Familial myelodysplastic syndromes: a review of the literature

Elena Liew and Carolyn Owen

Division of Hematology and Hematologic Malignancies, Department of Medicine, University of Calgary, Calgary, AB, Canada

ABSTRACT

Familial cases of myelodysplastic syndromes are rare, but are immensely valuable for the investigation of the molecular pathogenesis of myelodysplasia in general. The best-characterized familial myelodysplastic syndrome is that of familial platelet disorder with propensity to myeloid malignancy, caused by heterozygous germline *RUNX1* mutations. Recently, there has been an increase in the number of reported cases, allowing for better understanding of the incidence, clinical features, and pathogenesis of this disorder. These recent cases have highlighted the clinical variability of the disorder and confirmed that many patients lack a bleeding and/or thrombocytopenia history. Additionally, several cases of T-acute lymphoblastic leukemia have now been reported, confirming a risk of lymphoid leukemia in patients with inherited *RUNX1* mutations. Furthermore, an increased awareness of clinicians has helped detect a number of additional families affected by inherited myelodysplastic syndromes, resulting in the identification of novel causative mechanisms of disease, such as *RUNX1* deficiency resulting from constitutional microdeletions of 21q22 and myelodysplasia-associated with telomerase deficiency. Awareness of predisposition to myelodysplastic syndromes and acute myeloid leukemia in families may be of critical importance in the management of younger patients with myelodysplasia in whom allogeneic hematopoietic stem cell transplantation is considered. Such families should be investigated for inherited deficiencies of *RUNX1* and/or telomerase to prevent the use of an affected sibling as a donor for transplantation. Here we provide an update on familial platelet disorder in addition to a review of other known familial myelodysplastic syndromes.

Key words: myelodysplastic syndromes, familial, platelet disorder, transplantation, donor.

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Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by dysplastic changes in the bone marrow, ineffective hematopoiesis resulting in cytopenias, and an increased risk of developing acute myeloid leukemia (AML). MDS is predominantly a sporadic disease that affects the elderly, with a median age of diagnosis of over 70 years, and generally carries a poor prognosis.[1,2]

Significant progress has been made in delineating the molecular pathophysiology of MDS and AML. Ineffective apoptosis and disordered cell differentiation arise from the acquisition of genetic insults by a hematopoietic stem cell. These genetic lesions may be inherited or acquired, but their exact nature is poorly understood for most patients. The presence of an initiating event is required to increase the susceptibility of the affected progenitor cell to further DNA damage, leading to an accumulation of secondary genetic aberrations that ultimately results in the development of overt MDS/AML. These can include structural chromosomal abnormalities, gene mutations, and epigenetic changes, and may be influenced by immune dysregulation and the marrow microenvironment.[3,4] A history of prior chemotherapy or environmental/occupational exposure to radiation or toxins such as benzene may be associated with MDS development. This risk may be increased in subjects who have mutations of the carcinogen detoxifying enzyme NAD(P)H:quinone oxidoreductase.[5]

While the majority of MDS cases are sporadic, rare familial cases have been described. These familial cases are a precious resource as they have allowed key initiating germline mutations to be identified. The most clearly defined of the familial MDS syndromes is familial platelet disorder with propensity to myeloid malignancy (FPD/AML). Multiple new pedigrees have been recently described and further clarify the clinical presentation and outcome of this disease. The pathogenesis and presentation of recognized familial MDS syndromes will be reviewed here.

Syndrome-associated myelodysplastic syndromes

A number of inherited bone marrow failure syndromes are known to predispose to the development of malignancies, including MDS/AML (Table 1). These disorders are reviewed elsewhere[6,7] and will not be discussed in the context of this review.

EL and CO contributed equally to this manuscript.
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Correspondence: Carolyn Owen, Division of Hematology and Hematologic Malignancies, 601A South Tower, Foothills Medical Centre, 1403 – 29 St NW, Calgary, AB, T2N 2T9, Canada. Phone: international +1.403.9448047. Fax: international +1.403.2707891.
E-mail: carolyn.owen@albertahealthservices.ca

Familial platelet disorder with propensity to myeloid malignancy

FPD/AML is a rare autosomal dominant disorder characterized by quantitative and qualitative platelet defects with a predisposition for the development of myeloid malignancies. The disease appears to have complete penetrance but wide variability in clinical presentation. Reports of FPD/AML date back to 1978,[8] and so far there have been 30 pedigrees reported in the literature, with 10 reported in the last two years. This high reporting rate suggests that the prevalence of the disorder is likely higher than previously recognized and also highlights the increased awareness of FPD/AML by clinicians.

The first well-described pedigree was reported by Dowton *et al.* in 1985.[9] With additional pedigrees reported, it is apparent that the clinical presentation of FPD/AML is highly variable. A mild to moderate bleeding tendency due to quantitative and/or functional platelet defects is usually present from childhood, but many patients have no bleeding history. Thrombocytopenia is generally modest with normal-sized platelets. The pathogenesis underlying the thrombocytopenia and platelet dysfunction is not known. However, decreased expression of the thrombopoietin Mpl receptor has been reported in some patients,[10] which may explain low platelet counts, while several other dysregulated genes have recently been linked to the platelet dysfunction, including platelet myosin light chain gene *MYL9*, platelet protein kinase C-theta and platelet factor 4.[11-13] Platelet aggregation is typically abnormal, particularly in response to collagen and epinephrine. Both platelet storage pool deficiency[14] and impaired GPIIb-IIIa activation[12] have been described. Importantly, the presence of thrombocytopenia is not mandatory for a diagnosis of FPD/AML, as some affected individuals have displayed normal platelet counts, and could, therefore, escape detection within an affected family.[15,16] Furthermore, several affected individuals were noted to lack both thrombocytopenia and a bleeding history. It is not known whether these patients would manifest platelet function disorders if advanced platelet aggregation studies were to be performed, making this an interesting question for future study.

The incidence of MDS/AML in affected pedigrees is over 40%, with a median age of onset of 33 years. Although the highest likelihood of malignancy in patients with FPD/AML is of myeloid lineage, there is clearly also an increased risk of T-acute lymphoblastic leukemia (T-ALL), with 4 cases reported to date.[17-19]

Once a number of FPD/AML pedigrees were identified, a shared genetic lesion was postulated and linkage analysis of samples from the Dowton pedigree mapped the disease locus to chromosome 21q22.[20] Heterozygous inherited *RUNX1* mutations as the cause of the disorder was confirmed in 1999.[21] *RUNX1* (*CBFA2* or *AML1*) encodes the DNA-binding subunit of the core binding factor (CBF) transcription complex. Heterodimerization to its partner CBF-beta enhances the affinity of RUNX1 to DNA and protects it from proteolytic degradation. A highly conserved runt-homology domain (RHD), located near the N-terminus of RUNX1, mediates both DNA binding and heterodimerization. The CBF regulates expression of multiple hematopoiesis-specific genes and is essential for the establishment of definitive hematopoiesis.[22]

Mutations of *RUNX1* observed in FPD/AML are heterogeneous and tend to be specific to individual families. The most common mutations involve the RHD; C-terminal mutations have also been described but are less common. Deletional mutations, reported in 3 families, are not detectable by traditional direct sequencing methods and may involve the entire gene.[23] In fact, *RUNX1* was initially dismissed as the culprit gene in the Dowton pedigree because the original studies were unable to identify the causative large intragenic deletional mutation.[24] Individual mutations are thought to result in different degrees of functional loss of the RUNX1 protein, accounting for the

Table 1. Summary of familial syndromes predisposing to MDS/AML.

	Inheritance	Gene	Locus	Incidence of MDS/AML
Syndrome-associated familial MDS/AML				
Bone marrow failure syndromes				
Diamond-Blackfan anemia	AD	*RPS19*	19q13	0.5-1.0%
		RPS24	10q22	
		RPS17	15q25	
		RPL5	1p22	
		RPL11	1p35	
		RPL35A	3q29	
		RPS7	2p	
Severe congenital neutropenia	AD	*ELA2*	19q13	10%
		GFI1	1p22	
	AR	*HAX-1*	1q21	
Congenital amegakaryocytic thrombocytopenia	AR	*MPL*	1p34	Unknown
Shwachman-Diamond syndrome	AR	*SBDS*	7q11	10%
Dyskeratosis congenita	XL	*DKC1*	Xq28	3-5%
	AD	*TERC*	3q26	
		TERT	5p15	
		TINF2	14q11	
	AR	*NOP10*	15q14	
		NHP2	5q35	
DNA repair deficiency syndromes				
Fanconi anemia	AR XL	*FANC/BRCA* pathway		50%
Bloom syndrome	AR	*BLM*	15q26	25%
Li-Fraumeni	AD	*TP53*	17p13	~7.5%
Signal transduction aberration				
Noonan syndrome	AD	*RAS/MAPK* pathway		unknown
Neurofibromatosis I	AD	*NF1*	17p11	0.2-0.5%
Numerical chromosomal aberration				
Trisomy 21	Sporadic			2.5%
Pure familial MDS				
Familial platelet disorder with propensity to myeloid malignancy	AD	*RUNX1*	21q22	20-60%
Chromosome 21q22 deletions		*RUNX1*	21q22	unknown (~25%)
Telomere deficiency-associated familial MDS (occult dyskeratosis congenita)	AD	*TERC* *TERT*	3q26 5p15	unknown
Familial monosomy 7	AD	unknown	unknown	unknown

MDS: myelodysplastic syndrome; AML: acute myeloid leukemia,; AD: autosomal dominant; AR: autosomal recessive; XL: X-linked.

Table 2. Clinical features of syndromic deletion of chromosome 21q22 including *RUNX1*.

Reference	Sex	Age when thrombocytopenia first detected (platelet count [x10^9/L])	MDS/AML (age at diagnosis)	Growth delay	Mental retardation	Dysmorphisms and other abnormalities	Cytogenetic analysis
Huret[29]	F	Neonatal period (60-124)	Yes (8 years)	Yes	Yes	Hypertelorism, downslanting palpebral fissures, anteverted nares, broad nasal root, cleft palate, axial hypotonia	del(21)(q21.2-q22.3), with partial duplication suggested within 21q22.3
Beri-Dexheimer[30]	F	10 years	No (57)	Yes	Yes	Telecanthus, upslanting palpebral fissures, anteverted nares, ASD, cerebral micropolygyria	del(21)(q22.11q22.12)
Shinawi[31] Patient 1	M	18 months (41-119)	Yes (6 years)	Yes	No	Hypertelorism, anteverted nares, broad nasal root, high-arched palate, TGV, absent left testis, umbilical hernia	del(21)(q22.12)
Shinawi[31] Patient 2	F	19 months (30-90)	No	Yes	Yes	Hypertelorism, epicanthal folds, anteverted nares, smooth philtrum, hypoplastic toenails, dysgenesis of corpus callosum	del(21)(q22.11-q22.12)
Shinawi[31] Patient 3	F	9 months (61-83)	No	Yes	Yes	Hypertelorism, epicanthal folds, flat nasal bridge, small ears, epilepsy	del(21)(q21.3-q22.3)
Fujita[32]	M	NA (185)	No	Yes	Yes	Upslanting palpebral fissures, corneal clouding right eye, prominent nasal root, retrognathia, hypospadias	del(21)(q22.12-q22.2)
van der Crabben[33]	M	5 years (60-80)	Yes (5 years)	No	No	Flattened right helix, broad nasal bridge, prominent philtrum, umbilical hernia	del(21)(q22.11-q22.12)
Katzaki[34] Patient 1	F	Age NR (NR)	No	Yes	Yes	Downslanting palpebral fissures, broad nasal bridge, small low-set ears, dystrophic nails, hypotonia	del(21)(q22.11-q22.12)
Katzaki[34] Patient 2	M	13 months (NR)	No	Yes	Yes	Hypertelorism, downslanting palpebral fissures, anteverted nares, hypoplastic nails, epilepsy, agenesis of corpus callosum	del(21)(q22.11-q22.12)
Katzaki[34] Patient 3	F	Neonatal period (NR)	No	Yes	Yes	Broad nasal bridge, strabismus, thin upper lip, ASD, epilepsy	del(21)(q22.11-q22.13)
Thevenon[35]	M	Neonatal period (5-138)	No	Yes	Yes	Downslanting palpebral fissures, prominent nasal root, low-set ears, ASD, non-obstructive hypertrophic cardiomyopathy, facial diplegia, epilepsy, dysgenesis of corpus callosum	del(21)(q22.11-q22.12)
Byrd[36]	F	Neonatal period (16-100)	No	Yes	Yes	Downslanting palpebral fissures, cleft palate, low-set ears, micrognathia, ASD, movement disorder, hypoplastic corpus callosum	del(21)(q22.11-q22.13)

MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; ASD: atrial septal defect; TGV: transposition of the great vessels, NA: not applicable, NR: not reported.

variable phenotypes of FPD/AML between families. Mutations that cause haploinsufficiency are most frequent,[21] though some mutations are predicted to result in dominant-negative effects.[25,26] Dominant-negative proteins retain their ability to bind DNA or the CBF-beta partner, and thus reduce wild-type RUNX1 activity to below 50% by competing for DNA binding sites or for preferential binding to CBF-beta. Families with dominant-negative mutations are predicted to have a higher incidence of overt MDS/AML than those with mutations that act by haploinsufficiency,[25] suggesting that the dosage of RUNX1 is important in leukemogenesis. However, inherited *RUNX1* mutations by themselves are insufficient to cause overt MDS/AML. This is demonstrated in FPD/AML by the incomplete penetrance for malignancy and a variable latency until development of MDS/AML (up to 75 years), as well as the frequent additional karyotype abnormalities noted at the time of MDS/AML diagnosis. A key second hit seen in affected individuals at the time of MDS/AML diagnosis is that of biallelic *RUNX1* mutations.[18] A decrease in RUNX1 dosage resulting from the shift from heterozygous to homozygous loss of *RUNX1* is thought to be the necessary step for development of overt leukemia.[18] However, some affected individuals have not exhibited second *RUNX1* mutations, suggesting that other secondary events may also be sufficient for leukemogenesis.

The descriptions of recently reported families suggest that FPD/AML may be more heterogeneous than originally recognized. Exemplifying this is the increased risk of T-ALL in these families. The mechanisms underlying the development of T-ALL are unknown but constitute an area of active interest. Somatic *RUNX1* mutations have not been reported at the time of T-ALL diagnosis. In one case, the second hit was attributed to a translocation t(1;7)(p34.1;q22),[19] whereas the second hit is unknown in the other 3 cases. A predisposition to B-lymphoid cell malignancies may also be possible in *FPD/AML*, as *RUNX1* is expressed in adult B cells in addition to myeloid

Table 3. Telomerase disorders in familial MDS.

Pedigree	Affected genotyped individuals	Age at diagnosis (years)	Hematologic abnormality	Other medical history	Telomere studies Mutation	% Wild-type telomerase activity
1	Father	65	Anemia and thrombocytopenia	Died of myocardial infarction (70 years)	heterozygous TERC c.212C>G mutation	1
	Proband	45	MDS (RAEB-1)	-		
	Son	NR	Severe aplastic anemia	-		
2	Father	62	MDS (RCMD and ring sideroblasts)	Died of gastric cancer (65 years)	heterozygous TERC c.309G>T mutation	4
	Paternal uncle	~40	AML	-		
	Paternal uncle	NA	NR	Diagnosed with gastric cancer (63 years)		
	Proband	40	MDS (RCMD)	-		
	Paternal cousin	NA	NR	Died of pulmonary fibrosis/lung cancer (~40 years)		
3	Paternal grand-mother	NA	NR	Asymptomatic (82 years)	heterozygous TERT c.1892G>A mutation	~0
	Father	NR	MDS	Died (cause and age NR)		
	Proband	32	Aplastic anemia	Died of fibrosing alveolitis (age NR)		
4	Mother	NA	NR	Asymptomatic	heterozygous TERT c.2354C>T mutation	11
	Proband	30	Hypoplastic MDS → AML	Died of relapsed AML post-sibling HSCT		
	Sister	NR	Aplastic anemia	-		
	Sister	NA	NR	Asymptomatic		
	Sister	NA	NR	Asymptomatic		

TERC: telomerase RNA component; MDS: myelodysplastic syndrome; RAEB: refractory anemia with excess blasts; NR: not reported; RCMD: refractory cytopenia with multilineage dysplasia; AML: acute myeloid leukemia; NA: not applicable; TERT: telomerase reverse transcriptase; HSCT: hematopoietic stem cell transplantation.

and T cells.[27] An individual from one pedigree was noted to develop diffuse large B-cell lymphoma (C. Owen, unpublished data, 2011) but additional confirmed B-cell lymphoma cases have not been reported.

Syndromic cases of loss of chromosome 21q22

In addition to FPD/AML, other cases of germline *RUNX1* deletion have been reported in individuals with constitutional deletions of chromosome 21q22, with several cases showing congenital thrombocytopenia and subsequent development of MDS/AML. These cases typically lack a family history and are assumed to result from a sporadic germline mutational event. These deletions result in a complex phenotype, including dysmorphic features, organ malformations, growth delay, and mental retardation. The clinical features of reported cases where descriptions of hematologic findings were available are summarized in Table 2.[28-36] All but one case[32] reported thrombocytopenia, with qualitative platelet defects described in 2 cases.[30,36] MDS/AML developed in 3 cases, with a median age of onset of six years (range 5-8 years). This median age is much lower than that of traditional FPD/AML and suggests that other genes within the 21q22 locus may also be important in leukemogenesis.

A review of published cases of 21q deletions revealed that deletions involving the region spanning 21q22.1 – q22.2 present with a more severe phenotype than deletions in more proximal or distal regions.[37] MicroRNAs (miRNAs) have recently been proposed to have a role in determining disease phenotype. MiRNAs act post-transcriptionally within cells to regulate gene expression by binding to target messenger RNAs (mRNAs), causing either translation repression or cleavage of target transcripts.[38] Using bioinformatic analysis, Katzaki *et al.* found that 4 out of 9 patients with overlapping deletions of 21q22 had a deletion of the miRNA miR-802.[34] However, 2 of the patients who developed MDS/AML were included in the analysis and both retained expression of miR-802. Therefore, the role of miRNAs in FPD/AML leukemogenesis is still not clear and further studies are required to clarify whether miR-802 influences the hematologic phenotype.

Telomere disorders

Telomeres are repetitive non-coding DNA sequences found at the ends of chromosomes and maintain chromosomal stability. Telomeres shorten after each cell division, and signal cell senescence and apoptosis when they reach a critically short length. In order to counteract telomere shortening, highly proliferative cells such as hematopoietic stem cells express telomerase, a ribonucleoprotein complex consisting of a reverse transcriptase (TERT), a telomerase RNA component (TERC), and several ancillary proteins. The telomerase complex has been reported to be active and important in many cancers, both solid tumors and hematologic malignancies.[39]

Excessively short telomeres are reported in dyskeratosis congenita (DC), an inherited disorder of mutations affecting the telomerase complex. The classical clinical presentation of DC includes a mucocutaneous "diagnostic triad" (dystrophic nails, oral leukoplakia, abnormal skin pigmentation) in addition to bone marrow failure, pulmonary and

liver fibrosis, features of premature aging, and a predisposition to malignancy, including MDS/AML.[40,41] The inheritance patterns of DC include X-linked recessive, autosomal recessive, and autosomal dominant; the latter is caused by heterozygous mutations in *TERC*[42] or *TERT*.[43] Patients with autosomal dominant DC often do not exhibit any of the physical findings traditionally associated with the syndrome, and some have initially presented with MDS/AML, effectively appearing as pure familial MDS.[44-46] Kirwan *et al.* recently described 4 pedigrees with familial MDS/AML who harbored mutations in *TERC* or *TERT* and were entirely lacking the mucocutaneous features of DC.[47] Table 3 summarizes the clinical history of these kindreds. The telomerase activity in these affected families ranged from 0-11% of wild-type levels, with no clear difference between *TERC* or *TERT* mutations. The mutations demonstrated variable penetrance, and neither telomerase activity level nor mutation location could predict the clinical phenotype. Several asymptomatic carriers of *TERT* and *TERC* mutations are reported, and continued surveillance for the development of MDS/AML is important in these individuals. Similar to inherited *RUNX1* mutations, telomerase complex mutations alone are thus insufficient to cause MDS/AML and instead act as initiating mutations. Additional genetic lesions, necessary for overt malignancy, then result from the chromosomal instability caused by critically short telomeres. Acquired genetic lesions may also modify disease severity, explaining the variability within affected individuals in these reported telomere-deficiency families.

A particularly notable clinical feature of familial telomere deficiency-associated MDS is anticipation, the process where successive generations present with increasingly severe phenotypes at an earlier age.[43,48] This process likely results as each successive generation inherits progressively shorter telomeres that increasingly promote genomic instability and lead to earlier development of marrow failure, MDS or AML. This is of clinical importance in that an affected individual may present before a parent who carries the same mutation. Therefore, an inherited lesion should always be considered in a young patient presenting with MDS, even in the absence of pre-existing morphological or hematologic abnormalities.

Familial monosomy 7

Familial cases of MDS/AML associated with complete or partial loss of chromosome 7 have been reported in 14 pedigrees,[49] with significant variability in clinical presentations. Affected family members often present before the age of 18 years, and cytopenias in non-MDS/AML-affected family members are also reported. Monosomy 7 is a frequent acquired aberration in sporadic MDS and AML and confers an adverse prognosis. It is commonly associated with secondary MDS/AML following mutagenic exposures, such as chemotherapy with alkylating agents or occupational exposure to chemical toxins. Monosomy 7 is also the most frequently acquired abnormality in MDS/AML associated with inherited bone marrow failure syndromes.[50,51]

Initially, it was thought that familial monosomy 7 resulted from a germline mutation of a tumor-suppressor gene located on the retained chromosome 7, with loss of the wild-type chromosome 7 providing the second hit necessary for cancer development. This was disproved when studies showed different parental origin of the retained chromosome in several sibling pairs with familial monosomy 7.[52-54] Although the causative gene has not yet been identified, the pattern of inheritance appears to be autosomal dominant with variable penetrance. Monosomy 7 is not present in the germline in these individuals but instead presents as an acquired abnormality recurring within the family, with the lesion developing at any time in the course of the individual's hematologic disease. While the culprit gene is not on chromosome 7, it is interesting to note that *EZH2*, a commonly mutated gene in sporadic MDS, is located on 7q.[3] Since leukemogenesis is thought to result from the accumulation of multiple genetic insults, the loss of chromosome 7 may simply be a recurrent secondary event in the multi-hit model of AML.

Implications for hematopoietic stem cell transplantation

Currently, the only curative treatment for MDS, both sporadic and familial, is allogeneic hematopoietic stem cell transplantation (HSCT). In familial cases of MDS, the use of a related donor is problematic, due to the risk of using stem cells affected by the same inherited mutation. Given the increased recognition of familial MDS, many modern cases of FPD/AML are discovered while siblings are investigated as potential HSCT donors in an affected family. A comprehensive workup often only occurs if the potential donor is discovered to have hematologic abnormalities. This screening may not be sufficient given our current awareness that some patients with inherited *RUNX1* mutations have normal platelet counts, as may patients with inherited telomerase deficiency.

The outcomes of HSCT using affected siblings donors are clearly suboptimal. In FPD/AML, these include slow and incomplete engraftment (one case),[55] failed engraftment (one case),[17] early relapse (one case),[17] and EBV-associated lymphoproliferative disorders (2 cases).[17,55] Similarly, sibling-donor HSCT in families with telomerase mutations yields unfavorable results with poor stem cell mobilization in donors and one case of delayed engraftment resulting in death from neutropenic sepsis.[56] These cases underscore the importance of screening for inherited MDS in relatives of young patients with MDS. Because *RUNX1* mutations are known to predispose to myeloid malignancy, determination of *RUNX1* mutational status should be incorporated into the related donor screening workup prior to transplant of young patients with MDS/AML, especially in families with any history of bleeding or platelet abnormalities, however minor. While inherited *TERC* and *TERT* mutations are less frequently observed, screening for these abnormalities should also be considered, especially in the light of potential anticipation, such that a familial inheritance may not be evident when the index case presents.

Conclusions

Considerable advances have been made in understanding familial MDS. Heightened awareness of clinicians, as evidenced by the recent increase in reported cases, will continue to help identify familial cases of MDS. Investigation of families with both established and newer molecular genetic techniques may also identify novel causative mechanisms. This was demonstrated by Scott *et al.* who recently described 4 pedigrees with inherited MDS caused by heterozygous mutations in *GATA2*.[57] Despite the progress made so far, many cases of

familial MDS remain unexplained and additional genetic lesions must exist. Identifying familial MDS has significant implications for clinical practice, particularly in donor selection for allogeneic HSCT. Greater understanding of the molecular mechanisms leading to disease in families may also help in identifying potential novel targeted therapies, with the goal of improving outcomes for all patients with MDS.

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