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Hereditary Myeloid Malignancies

Hind Rafei, MD[1], **Courtney D. DiNardo, MD**[2]

[1]Division of Cancer Medicine, The University of Texas at MD Anderson Cancer Center, Houston, Texas

[2]Department of Leukemia, The University of Texas at MD Anderson Cancer Center, Houston, Texas,

Abstract

Myelodysplastic syndromes and acute myeloid leukemia are sporadic for the majority of cases affecting the elderly population. Inherited cases, however, do occur. Genetic predispositions to myeloid malignancies can be classified into three categories: familial cancer syndromes associated with increased risk of various malignancies including myelodysplasia and acute myeloid leukemia such as Li-Fraumeni syndrome and constitutional mismatch repair deficiency (CMMRD); germline mutations conferring a specific increased risk of myelodysplastic syndrome and acute myeloid leukemia such as mutations in *ANKRD26*, *CEBPA*, *DDX41*, *ETV6*, *GATA2*, *RUNX1*, *SRP72* genes; and finally primarily pediatric inherited bone marrow failure syndromes such as Fanconi anemia, dyskeratosis congenita, severe congenital neutropenia, Shwachman-Diamond syndrome and Diamond Blackfan anemia. The recognition of these germline syndromes is essential in the management and follow-up of patients. Herein, we review the conditions associated with hereditary myeloid leukemia with a special clinical focus on management and monitoring.

Keywords

Myelodysplastic syndrome; acute myeloid leukemia; germline; predisposition; hereditary; familial; genetic; bone marrow failure

Introduction

Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) present primarily as sporadic diseases affecting the elderly, with a median age of ≥ 65 years at presentation and increasing incidence with age in adulthood (1). However, there is increasing appreciation that hematologic malignancies can also be inherited and can be associated with specific

Corresponding author: Dr Courtney D. DiNardo, Department of Leukemia, The University of Texas at MD Anderson Cancer Center, Houston, Texas, CDiNardo@mdanderson.org.

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familial syndromes. Awareness and evaluation, particularly of younger patients or those with positive family history, is important for the optimal care of patients. The primarily solid cancer predisposition syndromes associated with an increased risk of myeloid malignancies include Li-Fraumeni syndrome (LFS), constitutional mismatch repair deficiency (CMMRD), Werner syndrome, Bloom syndrome, Nijmegen breakage syndromes, neurofibromatosis 1, as well as others.

In addition to cancer predisposition syndromes, there are specific inherited bone marrow failure syndromes which are associated with an increased risk of hematologic malignancy, particularly including the myeloid disorders MDS and AML (2). Inherited bone marrow failure syndromes are a heterogeneous group of diseases characterized by bone marrow failure often in childhood or adolescence, congenital abnormalities, and increased risk of malignancy (3). The tendency to develop MDS/AML varies between the different syndromes, with Fanconi anemia (FA) carrying the highest risk (4) and others such as severe congenital neutropenia (SCN) (5) dyskeratosis congenita (DC), Shwachman-Diamond syndrome (SDS) and Diamond Blackfan anemia (DBA) generally have lower or intermediate risks (6–8).

With the advent of precision medicine, a growing number of genes causing inherited forms of MDS/AML, often without syndromic presentations and occurring across different age groups, are now recognized. Studies suggest that around 4–10% of children and young adults with MDS or AML (9–11) and roughly similar percentages of adults with AML (12) may carry inherited mutations in genes predisposing to cancer. The genes implicated in myeloid malignancies are diverse, including hematopoietic transcription factors such as CEBPA, GATA2, RUNX1, ANKRD26, and ETV6, genes traditionally associated with solid tumors such as MSH6 and BRCA1, as well as more recently identified genes that are involved in leukemogenesis such as DDX41, SAMD9 and SAMD9L (13–16).

Herein, we review the various inherited cancer predisposition syndromes associated with MDS/AML as well as the inherited bone marrow failure syndromes. We also discuss the genetic aberrations associated with these disorders.

Molecular Aberrations Associated with Familial Myeloid Malignancies

Although most MDS and AML cases are sporadic, a subset may be familial (17). The 2016 WHO classification acknowledges AML and other myeloid neoplasms that are associated with germline mutations or a predisposition syndrome. A number of known mutations are associated with familial MDS/AML including mutations in the *ANKRD26*, *CEBPA*, *DDX41*, *ETV6*, *GATA2*, *RUNX1*, *SRP72* genes (Table 1).

- ANKRD26

ANKRD26-related thrombocytopenia (*ANKRD26*-RT) is an autosomal dominant thrombocytopenia caused by gain-of-function single nucleotide substitutions in the ankyrin repeat domain 26 (*ANKRD26*) gene, typically in the promoter region (18). *ANKRD26*-RT presents with moderate thrombocytopenia with a normal mean platelet volume. The age of diagnosis commonly ranges from the early 20s through the 70s; pediatric patients aged 2

to 16 years have also been reported (19, 20). Spontaneous bleeding is rare, and a number of patients have undergone surgeries without need for platelet transfusion, and most women in the studied families gave birth without bleeding complications (20).There are reports of partial responses to immune thrombocytopenia-directed therapies (19). Around 222 cases of *ANKRD26*-RT have been reported to date. These patient have an increased incidence of myeloid malignancies, estimated at 5% acute leukemia development, 2.2% MDS, and 1.3% developing CML, yielding an estimated risk of these malignancies that is 23-fold, 12-fold, and 21-fold higher than the general population, respectively (21).

- CEBPA

Familial AML with mutated CRBPA is an autosomal dominant familial AML syndrome with near complete penetrance, caused by germline mutations in the CCAAT enhancer binding protein-alpha (*CEBPA*). At the time of AML development, a somatic CEBPA mutation frequently occurs on the other allele (22) leading to bi-allelic *CEBPA* mutations. *CEBPA*-associated familial AML presents at a median age of 24.5 years (22). The presentation is, however, variable. A case of AML in monozygotic twins carrying the same germline *CEBPA* mutation, whose age at onset of AML differed by 13 years, has been reported (23). Survival outcomes are generally favorable, with recurrence typically caused by independent leukemic episodes (24).

- GATA2

GATA2 haploinsufficiency is an autosomal dominant bone marrow failure and primary immunodeficiency syndrome that predisposes to MDS and AML. It is caused by loss-of-function mutations or deletions in the *GATA2* gene. It is associated with a spectrum of described syndromes including Emberger syndrome (Primary Lymphedema and Myelodysplasia), MONOMAC syndrome (monocytopenia and mycobacterial infection syndrome), and DCML (dendritic cell, monocytes, B and NK lymphoid deficiency) (25–29). GATA2 is a zinc finger transcription factor that is essential in hematopoiesis (30). A cohort of 57 patients with GATA2 haploinsufficiency was reported by the National Institutes of Health (NIH) (25). The median age of initial presentation was 20 years (5 months to 78 years). The patients' presenting symptoms ranged from viral infections in 32% of cases, disseminated non-tuberculosis mycobacterial infections in 28%, MDS/AML in 21%, lymphedema in 9%, and invasive fungal infections in 4%. Cardinal findings in GATA2 haploinsufficiency include: severe viral or non-tuberculous mycobacterial infections, MDS/AML, pulmonary alveolar proteinosis, or lymphedema (25).

Some patients might also present with mild congenital neutropenia (31). Progression to myelodysplasia in GATA2 haploinsufficiency is frequently associated with monosomy 7 and trisomy 8 (25), as well as acquisition of somatic *ASXL1* mutations in ~30% of patients (32).

- RUNX1

RUNX1-associated familial platelet disorder with predisposition to MDS/AML (FPD/AML) is an autosomal dominant familial MDS/AML syndrome caused by inherited mutations in the RUNX1 gene that encodes a hematopoietic transcription factor (33). RUNX1 mutations lead to reduced hematopoietic progenitors and impaired differentiation of megakaryocytes

(34). The clinical presentation and course are highly variable. The age at presentation ranges from early childhood into the sixth decade (35, 36). There is commonly a history of thrombocytopenia accompanied by a mild to moderate bleeding tendency with aspirin-like platelet dysfunction. The rate of MDS/AML transformation in FPD/AML is estimated at 20–60%, with high variability even among families carrying the same mutation (37, 38).

- SRP72

Mutations in SRP72 lead to an autosomal dominant bone marrow failure syndrome; *SRP72*-associated aplasia and myelodysplasia. SRP72 is part of the signal recognition particle that is responsible of halting the translation of nascent secretory or extracellular proteins and directing them to the endoplasmic reticulum. Mutations in SRP72 lead to a decrease in the localization of the mutant protein in the endoplasmic reticulum and is a pathway for bone marrow failure and MDS. Mutations in SRP72 were detected in two kindreds with aplasia and MDS; both families had auditory abnormalities (labyrinthitis in one family and deafness in another). The age at onset of cytopenias and/or MDS ranges from 11 to 76 years (39).

- DDX41

DDX41-associated familial MDS/AML syndrome is an autosomal-dominant syndrome often presenting in mid to late adulthood, caused by germline mutations in the DEAD-Box helicase *DDX41*, leading to altered pre-mRNA splicing and RNA processing (16). *DDX41*-associated familial MDS/AML presents later in adulthood with an age at presentation ranging from 44 to 88 years, which notably overlaps with the average age of sporadic myeloid malignancies. Approximately half of patients had biallelic *DDX41* mutations with a second somatic event in the wild type allele, at specific recurrent hotspots. Additional somatic mutations were frequently found, most commonly mutations in *TP53*, *RUNX1*, and *LUC7L2* (16).

- ETV6

Germline mutations in the ETS family transcriptional repressor variant 6 (*ETV6*) cause altered DNA binding and ETV6 protein mislocalization, and are associated with familial thrombocytopenia and hematologic malignancy (40, 41). *ETV6* is a tumor suppressor frequently mutated by somatic alterations, such as the ETV6-RUNX1 fusion commonly seen in childhood leukemia. In contrast, patients with germline *ETV6* mutations typically present with bleeding, thrombocytopenia, and red cell macrocytosis (40, 41). Hereditary hematologic malignancies associated with familial cases include ALL, MDS RAEB-1, CMML, mixed phenotype acute leukemia, and multiple myeloma. There also appears to be a predisposition to other types of cancers such as skin and colon cancer (40–42).

Syndromes associated with myeloid malignancies (Table 2)

- Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is caused by germline mutations in in the *TP53* gene which leads to strong predisposition to various and primarily solid malignancies (43). LFS affects all ethnicities and has an estimated incidence of 1:5000 (44). LFS is inherited in an autosomal dominant pattern but can also occur *de novo* at a rate of 7–20% (45).

The tendency to develop malignancies in LFS stems from the central role that the p53 protein, encoded by the *TP53* gene, plays in the control of cell cycle arrest, senescence, and apoptosis (46, 47). This role confers a well-known tumor suppressor function to p53, which is often referred to as the "guardian of the genome" (48, 49). Patients with LFS are predisposed to a wide variety of cancers including breast cancer, sarcomas of the bone and soft tissues, adrenocortical carcinoma, brain cancers, and leukemia (50). Nearly 100% of individuals with Li-Fraumeni syndrome develop cancer by the age of 70, with the median age of first cancer at 20–30 years, and about 50% develop a second primary cancer within 10 years of their first cancer diagnosis (51).

The incidence of leukemia in patients with LFS is about 2–4% (52–54). Germline *TP53* mutations occur in high rates in certain leukemia subsets, particularly pediatric low hypodiploid acute lymphoblastic leukemia (ALL), defined as ALL containing 32–39 chromosomes (55). In *TP53* mutations carriers, myeloid malignancies and MDS are more likely to present as secondary cancers following the treatment of primary neoplasms although they can less likely be the presenting clinical manifestation (56). Testing for LFS should be considered in patients with hypodiploid ALL, as well as patients with myeloid malignancies and a strong family history that meet either the classic or the Chompret criteria for LFS (54, 57, 58). Testing can also be considered when myeloid malignancies develop following treatment for a primary cancer such as bone and soft tissue sarcoma, brain cancer, or breast cancer in younger individuals, etc. The management of patients with LFS and a myeloid malignancy includes limiting the exposure to radiation therapy if possible. When necessary, for example as part of allogeneic hematopoietic stem cell transplantation (HSCT), radiated sites need to be closely and regularly monitored for the development of site-specific radiation-induced neoplasms. Relatives should be screened for the presence of a familial *TP53* mutation prior to donor selection for HSCT. Ideally, tumor surveillance including annual MRI in those individuals should start in childhood (59).

- Constitutional Mismatch Repair Deficiency Syndrome

Constitutional mismatch repair deficiency syndrome (CMMRD) (also known as biallelic mismatch repair deficiency [BMMRD]) is caused by biallelic mutations in the mismatch repair (MMR) genes *MLH1, MSH2, MSH6, PMS2,* and, rarely, *EPCAM*. Heterozygous mutations in these genes cause Lynch syndrome, an autosomal dominant disorder that predisposes to adult-onset cancers, including colorectal, endometrial, breast cancers and others (60, 61). In contrast, when an individual inherits either homozygous or compound heterozygous mutations in an MMR gene, the autosomal dominant CMMRD syndrome occurs.

CMMRD confers a very high risk of cancer development in childhood and adulthood as well as characteristic physical features such as café-au-lait spots and skin-fold freckling. These manifestations can mimic those exhibited by individuals with neurofibromatosis 1 (NF 1) (62). Various cancers have been reported with CMMRD with the majority of affected patients diagnosed with their first malignancy in childhood (62, 63). In a report of 146 patients with this disease by the European Consortium "Care for CMMRD", 217 malignancies were documented, among which 2.3% were accounted for by AML (64). Other

common tumors included colorectal cancer (27.2%), high-grade glioma (26.7%), lymphoma (14.7%), and small bowel cancer (8.3%). Another report of 56 patients with CMMRD assessed 62 hematological malignancies of which 10 myeloid malignancies were reported in 9 patients (16% of reported hematologic malignancies) (65). Two of the nine patients with myeloid malignancies (one with AML and the other with atypical chronic myeloid leukemia [CML]) presented with primary leukemia. Another patient developed refractory anemia with excess blasts (RAEB) following treatment for medulloblastoma and then progressed to AML. The remaining 6 had AML secondary to the treatment of non-hematological malignancies. Tumors of individuals with CMMRD tend to express an exceedingly high mutational burden, thus the diagnosis should be considered in tumors with high mutated phenotypes (i.e. “MSI high phenotype”) and there are several recent reports of response to checkpoint inhibitor therapy in resistant cases(66, 67).

Patients with hematological malignancies associated with CMMRD tend to tolerate chemotherapy well without experiencing excessive treatment toxicity (65). However, they appear to have a high relapse rate as well as predisposition to secondary malignancies (68). Experts recommend the initiation of multisystem surveillance early in childhood for patients with CMMRD, including early brain imaging, gastrointestinal surveillance, and blood screening for hematologic malignancies (64, 69).

- Werner Syndrome

Werner syndrome, also known as “adult progeria”, is a syndrome of premature aging caused by biallelic mutations in the *WRN* gene and inherited in an autosomal recessive fashion (70, 71). The prevalence of Werner’s syndrome is estimated at 1:380,000–1,000,000 (72) with higher prevalence in Japanese (1:20,000–40,000) and Sardinian populations (1:50,000) due to founder mutations (73, 74). WRN, the Werner syndrome RecQ-like helicase protein, plays a role in senescence-associated pathways, which may account for the premature aging phenotype that is observed in patients with Werner syndrome (75).

Patients with Werner syndrome develop normally during the first decade of life with absence of a growth spurt in the teenage years. Clinical features do not commonly start to appear before the 20s (70). The cardinal features present in all individuals with Werner’s syndrome include bilateral cataracts, premature graying/thinning of the hair, scleroderma-like skin changes, and short stature. The presence of ulcerations around the Achilles tendon and malleoli is pathognomonic. Patients with Werner’s syndrome tend to develop other comorbidities including osteoporosis, type 2 diabetes, and atherosclerosis; causing a short life expectancy averaging mid-40s as patients die as a result of atherosclerosis or malignancies (70).

Malignancies associated with Werner’ syndrome include hematological neoplasms (9.3% of all tumors) including AML and MDS (76), thyroid tumors (16.1%), melanoma (13.3%), meningioma (10.9%), sarcomas (10.1%) and osteosarcoma (7.7%) (76). There appears also to be a susceptibility to breast cancer as some suggested that variants in *WRN* function as low-penetrance cancer predisposition alleles in the heterozygous state (77, 78).

Counseling parents and patients about the risk of malignancies and comorbidities play a crucial role in the care of patients with Werner's syndrome. Individuals should be screened yearly for type 2 diabetes, ocular pathology and lipid abnormalities. Tumor surveillance is currently limited to annual physical examination with special attention to the skin (79). Treatment is mainly supportive with a multidisciplinary approach including ophthalmology, orthopedics, and endocrinology services.

- Bloom Syndrome

Bloom syndrome is a rare genetic syndrome with hundreds cases reported to-date worldwide (80). It is caused by biallelic mutations in the *BLM* gene (81, 82). It is more common in Ashkenazi Jews of Polish descent due to the presence of a founder mutation (83). If molecular testing is inconclusive, cytogenetic evaluation of sister-chromatid exchanges (SCEs) might help (80). Bloom syndrome patients have a short stature and the majority have characteristic skin lesions including an erythematous butterfly-shaped facial rash over the cheeks and nose (84). They can also have early-onset feeding difficulties that may be present through young childhood, and immunodeficiency, which can cause recurrent infections. Men with Bloom syndrome are infertile and women undergo premature menopause (84).

Cancer risk is high in Bloom syndrome and is the leading cause of death in this patient population. In a report from the Bloom Syndrome Registry of 131 patients, AML represented 12.5% of all tumors (80). Other tumors include lymphoma (16.9%), GI cancers (15%), skin cancer (13%), and cancers of upper GI and respiratory tract (10.6%). There are 23 cases of MDS reported to-date in the Bloom Syndrome Registry with leukemia progression in seven individuals. Twenty of these 23 patients were treated for prior malignancies with chemotherapy, suggesting that the risk for MDS in this population may be largely treatment-related. Chromosome 7 anomalies including full and partial deletions are common cytogenetic abnormalities in these AML and MDS patients (85).

In patients who develop malignancies, special consideration should be given to the dose of radiation and type of chemotherapy given due to the high sensitivity in these individuals to DNA-damaging agents.

- Nijmegen Breakage Syndrome

Nijmegen breakage syndrome (NBS) is caused by biallelic mutations in the *NBN* gene (86). It is a rare syndrome with an estimated prevalence of 1:100,000 individuals affected worldwide (87). It is more common in individuals of Slavic descent tracing ancestry to Eastern European countries such as Poland, Ukraine, and the Czech Republic due to the presence of a founder mutation (87). The syndrome is mainly due to deficiency in nibrin which leads to increased cellular radiosensitivity and chromosome instability (88).

NBS is associated with characteristic physical features, including progressive microcephaly, short stature, café-au-lait macules, and distinctive facial features including a receding forehead, prominent midface, retrognathia, epicanthal folds, and upslanting palpebral fissures. Patients may also have immunodeficiency and cognitive deficits (89). Primary ovarian insufficiency could occur in females (90). Aplastic anemia has been reported in a small number of affected individuals (91).

There is a substantial increase in the risk of malignancy in patients affected with NBS with 40% occurring by the second decade of life. Lymphoma accounts for the majority of reported malignancies, with other cancers including acute leukemia (mostly lymphoblastic although myeloid has been reported), brain tumors and sarcomas being reported as well (42).

While reduced dosage of chemotherapy in the management of NBS-associated malignancies is a reasonable consideration due to the known increased risk of treatment toxicity as is the case with other DNA repair syndromes, it, however, has not been effective in achieving remission in this patient population (92). HSCT has been successfully performed for treatment-resistant hematologic malignancies (93).

- Down Syndrome

Individuals with Down Syndrome (DS) have various developmental abnormalities, including craniofacial dysmorphology, cardiovascular defects and cognitive impairment. Paradoxically, individuals with DS have a decreased frequency of solid tumors (94–96), but a higher incidence of leukemia (10–20 fold) (97). There is a well-defined preceding transient myeloproliferative disorder (TMD), also called transient leukemia (TL), occurring in the neonatal period in 10% of infants with DS (98–100). TMD is a clonal preleukemic evolution characterized by an accumulation of immature megakaryoblasts in the fetal liver and peripheral blood (101). Children with DS who are younger than 4 years have a 500-fold increased incidence of acute megakaryoblastic leukemia (AMKL, also known as ML-DS) (101). It is thought that trisomy 21 directly contributes to the malignant transformation of hematopoietic cells. In addition, somatic mutations of the *GATA1* gene have been detected in nearly all DS AMKL cases and are notably absent in non-DS AMKL.

Treatment of patients with DS-associated AML with high dose cytarabine and anthracycline-based therapy showed an increased sensitivity to this regimen with a significantly greater event-free survival (EFS) compared to non-DS AML patients (3-year EFS 100% in DS-AML compared to 33% in non-DS AML) (102). However, intensive regimen has been shown to be associated with increased toxicity and mortality in subsequent trials, as have autologous and allogeneic transplant (103). AMKL has been treated on protocols with conventional (104) or high dose cytosine arabinoside (Ara-C) with reported 3-year overall survival (OS) greater than 80%. However, high dose Ara-C was associated with increased risk of toxicity (105–107). Low dose subcutaneous Ara-C induced remission in almost all cases of AMKL and complicated TMD with 5-year EFS and OS similar with standard chemotherapy (108–110). Due to the limitations of toxic deaths, infections, and cardiac toxicity in treating DS-AMKL, newer, less-intensive protocols have been conducted in the United States, Japan and Europe (105, 111).

- Leopard/Noonan Syndrome

Noonan syndrome (NS) is a relatively common (1/2000 births) developmental disorder characterized by reduced postnatal growth, congenital heart defects and cardiomyopathy, variable cognitive deficits, and distinctive facial dysmorphism (112). NS has an equal male to female ratio (113, 114). Familial cases correspond to approximately 20% of the cases and

exhibit primarily an autosomal dominant inheritance with a near complete penetrance (115, 116).

Germline mutations in components of the RAS-MAPK (mitogen-activated protein kinase) are thought to be involved in the pathogenesis of NS and of four rare syndromes with NS overlapping features: Leopard syndrome, cardio-facio-cutaneous syndrome (CFC), Costello syndrome and neurofibromatosis type 1 (NF1) (117).

NS patients have an increased risk of developing several types of malignancies (112, 118) including myeloproliferative disorders (MPN) resembling juvenile myelomonocytic leukaemia (JMML) (119). JMML is a rare and aggressive myelodysplastic and myeloproliferative neoplasm of early childhood, associated with excessive monocytic and macrophagic proliferation (120). Patients typically present with anemia, thrombocytopenia, splenomegaly, monocytosis, and elevated fetal hemoglobin (HbF) (121). JMML is characterized by the hypersensitivity of myeloid progenitors to granulocyte-macrophage colony-stimulating factor (GM-CSF) (122). Sporadic JMML has a poor prognosis and the only curative treatment is allogeneic bone marrow transplantation, with a relapse rate of 30– 40%. However, NS-related JMML is often benign and may even resolve spontaneously within one year of presentation (119, 123–127).

Most patients with NS and MPN harbor a PTPN11 mutation (126, 128) and about 35% of sporadic JMML cases display an acquired somatic PTPN11 mutation. PTPN11 encodes the cytoplasmic phosphatase SHP2, which enhances the signal transduction of growth factors and cytokines by upregulating RAS/MAPK pathway activation (129).

- Neurofibromatosis I

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder, characterized by the development of peripheral nerve sheath tumors called neurofibromas. Patients affected with NF1 also have café-au-lait macules, skeletal anomalies, and cognitive deficits. Despite the low incidence of malignancy in NF1, cancer remains an important cause of morbidity and mortality. While neurofibromas are benign tumors, malignant peripheral nerve sheath tumors (MPNST) may also occur. In addition, gliomas, particularly pilocytic astrocytomas of the optic nerve, and leukemia, have an increased frequency in NF1 (130). The gene involved in NF1 encodes a protein called neurofibromin (130–133). Although the function of neurofibromin is not completely understood, it is known to include a GTPase activating protein (GAP) domain that regulates hydrolysis of Ras-GTP to Ras-GDP (134–137).

Children with NF1 have an increased prevalence of myeloid leukemia (138). A population-based study found an increased relative risk of chronic myelomonocytic leukemia, acute lymphoblastic leukemia, and non-Hodgkin’s lymphoma in the NF1 population. Juvenile xanthogranuloma (JXG) which is a form of histiocytosis manifesting as cutaneous nodules is found with increased frequency in children with NF1 and also has been correlated with risk of juvenile chronic myelogenous leukemia (JCML) in the general population (139). This however has not been validated and hence it is not clear that there is clinical benefit to closely observe of children with NF1 and JXG for leukemia. In contrast with many non-NF1-associated myeloid malignancies, leukemic cells from NF1 patients have

loss of heterozygosity for the *NF1* gene but do not have activating Ras mutations (140) . Increased levels of Ras-GTP are found in the NF1-associated leukemias (141) which show an increased sensitivity to GM-CSF and other cytokines (142).

Inherited Bone Marrow Failure Syndromes (Table 3)

- Fanconi Anemia

Fanconi anemia (FA) is an autosomal or X-linked recessive inherited bone marrow failure syndrome characterized by growth retardation, congenital abnormalities, bone marrow failure with predisposition to AML, increased risk of other solid tumors (143). Congenital abnormalities include short stature, abnormal skin pigmentation, radial ray defects, and abnormalities of various organs, including arms, head, eyes, ears, and kidneys. However, it is important to note that 25–40% of patients lack physical abnormalities (144). The age at presentation is variable and spans the pediatric and adult age groups with a median age at diagnosis of 6.5 years for boys and 8 years for girls. The median age of development of bone marrow failure is 7 years (145). The cumulative incidence of bone marrow failure by the age of 40 is 90% and the median overall survival is 24 years (146).

Fifteen genes have been identified to be associated with FA (144). *FANCA* mutations are the most common. FANCB mutations confer an autosomal recessive inheritance pattern due to the location of FANCB on the X-chromosome (147). FA genes are involved in DNA crosslinks repair involved in the FA/BRCA pathway. *FANCD1* is identical to *BRCA2* with homozygous mutations leading to an increased susceptibility to breast, ovarian, and pancreatic cancer (148). MDS/AML that develops in the setting of FA tend to harbor certain cytogenetics more commonly, including +3q (41%), −7/7q (17%), and −11q (14%). Cryptic rearrangements of *RUNX1*, including translocations and deletions, as well as point mutations are also seen in ~21% of patients with FA (149). FA is diagnosed by the chromosome breakage test demonstrating an increased number of chromosomal breaks. HSCT offers the only cure for this condition. Sibling-matched transplantation is the preferred modality. Due to the high mortality with cyclophosphamide, reduced intensity conditioning regimens are preferred. Current data support the feasibility of reducing radiation dosages from the standard conditioning regimens in matched-unrelated donor transplants, and perhaps elimination of radiation in sibling-matched transplants (150).

- Dyskeratosis Congenita

Dyskeratosis congenita (DC) is an inherited bone marrow failure syndrome, often characterized by the triad of mucosal leukoplakia, abnormal skin pigmentation and nail dystrophy (151). Abnormalities of other organs include gastrointestinal, genitourinary, dental, ophthalmic, pulmonary, neurological, and skeletal and in particular hepatic and pulmonary fibrosis. Inheritance pattern can be X-linked, recessive, or autosomal dominant depending on the mutation. Genes identified to cause DC include *CTC1*, *DKC1*, *TERC*, *TERT*, *TINF2*, *NHP2*, *NOP10*, *RTEL1*, and *WRAP53*, although pathogenic germline mutations can be detected in only ~80% of individuals with a clinical diagnosis of DC. *DKC1* encodes dyskerin, a highly conserved nucleolar protein (152), which is important in the process of ribosomal RNA maturation as well as stabilization of the telomerase complex,

which in turns is critical in the maintenance of telomeres (153). Heterozygous mutations in *TERC, TERT* (telomerase reverse transcriptase) and RTEL1 are often identified in adult patients with autosomal dominant dyskeratosis congenita and in some patients with aplastic anemia, MDS and pulmonary fibrosis (154, 155). Individuals with DC are at increased risk for MDS/AML, solid tumors (typically squamous cell carcinomas of the head, neck, anogenital tract), and pulmonary fibrosis. The median age at onset of MDS is 35 years (range 19–61) (2). Telomere length analysis in total leukocytes and a panel of six leukocyte subsets (granulocytes, naïve T-cells, memory T-cells, B-cells, and NK cells) by flow-FISH is recommended for the diagnosis of DC (156).

HSCT is the only cure for patients with bone marrow failure and MDS/AML in the setting of DC. However, there is an increased rate of complications in patients with DC undergoing HSCT, including graft failure, graft *vs*. host disease, sepsis, pulmonary fibrosis, hepatic cirrhosis, and veno-occulsive disease (157) so care for a non-myeloablative conditioning regimens are paramount.

- Ataxia-Pancytopenia Syndrome

Ataxia-pancytopenia syndrome (ATXPC) is an autosomal dominant disease of characteristic neurological deficits as well as hematological abnormalities. Neurological deficits include early-onset gait and balance impairment, nystagmus, mild pyramidal signs, and marked cerebellar atrophy. Hematological abnormalities include pancytopenia, bone marrow failure and progression into MDS and AML. Elimination of the germline *SAMD9L* mutation by loss of chromosome 7(q) can result in myeloid malignancies (158). ATXPC has so far been described in 5 families (14, 158–161). Missense mutations in sterile alpha motif domain–containing protein 9-like (*SAMD9L*) have been identified as the cause of ATXPC in 4 of these families (14, 158–161).

- MIRAGE Syndrome

MIRAGE syndrome is a multiorgan disorder characterized by six core features: bone marrow failure and myelodysplasia, infection, intrauterine growth restriction, adrenal hypoplasia, genital phenotypes and enteropathy (162) which has been recently recognized as related to heterozygous SAMD9 mutation. Chronic diarrhea with colonic dilatation was observed in almost all patients in previous reports (13, 162). It is caused by de novo germline heterozygous gain-of-function mutations in *SAMD9*, a growth-restricting protein that plays a major role in the development of many systems and leads to intrauterine growth retardation and a marked effect on adrenal gland and testes differentiation. Progressive loss of mutated *SAMD9* through the development of monosomy 7 (–7), deletions of 7q (7q–), and secondary somatic loss-of-function (nonsense and frameshift) mutations in *SAMD9* rescue the growth-restricting effects of mutant SAMD9 proteins in bone marrow and is associated with increased length of survival in one study (13).

- Shwachman-Diamond Syndrome

Shwachman-Diamond Syndrome (SDS) is an autosomal-recessive disorder, primarily diagnosed in childhood, characterized by malabsorption and failure to thrive. Patients also have abnormal physical findings including short stature, with metaphyseal dysostosis

particularly at the hips and femurs in about half the patients. Some patients have cognitive deficits. Neutropenia is usually identified during the general evaluation (163). Other cytopenias and macrocytosis may be observed, and many patients evolve to aplastic anemia, MDS, or AML. The median age for the transformation to leukemia is 18 years, and the age-dependent cumulative probability of leukemia is greater than 70% (164).

The diagnosis of SDS relies on proving exocrine pancreatic insufficiency. This is demonstrated by reduced levels of serum trypsinogen and isoamylase and/or detection of a fatty pancreas by imaging (165). In addition, neutropenia below 1500/μL must be documented on more than one occasion (166). Patients with SDS often have bone marrow cytogenetic clones, particularly monosomy 7, der(7), and i(7q), as well as del(20q). The prognostic significance of the cytogenetic clones is unclear. More than 95% of patients who meet the diagnostic criteria for SDS have biallelic mutations in *SBDS* (Shwachman-Bodian-Diamond syndrome), a gene which plays a role in ribosome formation. Most mutations are due to gene conversion between the *SBDS* gene and an adjacent pseudogene. However, the reason for bone marrow failure in patients with *SBDS* mutations remains unclear (167, 168).

The management of patients with SDS is multifaceted and aims at improving malabsorption as well as close monitoring for the development of myelodysplasia. Malabsorption is treated by administration of pancreatic enzyme supplements and fat soluble vitamins (A, D, E, K). Pancreatic function often improves with age, and fewer or no supplements may be needed by adult patients. Neutropenia is rarely of clinical significance and usually improves with growth factors. Bone marrow function does not improve with age, and clonal cytogenetics, MDS, and leukemia may develop. HSCT has been successfully used for patients with SDS, although care should be taken as there is an increased risk of cardiac toxicity from preparative regimens that include cyclophosphamide (164).

- Severe Congenital Neutropenia

Severe congenital neutropenia (SCN) is a heterogeneous group of hematological diseases that are characterized by impaired maturation of neutrophil granulocytes. SCN patients are at increased risk for recurrent and often life-threatening infections beginning in their first months of life (169). SCN is most commonly caused by autosomal dominant mutations in *ELANE*, which encodes neutrophil elastase, and autosomal recessive mutations in *HAX1*, which contributes to the activation of the granulocyte-colony stimulating factor signaling pathway (170, 171). SCN is a bone marrow failure syndrome that predisposes to MDS and AML. Molecular events in the malignant progression include acquired mutations in *CSF3R* (encoding G-CSF receptor) and subsequently in other leukemia-associated genes (such as *RUNX1*) in a majority of patients (172). Diagnosis is based on clinical manifestations, blood neutrophil count, bone marrow examination, and genetic and immunological analyses. Daily subcutaneous G-CSF administration is the treatment of choice and leads to a substantial increase in blood neutrophils count, reduction of infections and drastic improvement of quality of life (173, 174). HSCT is the alternative treatment (175). Close clinical observation including yearly bone marrow evaluations to detect chromosomal abnormalities such as trisomy 21 and monosomy 7 as well as somatic leukemogenic mutations is highly recommended (164).

- Diamond-Blackfan Anemia

Diamond-Blackfan Anemia (DBA) is a bone marrow failure syndrome characterized by the diagnosis of anemia in utero, at birth or within the first year of life. While physical abnormalities might also be present including thumb abnormalities and short stature, the majority of patients have few or subtle abnormalities. Spontaneous remission happens in 20% of patients with DBA with no further need of corticosteroids or transfusions. Other patients might remain anemic and require HSCT (176). Patients with DBA have an estimated 5-fold increase risk of cancer, including osteogenic sarcoma, AML and colon cancer (8, 177).

Indications for HSCT in patients with DBA include refractory disease despite corticosteroids and transfusions or to avoid toxicities from steroids and iron overload from chronic transfusions.. There are no data on the use of reduced-intensity HSCT regimen and standard myeloablative regimens are recommended, however (178) iron overload post-HSCT is a major challenge. Monitoring post-SCT includes iron chelation as well as routine phlebotomy for an extended period, and MRI monitoring of heart and liver iron burdens. Another problem post-HSCT is development of malignancies but the small number of patients makes it difficult to determine whether this increased risk is significant (179).

Summary

Multiple hereditary predispositions to myeloid malignancies have been and continue to be identified, particularly in the setting of increasingly available and comprehensive genetic testing that is now integrated into the evaluation, prognostication, and treatment of patients with MDS and AML. Patients with inherited MDS/AML should be treated differently from sporadic cases with unique considerations particularly in regards to allogeneic SCT; both intensity of transplant regimens and donor selection. Clinicians should be able to recognize the characteristic features of hereditary predispositions to hematologic malignancies, and obtain a careful family and medical history in all patients with MDS and AML to identify patients who may be appropriate for further genetic counseling and testing. It is important to note that genetic testing in hematological malignancies differ from that in solid tumors where peripheral blood is the usual source of DNA. In hematological malignancies, peripheral blood is usually contaminated with cancer cells, thus, genetic testing on blood is somatic and not germline. Skin fibroblasts are the gold standard source of germline DNA for individuals with hematologic malignancies for germline analysis. Standard skin punch biopsies can provide a quick and practical way for obtaining cultured skin fibroblasts.

The recognition of inherited cancer predisposition syndromes is essential for the optimal management and treatment of patients. Management of patients with familial syndromes is ideally multidisciplinary, involving different specialists depending on the organ systems involved, with care to avoid risks of increased toxicity seen in many inherited bone marrow failure syndromes. In affected patients, close monitoring for early identification of malignant transformation is recommended.

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Practice Points

- Familial forms of myelodysplastic syndromes and myeloid leukemia have traditionally been considered rare, especially in adults; however, the increasing awareness and availability of genetic testing has identified multiple susceptibility genes.
- Bone marrow failure syndromes such as Fanconi anemia, dyskeratosis congenita, Diamond–Blackfan anemia, and Shwachman–Diamond syndrome, are often characterized by clinically-recognizable phenotypes and have significantly increased risks for myelodysplasia and/or acute myeloid leukemia in the setting of bone marrow failure.
- An increasing number of genes conferring inherited risks for myelodysplastic syndrome and/or acute myeloid leukemia as the primary malignancy have been identified including *RUNX1*, *ANKRD26*, *DDX41*, *ETV6*, *GATA2*, and *SRP72*.
- Some cancer predisposition syndromes are associated with a significant increase in the risk of development of myelodysplasia and myeloid leukemia including Li-Fraumeni syndrome, constitutional mismatch repair deficiency (CMMRD), Werner syndrome, Bloom syndrome, Nijmegen breakage syndromes, neurofibromatosis 1, etc.
- The management of patients with inherited myeloid malignancies is different from that of sporadic cases and hence the recognition of these syndromes is of paramount importance.

Table 1:

Genetic predisposition to MDS/AML

Gene	Syndrome	Hematologic malignancies	Other hematologic manifestations	Nonhematologic manifestations
CEBPA	Familial AML with mutated *CEBPA*	–	–	–
DDX1	Familial AML with mutated *DDX41*	MDS, CMML	–	–
RUNX1	Familial platelet disorder with propensity to myeloid malignancies	MDS, T-ALL	Thrombocytopenia, bleeding propensity	Eczema
ANKRD26	Thrombocytopenia 2	MDS	Thrombocytopenia, bleeding propensity	–
ETV6	Thrombocytopenia 5	MDS, CMML, B-ALL, PCM	Thrombocytopenia	Possible Risk for solid tumors
GATA2	Familial MDS/AML with mutated *GATA2*	MDS, CMML	MonoMAC syndrome	Lymphedema, hearing loss, extragenital warts
SRP72	SRP72-associated familial aplasia and myelodysplasia	MDS	Aplastic anemia	Deafness
SAMD9	MIRAGE syndrome	MDS		Infections, intrauterine growth restrictions, adrenal hypoplasia, enteropathy
SAMD9L	Ataxia-pancytopenia syndrome	MDS	Pancytopenia	Neurological deficits

Table 2:

Cancer predisposition syndromes

Syndrome	Mechanism	Inheritance	Gene(s)	Characteristics	Diagnostic Test	Risk of MDS/AML
Bloom Syndrome	DNA repair	AR	*BLM*	Short stature, immunodeficiency, microcephaly, highpitched voice, hypogonadism	gene sequencing	15–25%
Li-Fraumeni Syndrome	TP53	AD	*TP53, CHEK2*	Cancer predisposition	gene sequencing	8%
Neurofibromatosis Type I	Ras signaling	AD	*NF1, SPRED1*	café-au-lait spots, axillary/inguinal freckling, neurofibromas, Lisch nodules, optic gliomas, bony dysplasia	gene sequencing	<1%
Noonan Syndrome	Ras signaling	AD	*PTPN11, KRAS, RAF1, SOS1, CBL*	Short stature, facial dysmorphology, congenital heart defect	gene sequencing	Unknown

AD: autosomal dominant; AR: autosomal recessive; XLR: X-linked recessive

Table 3:

Inherited bone marrow failure syndromes

Syndrome	Mechanism	Inheritance	Gene(s)	Characteristics	Diagnostic Test	Risk of MDS/AML
Diamond-Blackfan Anemia	Ribosome biogenesis	AD, XLR	*RPS19, RPS17, RPS24, RPL35A, RPL5, RPL11, RPS7, RPS26, RPS10, GATA1*	Short stature, congenital anomalies (head and neck, cardiac, thumb)	Elevated erythrocyte adenosine deaminase and HgF; gene sequencing	1–20%
Dyskeratosis Congenita	Telomere maintenance	XLR, AD, AR	*DKC1, TERT, TERC, TINF2, RTEL1, NOP10, NHP2, WRAP53, CTC1, PARN*	Nail dystrophy, lacy skin pigmentation, oral leukoplakia, pulmonary fibrosis, hepatic fibrosis, cancer predisposition	Telomere lengths; gene sequencing	30%
Fanconi Anemia	Homologous DNA repair, impaired tolerance of reactive metabolites	AR, XLR	*FANCA, FANCC, FANCD1/BRCA2, FANCD2, FANCE,FANCF, FANCG/XRCC9, FANCI, FANCJ/BACH1/BRIP1, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51C,FANCP/SLX4, FANCQ(ERCC4), FANCB*	Radial anomalies, caféau-lait spots, short stature, microcephaly, GU anomalies, hip dysplasia, cancer predisposition	Chromosome breakage studies; gene sequencing	40%
Severe Congenital Neutropenia	Various	AR	*ELA2, HAX1, GFI1*	Neutropenia, frequent Infections	gene sequencing	10%
Shwachman-Diamond Syndrome	Ribosome biogenesis	AR	*SBDS*	Short stature, pancreatic insufficiency, skeletal abnormalities	stool studies; gene sequencing	20–30%

AD: autosomal dominant; AR: autosomal recessive; XLR: X-linked recessive; GU: genitourinary