beyond donor selection, identification of germline predisposition conditions may change the conditioning regimen used in SCT to reduce non-relapse mortality (NRM). NRM is a significant complication in SCT for many predisposition conditions such as TBD (147) and FA, where there is a clear benefit for reduced intensity conditioning (RIC). For pediatric patients with MDS, SCT often involves myeloablative conditioning (MAC) regimens, although some RIC regimens are also used. A randomized trial in adults with MDS showed comparable relapse outcomes for patients receiving RIC versus MAC (148). Hence, the presence of certain germline predisposition conditions, particularly those associated with DNA-damage repair mechanism or high NRM, may benefit from receiving RIC and not MAC regimens to reduce NRM. Lastly, SCT outcomes may be affected by the underlying germline condition and associated comorbidities (2, 120) and should be considered at the time of transplantation planning.

Caring of patients during and after SCT for MDS may also be influenced by a germline predisposition condition. For example, in a single center cohort of patients undergoing SCT for GATA2 deficiency-related blood disorders, we found an increased risk of thrombotic and neurological complications, compared to patients with GATA2 wild-type MDS or ALL (147). A second cohort of patients with GATA2 deficiency-related MDS who underwent SCT reported four cases of neurological complications and several patients with transplant-associated thrombotic microangiopathy (149). Patients may also experience clinical signs of non-hematologic organ toxicity, which do not correct with SCT, such as GATA2 deficiency-related lymphatic dysfunction, or lung and liver disease in TBD.

Altering MDS Care for Patients With Germline Predisposition

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Attention to post-SCT monitoring is needed for a patient with germline predisposition conditions with an increased risk of solid tumors [for example, FA, LFS, GATA2 deficiency (103), and DBA (150)].
CONCLUDING REMARKS

We have gained valuable insight about MDS pathogenesis from pediatric MDS with germline predisposition conditions. Expanding the systematic evaluation for these conditions to adults with MDS will guide medical management and improve outcomes with tailored therapies, appropriate management of co-morbidities, and inform donor selection. Hematologists should be alert to potential red flags from personal and family history, physical exam, blood and marrow examination, and somatic NGS results, which are suggestive of genetic predisposition in adult patients with MDS.

Investigations into germline predisposition to hematologic malignancies continue to address unanswered questions of disease penetrance, incidence, mechanisms of somatic genetic rescue, and prognostic markers of MDS risk once a condition is identified in asymptomatic patients. Adults with germline predisposition to MDS may present without a suggestive childhood history. The identification of older adult-onset MDS for genetic predisposition conditions such as DDX41 or TBD-related MDS has expanded the age spectrum of consideration of germline conditions in MDS. Increasing awareness and evaluation for genetic predisposition to MDS in the diagnostic workup of adult patients will improve patient care, guide therapies, and inform monitoring of toxicities and comorbidities with the goal of improving patient outcomes.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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