REVIEW SERIES

Germline and somatic genetic landscape of pediatric myelodysplastic syndromes

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Abstract

Pediatric myelodysplastic syndromes (MDS) represent a rare group of clonal hematopoietic stem cell disorders accounting for approximately 5% of pediatric hematologic malignancies. They are characterized by ineffective hematopoiesis, cytopenia, and dysplastic changes in the bone marrow with variable risk of progression to acute myeloid leukemia. Unlike adult MDS, pediatric cases predominantly present with hypocellular bone marrow, with monosomy 7 and trisomy 8 as the most common cytogenetic aberrations. Pediatric MDS can manifest as primary disease or arise secondary to classical inherited bone marrow failure syndromes, prior cytotoxic therapy, or acquired aplastic anemia. In recent years, new germline syndromes have been identified in a substantial proportion of patients with "primary" MDS. The most common are GATA2 deficiency and SAMD9/SAMD9L syndromes, accounting for at least 7% and 8% of cases, respectively. The somatic mutational landscape is different from adult MDS, with recurrent mutations affecting *SETBP1*, *ASXL1*, *RUNX1*, and RAS pathway genes (*PTPN11*, *NRAS*, *KRAS*, *CBL*), while mutations in spliceosome components and epigenetic regulators, which are common in adults, are virtually absent in children. Monosomy 7 serves as a "central hub" in disease evolution, associating with somatic leukemia driver mutations. On the other hand, somatic *UBTF-TD* and *NPM1* mutations define a subtype of MDS with excess blasts with predominantly normal karyotype without known germline predisposition. Hematopoietic stem cell transplantation is the only curative option for pediatric MDS. Understanding the unique genetic profile of pediatric MDS has implications for diagnosis, therapy, donor selection and long-term surveillance, particularly for patients with germline predisposition syndromes. This review discusses current classification systems (WHO and ICC), provides a detailed overview of the germline and somatic genetic landscape of pediatric MDS, and highlights clinical implications of these genetic alterations.

Introduction

Myelodysplastic syndromes (MDS) in the pediatric population represent a rare and heterogenous group of clonal hematopoietic stem cell disorders, accounting for approximately 5% of hematologic malignancies in children and adolescents (Figure 1).[1-5] The hallmark of these disorders includes ineffective hematopoiesis leading to cytopenia and dysplastic changes in the bone marrow (BM) with varying propensity for transformation to acute myeloid leukemia (AML). The majority of pediatric MDS cases arise as primary (*de novo*) disease but some patients develop MDS secondary to pre-existing conditions, including inherited bone marrow failure syndromes (IBMFS), prior exposure to chemotherapy or radiation, or acquired severe aplastic anemia. Over the past two decades, germline predisposing variants in more than 100 genes have been identified as contributors to the pathogenesis of MDS.[6,7]

Distinct features including morphology, clinical presentation and etiological factors separate pediatric MDS from its adult-onset counterpart.[8] Unlike in adults, most children with MDS present with hypocellular bone marrow; monosomy 7 and trisomy 8 represent the most frequent karyotype abnormalities. The rarity of pediatric MDS has historically posed challenges for systematic investigation, but recent molecular studies have advanced our understanding of its unique genetic profile, further supporting the distinction from adult MDS (Table 1).[6,9-11] While adult MDS is predominantly driven by somatic mutations in spliceosome components, epigenetic regulators (i.e., *DNMT3A*

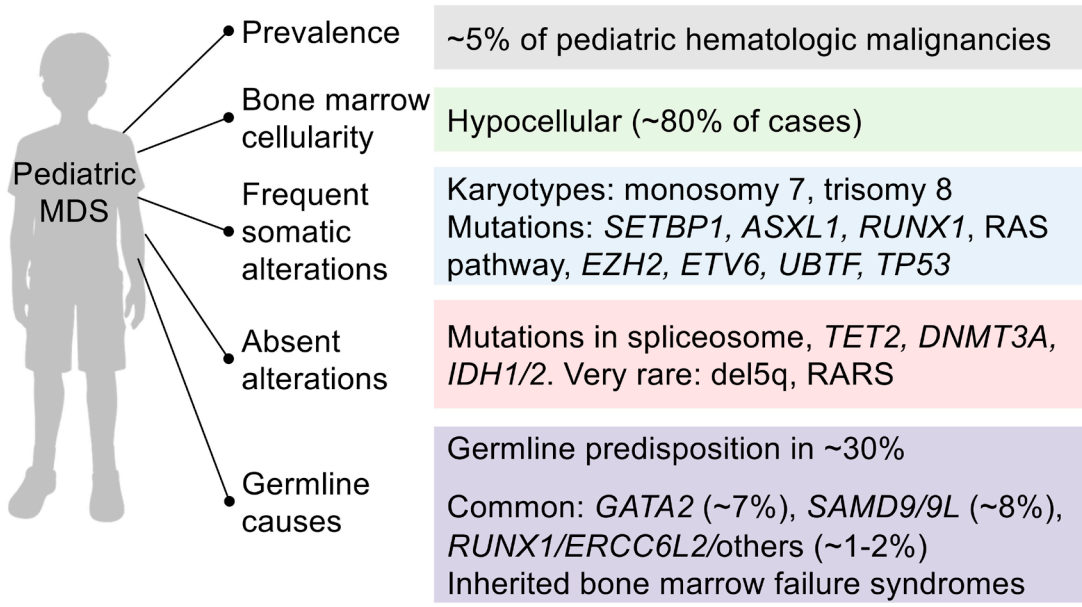

Figure 1. Clinical and genetic characteristics of pediatric primary myelodysplastic syndromes.

and *TET2*) or deletions of chromosome 5q, these alterations are virtually absent in pediatric cases (Figure 1). Instead, a majority of pediatric MDS has specific somatic alterations affecting the RAS pathway and other proto-oncogenes.[9,10] The only curative option in pediatric MDS is hematopoietic stem cell transplantation (HSCT) as chemotherapy alone is ineffective for disease remission. In this review, we provide an overview of the current understanding of the germline and somatic genetic landscape of pediatric MDS and highlight key clinical implications associated with these genetic changes.

Diagnostic definitions

Current hematopathology classification systems have adopted distinct terminology for pediatric MDS, reflecting key morphological and molecular features (Figure 2). The 5th edition of the World Health Organization (WHO) classification[12] stratifies cases into 'childhood MDS with low blasts' (cMDS-LB, <5% blasts in BM and <2% in peripheral blood [PB]) and 'childhood MDS with increased blasts' (cMDS-IB, 5-19% blasts in BM and/or 2-19% in PB). The 2022 International Consensus Classification (ICC)[13,14] maintains some traditional terminology while incorporating recent biological insights. For most patients with persistent cytopenia and BM dysplasia without blast expansion, ICC retains the category 'refractory cytopenia of childhood' (RCC), initially coined as provisional entity over two decades ago.[15] Cases that do not meet the criteria for classic RCC morphology (no dysplasia) but carry MDS-defining monosomy 7 alteration are classified as 'MDS, not otherwise specified' (MDS-NOS). Patients with BM blasts between 5-19% and/or PB blasts between 2-19% receive the diagnosis 'MDS with excess blasts' (MDS-EB). The predominant presentation in about one-third of cases is RCC/cMDS-LB, with approximately 80% of these patients presenting with hypocellular BM.[16-18] RCC is characterized by specific dysplastic features defined as either dysplasia in ≥1 cell lineage, or dysplasia in ≥10% of cells in one lineage. This criterion is an important factor to differentiate RCC from acquired aplastic anemia which presents with hypocellular BM but lacks dysplastic changes and is driven by immune dysregulation. Beyond morphology-based assessment, both WHO and ICC include distinct terminology for MDS associated with germline predisposition (WHO: myeloid neoplasms with germline predisposition; ICC: hematologic neoplasms with germline predisposition). Of note, both classification systems have also established important diagnostic thresholds for AML (Figure 2): WHO permits AML diagnosis with <20% blasts in the presence of specific molecular alterations (*NPM1* mutations, *KMT2A*/*MECOM*/*NUP98* rearrangements); ICC maintains the blast percentage as a criterion but lowers the threshold to 10% for cases with AML-defining genetic changes. This nuanced approach recognizes that genetic alterations may precede obvious morphologic changes in disease evolution.

Germline genetic factors predisposing to pediatric MDS

Historically, MDS arising after IBMFS has been called "secondary" MDS because it typically manifests after years to decades of pre-existing cytopenia and progressive marrow failure. While MDS risk in Fanconi anemia (FA),[19] Shwachman-Diamond syndrome,[20,21] and severe congenital neutropenia (SCN)[22] often manifests during childhood or adolescence, it continues to increase with age and may present in adulthood. In contrast, Diamond-Blackfan anemia,[23] and telomere biology disorders[24] typically demonstrate adult-onset MDS development. Other etiologies of secondary MDS include prior radiation or chemotherapy and aplastic anemia (Figure 3). In IBMFS-associated MDS, somatic mutations may precede MDS diagnosis and many IBMFS demonstrate unique somatic mutation profiles associated with the spe-

Table 1. Summary of studies investigating somatic mutations in primary pediatric myelodysplastic syndromes.

First author	Year	Cohort description	N of cases	Median age at dx in years	MDS with excess blasts	Interrogated genes/regions	Prevalence of somatic mutations	Recurrently mutated genes	PMID/DOI number
Hirabayashi	2012	Primary and secondary MDS	179 primary; 68 secondary	10.5	34.2% (56/179 among primary MDS)	Only *SF3B1*, *U2AF35*, *SRSF2*	0% (0/249) among primary MDS	-	22238327
Shiba	2012	Primary MDS	24	NA	NA	Only *DNMT3A*	0% (0/24)	-	21981547
Velloso	2013	MDS	84	NA	57.1% (48/84)	Only chromosomal changes	RCC: 27.2% (2/11); RAEBt: 37.5% (18/48)	-	23314345
Kozyra	2015	Primary and secondary MDS	467 primary; 117 secondary	NA	NA	28-gene panel	22% (103/467) among primary MDS	RAS pathway, *SETBP1*, *ASXL1*, *RUNX1*, *BCOR/BCORL*, *TP53*	10.1182/blood.V126.23.1662.1662
Pastor	2017	Primary MDS (enriched for high risk)	50	9	38% (19/50)	105-gene panel	RCC: 13% (4/31); MDS-EB: 68% (13/19)	RAS pathway, *SETBP1*, *ASXL1*, *RUNX1*	27876779
Schwartz	2017	Primary MDS and MPN	46 primary MDS	RCC: 8.4; RAEB: 11.7	50% (23/46)	Whole exome, gene panel	RCC: 17.4% (4/23); RAEB: 65.2% (15/23)	RAS pathway, *SETBP1*, *RUNX1*, *ETV6*	29146900
Sahoo	2021	SAMD9/9L-MDS (and primary MDS)	SAMD9/9L: 67; all MDS: 570	9.9	14.8% (81/548)	Whole exome, gene panel	*SAMD9/9L*: 30% (19/64); all MDS: 13.5% (77/570)	RAS pathway, *SETBP1*, *ASXL1*, *RUNX1*, *EZH2*, *ETV6*	34621053
Coutinho	2021	RCC	20	5	0% (0/20)	37-gene panel	15% (3/20)	Only singleton mutations in *CBLB*, *TP53*, *DNMT3A*, *ASXL1*	10.1016/j.phoj.2021.04.180
Erlacher	2022	Primary MDS-EB	104	9.8	100% (104/104)	*UBTF*-TD, 75-gene panel	24% (25/104) for *UBTF*-TD; 88% (22/25) for other mutations in the *UBTF*-TD cohort	*WT1*, *MYC*, *FLT3*, RAS pathway, *SMC1A*, *TET2*, *MPL*	10.1182/blood-2022-159002
Yoshimi	2023	Primary MDS-EB	235	12.7	100% (235/235)	Gene panel	6% (14/235) for *NPM1*	*NPM1*, *RAS* pathway, *WT1*	10.1016/j.ejcped.2023.100071
Li	2024	Primary MDS	26	5.87	38.5% (10/26)	Whole exome, 67-gene panel	RCC: 50% (8/16); advanced MDS: 40% (4/10)	*BCOR*, *SETBP1*, *ASXL1*	38191334

Dx: diagnosis; MDS-EB: myelodysplastic syndromes with excess blasts; MPN: myeloproliferative neoplasm; N: number; NA: not available; RAEBt: refractory anemia with excess blasts in transformation; RAS: *KRAS*, *NRAS*, *PTPN11*, *CBL*; RCC: refractory cytopenia of childhood; tMDS/tAML: therapy-related MDS/AML; *UBTF*-TD: *UBTF* tandem duplication.

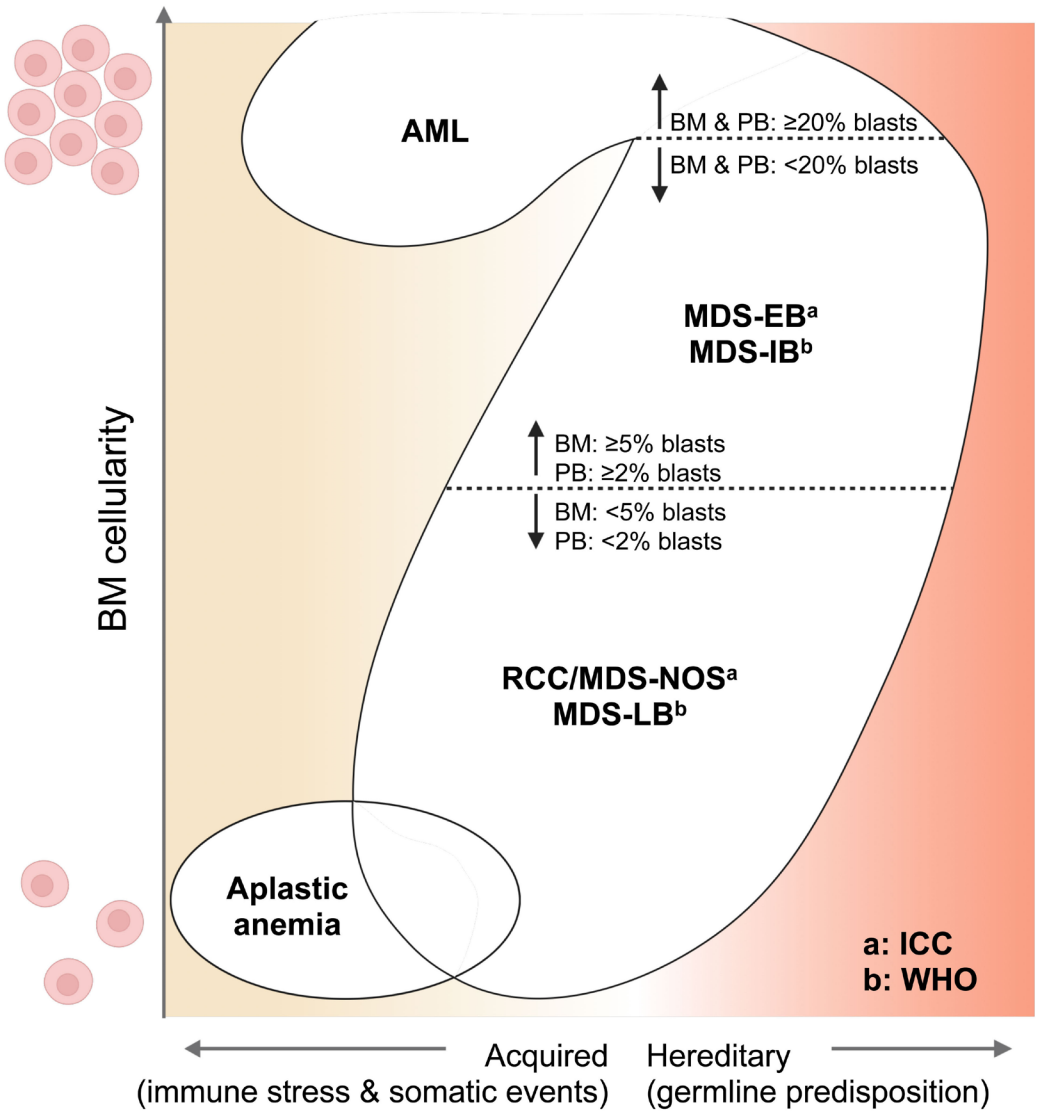

Figure 2. Classification of pediatric primary myelodysplastic syndromes. The relationship between pediatric myelodysplastic syndromes (MDS), aplastic anemia, and acute myeloid leukemia (AML). Dashed lines represent blast thresholds in bone marrow (BM) and peripheral blood (PB) defined by current classification systems: the 2022 International Consensus Classification (ICC) and the World Health Organization (WHO). WHO criteria permit AML diagnosis with <20% blasts when specific genetic alterations are detected (*NPM1* mutations, *KMT2A/MECOM/NUP98* rearrangements), while the ICC retains blast excess as a criterion for AML diagnosis but lowers the threshold to 10% in cases with AML-defining genetic abnormalities. Monosomy 7/del(7q) is MDS-defining even without dysplasia/blast increase (classified as MDS, not otherwise specified [MDS-NOS]). Immune dysregulation is a major driver in aplastic anemia and some cases of pediatric MDS, while germline predisposition is exclusive to pediatric MDS. BM: bone marrow; MDS-EB/IB: MDS with excess blasts/increased blasts; MDS-LB: MDS with low blasts; PB: peripheral blood; RCC: refractory cytopenia of childhood.

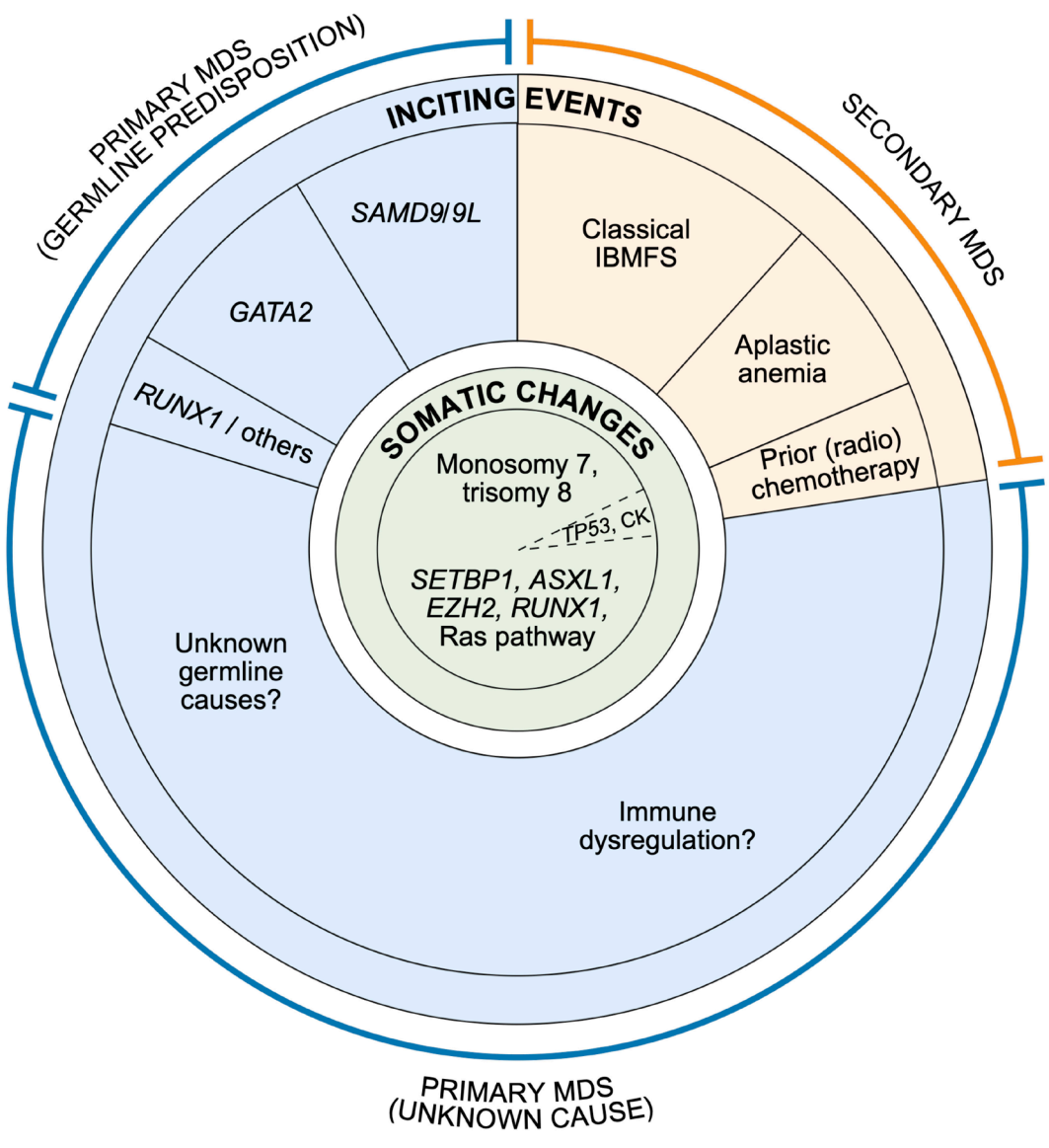

Figure 3. Inciting drivers and acquired somatic events across pediatric myelodysplastic syndrome spectrum. The chart illustrates the inciting events of pediatric myelodysplastic syndromes (MDS) (outside circle) along with associated somatic changes (inside circle). Blue wedges represent MDS caused by germline predisposition or by yet unknown causes (collectively termed "primary MDS"). Pink wedges correspond to MDS arising from pre-existing conditions (classically referred to as "secondary MDS"). CK: complex karyotype; IBMFS: inherited bone marrow failure syndromes.

cific underlying disorder as well as cytogenetic changes that may or may not be disease-specific. For example, 1q/3q gain is associated with FA,[19] biallelic *TP53* mutations are mostly associated with Shwachman-Diamond syndrome,[21,25] while *CSF3R* and *RUNX1* mutations are associated with SCN.[26] Cytogenic abnormalities commonly include monosomy 7, trisomy 8 but these are not syndrome-specific[27] (Table 2). In recent years, genomic sequencing of primary MDS cohorts (with previously unknown etiology) has revealed the presence of new monogenic disorders collectively referred to as 'MDS predisposition syndromes'.[28,29] These often present without clinically apparent cytopenia prior to MDS development and thus many experts maintain the terminology primary MDS despite the hereditary cause. Cohort studies have shown that 7-31% of pediatric MDS patients harbor germline variants in MDS predisposing genes.[9,11,30-32] The most common hereditary drivers of MDS are GATA2 deficiency and SAMD9/9L syndromes, which together account for approximately 15% of primary pediatric MDS.[11,31] Less frequent germline predispositions associated with primary MDS include hereditary platelet disorders with underlying germline variants in *RUNX1* and *ETV6* genes, and ERCC6L2 syndrome.[33,34] However, as of 2025, the majority of primary MDS cases still have unknown etiology (Figure 3). It is expected that more hereditary syndromes might be identified within this subgroup; additionally, it is possible that reduced immunosurveillance or immune dysregulation might be etiologic drivers.[35,36]

While this manuscript uses the classical terminology 'primary' and 'secondary' MDS for simplicity, the nomenclature is evolving. Future classifications may adopt more precise categories based on etiology rather than historical context. For example, it makes sense to group all MDS following germline predisposition (including IBMFS and MDS predisposition syndromes) under one unified category.

This manuscript focuses on primary pediatric MDS with emphasis on recently discovered MDS predisposition syndromes; comprehensive reviews of classical IBMFS are available elsewhere.

Table 2. Association of pediatric myelodysplastic syndromes with monosomy 7.

Condition	Occurrence of monosomy 7
Primary MDS	~20% of cases
Specific MDS predisposition syndromes:	
GATA2	+++[a]
SAMD9 and SAMD9L	+++[b]
RUNX1, ERCC6L2 and others	+
Secondary MDS after inherited bone marrow failure	
Fanconi anemia	+++[c]
Severe congenital neutropenia	++[d]
Shwachman-Diamond syndrome	+++[e]
Dyskeratosis congenita and Diamond Blackfan anemia	(+)[f]
Secondary MDS	~33% of cases
Therapy-related (after radio-/chemotherapy)	+++[c]
After severe aplastic anemia	(+)[g]

[a]Several cases reported with unbalanced translocation der(1;7)(q10;p10). [b]Transient monosomy 7 reported in young children (monosomy 7 can completely disappear). [c]Often in association with gains of 3q and 1q and complex karyotype. [d]Frequently co-occurring mutations in *CSF3R* and *RUNX1*. [e]Often in association with somatic *TP53* loss (bi-allelic *TP53* mutations, LOH 17p). [f]Exceedingly rare in children (no pediatric cases). [g]Myelodysplastic syndrome (MDS) evolution is rare in children with severe aplastic anemia (~2-3%).

GATA2 deficiency

GATA2 deficiency is a highly penetrant, autosomal dominant disorder with high propensity for childhood-onset MDS and progressive immunodeficiency. The *GATA2* gene encodes a transcription factor that is essential for hematopoiesis and immune function.[37] Median age at MDS diagnosis is estimated at 16-19.7 years.[38-40] *GATA2* variant carriers have increasing risk of MDS with age (Figure 4), and high life-time penetrance, with approximately 75% of variant carriers developing MDS in their lifetime.[39-42] While many pediatric patients present with acute-onset MDS without pre-existing cytopenia, others can initially present with single- or multi-lineage cytopenia (often neutropenia and monocytopenia), immunodeficiency (with loss of B/NK cells and asymptomatic to life-threatening infections) and constitutional features, including lymphedema, hydrocele and sensorineural deafness.[40,41,43-46] Germline *GATA2* variants account for approximately 7% of all pediatric MDS and approximately 15% of advanced MDS (MDS-EB/cMDS-IB)

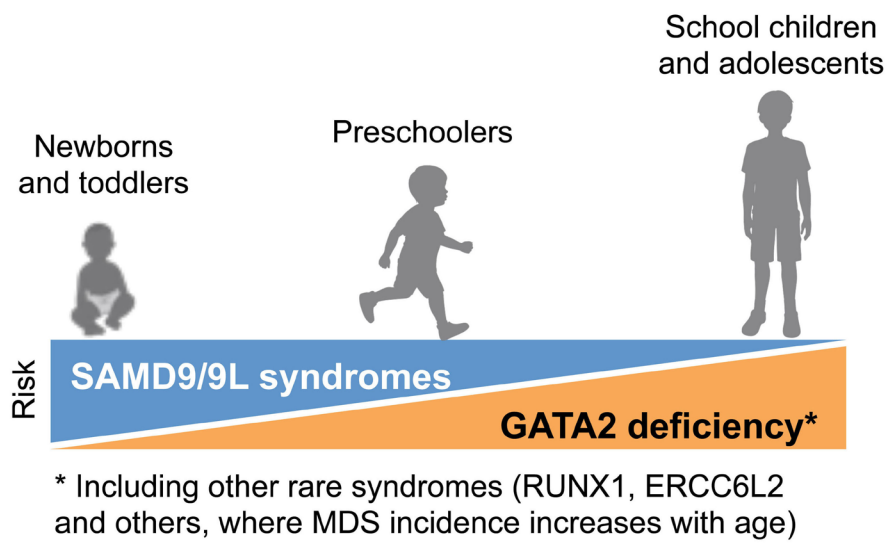

Figure 4. Risk for myelodysplastic syndrome development in common pediatric predisposition syndromes. Decreasing risk of myelodysplastic syndromes (MDS) over time in children with SAMD9/9L syndromes (blue) is depicted against the increasing risk seen in GATA2 deficiency (orange).

cases.[11] Based on the combined analysis of 480 published cases, mutations in the GATA2 transcription factor are associated with distinct phenotypic profiles depending on their effect on protein function or expression.[39] The majority of *GATA2* variants classify into 3 main categories: i) 'null' variants affecting the protein structure (frameshift truncating, nonsense, silent [synonymous RNA deleterious variants], splice region variants, whole exon/gene deletions); ii) missense variants within the zinc finger 2 domain disrupting DNA binding and transactivation capacity; and iii) regulatory variants in the +9.5kb intron 4[47,48] and the -110kb upstream[49,50] autoregulatory regions reducing allelic expression.[42,51] There is some genotype-phenotype correlation in this disorder with null variants linked to earlier disease onset.[52,53] Based on our unpublished observations in pediatric MDS, null variants are associated with higher risk of MDS, while regulatory variants may exert hypomorphic effect with reduced penetrance for MDS. Recently, we compiled curated data on 900 cases with GATA2 deficiency aiming to improve variant interpretation and phenotype assessment (*L. Kotmayer, unpublished data, 2025*; www.stjude.org/gata2).

The most common somatic alterations in GATA2-related MDS are chromosome 7 loss events (monosomy 7, der(1;7) and del7q) present in up to 75% of cases.[54,55] Other recurrent changes include trisomy 8 and somatic mutations of *SETBP1*, *ASXL1*, *STAG2*, *RUNX1*, *RAS* pathway genes, *EZH2* and *ETV6*.[52,56-67] It is important to note that these somatic alterations are not specific to GATA2 deficiency but rather represent the common clonal evolution pattern observed in pediatric MDS which is independent of underlying germline predisposition (as discussed below).

SAMD9/9L syndromes

Germline variants in *SAMD9* and its paralogue *SAMD9L* had initially been identified in patients diagnosed with MIRAGE (Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital phenotypes, Enteropathy) and ataxia-pancytopenia syndromes, respectively.[68,69] Over the years, *SAMD9/9L* variants have also been recognized as a common predisposition to pediatric MDS with monosomy 7 and are mutually exclusive with GATA2 deficiency.[31,70,71] SAMD9/9L syndromes account for 8-18.6% of pediatric MDS, which typically presents in preschool-aged children after infectious illness.[9,31,64,72] A unique feature of this syndrome is the high rate of somatic genetic rescue which leads to compensation in the hematopoietic system over time.[72] Due to these common rescue event restoring hematopoiesis, the risk for MDS development actually decreases as SAMD9/9L patients grow older (Figure 4). This pattern differs from other MDS predisposition syndromes where the risk always increases over time.

In contrast to *GATA2*, *SAMD9/9L* variants are more common in patients with RCC/cMDS-LB (90%), suggesting a bone marrow failure (BMF)-like phenotype rather than high-risk MDS.[31] SAMD9/9L patients frequently present with cytopenia (thrombocytopenia, pancytopenia with hypocellular BM), immunodeficiency (lymphopenia, severe infections) and systemic symptoms, such as failure to thrive, short stature and developmental delay.[72] Additional syndromic features are found in half of the patients with *SAMD9/9L*-related MDS, frequently involving the nervous system, urogenital and gastrointestinal tract, head and neck, and cardio-pulmonary system.[31]

Over 90% of germline *SAMD9/9L* variants are missense, with a handful of protein truncating variants observed in *SAMD9L* so far that are associated with early-onset systemic inflammatory disease.[72,73] Intriguingly, all functionally evaluated pathogenic variants have been shown to exhibit gain-of-function phenotypes by amplifying the growth-suppressive properties of SAMD9/9L.[9,31,71,72,74-77] Mechanistically, these variants were proposed to repress translation and induce cell death.[31,73,77] Similar to the GATA2 registry, we compiled clinical, genetic and functional data from approximately 300 individuals with germline *SAMD9/9L* mutation assessment (*S. Sahoo, unpublished data, 2025*; www.stjude.org/samd9).[72]

The somatic landscape of *SAMD9/9L*-related pediatric MDS is predominantly defined by the loss of the chromosome 7. This genetic selection is non-random in that the allele harboring the germline *SAMD9/9L* mutation is selectively lost while the resulting monosomy 7 retains the wild-type *SAMD9/9L* allele. In preschool-age children, we often observe spontaneous disappearance of monosomy 7, transient monosomy 7,[75] associated with hematologic remission. Moreover, longitudinal observation of SAMD9/9L with monosomy 7 shows relatively low rates of malignant MDS progression.[78] This suggests that the initial monosomy 7 clone which emerges as escape mechanism from the severe growth suppressive effect of *SAMD9/9L* variants, represents a non-malignant clone that can later disappear and be outcompeted by alternative reversion events. For this reason, SAMD9/9L disorders represent the only MDS predisposition where close surveillance is reasonable for stable patients with acquired monosomy 7.[72] Other somatic rescue events which are truly benign and capable of restoring multilineage hematopoiesis include copy-neutral uniparental isodisomy of 7q (UPD7q) resulting in elimination of *SAMD9/9L* mutant and compensatory somatic *SAMD9/9L* mutations. However, leukemia-driving somatic mutations have been observed in a subset of SAMD9/9L syndrome patients with progressed MDS/monosomy 7: *SETBP1*, *ASXL1*, *STAG2*, *RUNX1*, RAS pathway members, *EZH2* and *ETV6*.[9,31,64,70,74,79] Unlike monosomy 7, which is found across all MDS predisposition syndromes (Table 2), somatic *SAMD9/9L* mutations and UPD7q and are highly specific and 'diagnostic' for *SAMD9/9L* syndromes (with rare exceptions of UPD7q in Shwachman-Diamond syndrome).

Other germline syndromes associated with primary pediatric myelodysplastic syndromes

Germline variants in *RUNX1* and *ERCC6L2* continue to be found in young individuals with MDS, although the likelihood

of MDS development is highest in the adult population. For further information on other more rare conditions associated with MDS, we direct readers to recent reviews on the topic of germline predisposition, including DNA repair disorders and immunodeficiencies.[80-82]

RUNX1 syndrome

Germline variants of *RUNX1*, *ETV6* and *ANKRD26* cause hereditary disorders characterized by thrombocytopenia, functional platelet defects, and increased risk of hematologic malignancy.[6,83] Among them, germline *RUNX1* variants have been repeatedly reported in pediatric MDS.[84] Loss-of-function or dominant negative variants in *RUNX1* lead to familial platelet disorder with associated myeloid malignancy (FPD-MM). FPD-MM typically presents as thrombocytopenia with increased bleeding tendency that progresses to MDS/AML in approximately 40% of patients.[85,86] Notably, patients develop hematologic malignancy at an estimated median age of 29 (range: 2-72) years,[87,88] establishing RUNX1 syndrome as a less frequent underlying cause of pediatric MDS. Combined analysis of 259 families identified 2 carrier children who developed MDS,[89,90] and cohort studies found germline *RUNX1* variants in approximately 1-2% of pediatric MDS.[9,10]

Notably, somatic mutations in CHIP genes are detected in 49% of FPDMM patients without hematologic malignancy, with BCOR being the most frequently mutated.[91] Other recurrent somatic changes are trisomy or uniparental disomy of chromosome 21 involving the *RUNX1*-mutant allele, and somatic mutations in *PHF6*, *WT1*, *TET2*, *DNMT3A*, *ASXL1*, *KRAS*, *SRSF2*, *RUNX1*, *LRP1B*, *IDH1*, and *KMT2C*.[83,91-93]

ERCC6L2 syndrome

ERCC6L2 syndrome is a recently described BMF disorder with high MDS/AML risk, caused by biallelic germline variants in the non-homologous end-joining factor ERCC6L2. Among the around 75 cases reported to date, most patients were diagnosed with hypocellular BMF as children or young adults. Approximately half of them presented with additional constitutional features, including microcephaly and developmental delay.[33,34,94,95] In the largest reported cohort, most common initial presentation was hypocellular BMF with cytopenia (approx. two-thirds of the cases), followed by progression to MDS/AML in 29%, and asymptomatic carrier status in 10% of the cases.[33] The majority of affected individuals harbor biallelic loss-of-function *ERCC6L2* variants. Similarly to Shwachman-Diamond syndrome[21] and xeroderma pigmentosum,[96] ERCC6L2-related MDS/AML is characterized by recurrent somatic *TP53* mutations, often with high allelic mutation burden, consistent with bi-allelic *TP53* inactivation.[33,34]

Somatic (acquired) genetic alterations

Cytogenetics

Depending on morphological subtype at diagnosis, 20-60% of primary pediatric MDS patients have abnormal cytogenetics at diagnosis: approximately 20-30% of cases with RCC/cMDS-LB and approximately 55-60% of cases with MDS-EB/cMDS-IB.[18,97,98] The most common cytogenetic abnormalities are complete (monosomy 7) or partial [del(7q)] loss of chromosome 7, observed in 6-12% of RCC/cMDS-LB[17,18,99,100] and 27-32% of MDS-EB/cMDS-IB.[100-102] Other recurrent lesions include trisomy 8 and complex karyotype (≥3 cytogenetic aberrations), identified in approximately 4% and approximately 7% of primary MDS cases, respectively.[98,100] Interestingly, del(5q), the most common cytogenetic abnormality in adults, is almost non-existent in children.[100-102]

Central role of monosomy 7 in the evolution of pediatric myelodysplastic syndromes

Monosomy 7, del(7q) and the unbalanced translocation der(1;7)(q10;p10) (henceforth referred to as 'monosomy 7') have emerged as a 'central hub' associated with MDS progression and acquisition of somatic driver mutations. Monosomy 7 occurs not only in primary MDS, but it is also common in MDS arising from various IBMFS, after cytotoxic therapies or aplastic anemia (Table 2, Figure 3).[102]

An early study found that monosomy 7 is the key contributor of progression of RCC to advanced MDS or AML.[103] The median time to progression among 20 children with RCC and monosomy 7 was 1.7 years, and the cumulative incidence of progression was higher compared to patients with other chromosomal abnormalities or a normal karyotype.[103] Because of the progressive and malignant nature of monosomy 7, the European Working Group of MDS in Childhood (EWOG-MDS) recommends HSCT as the preferred upfront treatment for these patients.[97] Based on the results of a 2016 EWOG-MDS study involving 100 children with MDS and monosomy 7, 5-year event-free and overall survival rates were 66% and 69%, respectively, following HSCT.[11] In another study, the 5-year overall survival after HSCT in 40 RCC patients with monosomy 7 who had GATA2 deficiency, SAMD9/9L syndromes, or unknown genetic etiology was 69%, 77%, and 82%, respectively, with no significant differences between genetic subgroups.[31]

However, recent evidence suggests that SAMD9/9L-associated monosomy 7 requires a distinct approach, depending on patient status. Unlike in GATA2 deficiency where monosomy 7 necessitates urgent HSCT due to the high risk of leukemic progression, children with *SAMD9/9L* variants may experience spontaneous disappearance of monosomy 7 (transient monosomy 7) and stabilization of cytopenias.[31,64,75] The possibility for long-lasting remission without HSCT permits watchful waiting in children who are of a young age (preschool) and have no significant cytopenia or additional MDS-defining somatic lesions.[72,78] For this patient population, HSCT is indicated in patients who develop progressive immunodeficiency, worsening cytopenia, or who experience morphological/molecular MDS progression. On the other hand, older SAMD9/9L children (>5 years) with monosomy

7 should still proceed to timely HSCT regardless of their genetic background because there is not enough evidence of sporadic remission in older children.

Monosomy 7 has long been recognized as a diagnostic red flag for underlying germline predisposition syndromes. Recent population-based studies have revealed that around half of pediatric MDS with monosomy 7 arise from germline predisposition (primarily GATA2 and SAMD9/9L syndromes)[11,31,76] (Figure 5). Our genomic analysis of 50 pediatric primary MDS cases first demonstrated that children with monosomy 7 carry a higher burden of somatic mutations compared to those with normal karyotype (56% *vs*. 18%).[10] These monosomy 7 cases show enrichment of specific oncogenic drivers, particularly *SETBP1*, *ASXL1*, *RUNX1*, and RAS pathway mutations.[10] Subsequent studies have confirmed these results and have further shown that these somatic mutations are generally independent of germline *GATA2* and *SAMD9/9L* mutations. This suggests that monosomy 7 rather than germline predisposition primarily determines the somatic mutation spectrum (Table 1).[9,11,31,52]

Somatic mutational landscape of primary childhood myelodysplastic syndromes

Our understanding of somatic mutations in pediatric MDS lags behind adult-onset disease due to the rarity of pediatric cases. Data on somatic mutations in pediatric primary MDS comes only from a handful of studies with heterogeneous cohorts and mostly biased gene sets (Table 1).[9,10,31,52,62,104-108] In larger pediatric studies (>40 patients), advanced MDS (MDS-EB/cMDS-IB) show an expectedly higher somatic mutation burden compared to RCC/cMDS-LB, with somatic mutations identified in approximately 65-68% *versus* 13-27% of the patients, respectively.[9,10,30,31,104]

Understanding the distribution and frequency of somatic mutations in pediatric MDS has implications for therapy stratification and disease monitoring. Initial studies in pediatric MDS focused on adult MDS-type genes (*DNMT3A*, *TET2* and spliceosome genes including *SF3B1*, *U2AF35*, and *SRSF2*)[89,109] and the absence of these mutations confirmed that they do not play a role in primary pediatric MDS.[105,110] Larger cohort studies have identified genes recurrently affected in primary pediatric MDS (Table 3). The most commonly mutated genes in primary MDS are *SETBP1*, *ASXL1*, *RUNX1*, and RAS pathway genes (including *PTPN11*, *NRAS*, *KRAS*, and *CBL*).[9,10,104] Combined, RAS pathway mutations are found in up to 33% of pediatric primary MDS. Less frequent recurrently mutated genes include *EZH2*, *ETV6*, *TP53*, *GATA2*, *STAG2*, *CTCF*, *JAK3*, *CSF3R*, *FLT3*, *RAD21*, *SH2B3*, *STAG2*, *MYB*, *MPL* and *WT1*.[9,10,31,52,104]

Recently, EWOG-MDS investigators reported on the high prevalence of *UBTF* tandem duplication (TD, 24%) and *NPM1* mutations (6%) in patients with MDS-EB/cMDS-IB[107,108] (Table 1). Strikingly, these somatic alterations predominantly had a normal karyotype (lacking monosomy 7) and absence of germline predisposition (Figure 5). Both UBTF-TD and *NPM1* mutated cases were also enriched for *WT1* mutations but not FLT3-ITD. In summary, a high proportion of patients with advanced MDS, normal karyotype, and no germline

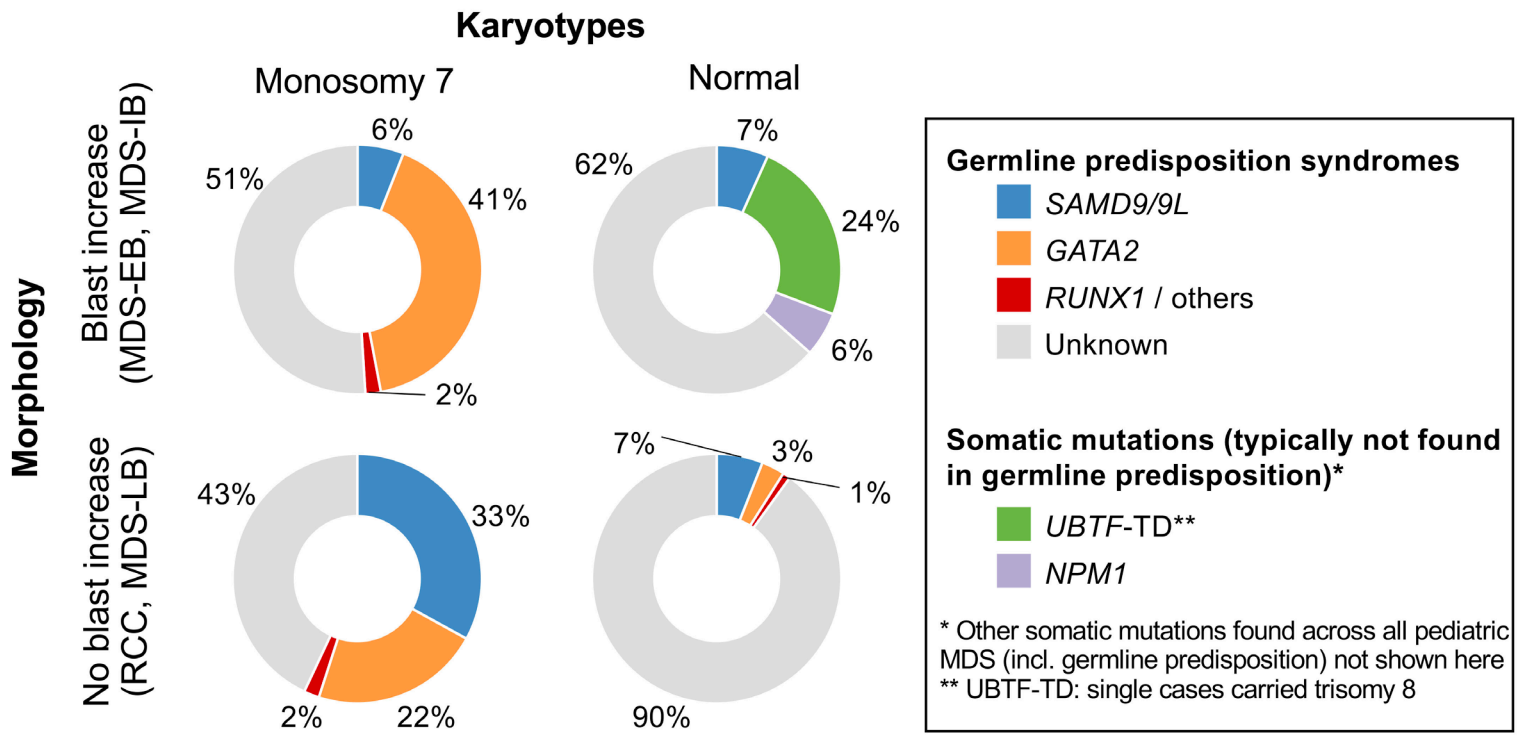

Figure 5. Distribution of genetic changes across pediatric primary myelodysplastic syndromes. Prevalence of most common germline predisposition syndromes is shown across myelodysplastic syndrome (MDS) morphologic subtypes (MDS with or without blast increase) and major cytogenetic groups (monosomy 7 *vs*. normal karyotype). *UBTF-TD* and *NPM1* mutations are found only in cases with blast increase and are mutually exclusive with germline predispositions. In contrast, common somatic mutations are found across all MDS subtypes/karyotypes and germline diseases (not shown here). Data used to generate prevalence estimates were aggregated from Sahoo *et al.*,[31] Schwartz *et al.*,[9] Erlacher *et al.*,[107] and Yoshimi *et al.*[108] incl: including; MDS-EB/IB: MDS with excess blasts/increased blasts; MDS-LB: MDS with low blasts; RCC: refractory cytopenia of childhood; UBTF-TD: UBTF tandem duplication.

predisposition can be attributed to somatic UBTF-TD and *NPM1* driver mutations. Under the current ICC and WHO classifications, cases with *NPM1* mutations and a blast percentage >10% (ICC) or any blast count (WHO) would be categorized as AML, suggesting that many, if not all, NPM1-mutated MDS-EB cases biologically may be reclassified as AML.[12,13]

Co-operating genetic events in myelodysplastic syndrome evolution

Myelodysplastic syndromes emerge through a complex interplay of genetic alterations that drive disease progression. Up to 35% of pediatric MDS patients had ≥2 co-occurring somatic mutations alongside cytogenetic abnormalities, suggesting that these genetic events co-operate in disease evolution.[10,52,57,106,111] Corroborating this, findings from 3 cohort studies in primary and *GATA2*-related pediatric MDS suggest that a higher somatic mutation burden is associated with more advanced disease.[9,10,52]

Co-operative mechanisms of co-occurring clonal events are particularly well-documented in the context of monosomy 7: studies have shown a strong association between monosomy 7 and oncogenic driver gene mutations.[10,31,52,104] In a cohort of 68 children with pediatric MDS, monosomy 7 was present in 100% of *EZH2*-, 90% of *SETBP1*-, 79% of *RUNX1*-, and 74% of *ASXL1*-mutated cases.[104] Other studies have revealed similar patterns with these gene mutations predominantly emerging in the monosomy 7 background.[9,10,31,52,104] Mutations in *PTPN11* and *NRAS* more frequently co-occur with other cytogenetic abnormalities and normal karyotype.[9,10] UBTF-TD and *NPM1* mutations are found mostly in children with normal karyotypes and are negative for germline predisposition.[107,108,112,113]

Somatic genetic rescue

Somatic genetic rescue (SGR) is a process where cells spontaneously acquire somatic changes that mitigate the deleterious effect of germline variants. SGR events are inherently adaptive at the cellular level, as they confer a context-dependent improvement in stem cell function and hematopoietic output.[114] However, improvement at the cellular level does not always translate to a clinical benefit for the individual. While the downstream clinical consequences of some SGR can be considered adaptive (associated with clinical improvement) other 'maladaptive' SGR can result in increased risk of malignant transformation.[21,114] In SAMD9/9L-related MDS, SGR events occur in approximately 61% of cases.[31] Monosomy 7 represents a frequent SGR mechanism which also has a pre-leukemic potential with risk for MDS/AML.[31,70,72,75,114,115] In contrast, the copy neutral loss of 7q through UPD7q is an adaptive SGR event with complete rescue potential. UPD7q results in the duplication of the wild-type *SAMD9/9L* allele and has been shown to promote stable hematopoiesis and clinical remission.[71,75,114] Additionally, many SAMD9/9L syndrome patients acquire compensatory *SAMD9/9L* mutations, representing adaptive SGR.[31] SGR is commonly observed across various BMF and MDS predisposition syndromes.[114] GATA2 deficiency thus far has not been recurrently associated with SGR events that directly rescue the *GATA2* locus. However, somatic *STAG2* mutations appear to improve stem cell fitness and protect from MDS evolution in these patients[52] (and are very rare in non-GATA2-related MDS), suggesting that these mutations act as an indirect SGR mechanism to improve GATA2 deficiency phenotype.

Table 3. Frequency of common somatic mutations in primary pediatric myelodysplastic syndromes.

	Kozyra[104] N=469, %	Pastor[10] N=50, %	Sahoo[31] N=570, %	Schwartz[9] N=46, %
SETBP1	7	18	4.2	6.5
ASXL1	6	8	3.9	0
RUNX1	3	6	3.7	2.2
RAS pathway*	8	5.5	6.7	32.6
EZH2	<1	2	0.9	0
ETV6	NA	NA	0.7	6.5
TP53	0	0	0	6.5

*Includes *KRAS*, *NRAS*, *CBL* and *PTPN11*. NA: not available.

Clinical implications

The genetic profile of pediatric MDS includes both germline mutations and acquired somatic alterations that substantially differ from adult MDS. Germline mutations in primary MDS predominantly involve *GATA2* and *SAMD9/SAMD9L* genes (together making up at least approx. 15% of cases), with less frequent prevalence of *RUNX1* and ERCC6L2 disease (Figure 3). Common somatic mutations across all pediatric MDS affect RAS pathway genes (*PTPN11, NRAS, KRAS, CBL*), *SETBP1*, *ASXL1*, and *RUNX1*; in contrast adult MDS-type mutations in spliceosome machinery and epigenetic regulator genes are virtually absent in pediatric MDS. Understanding the interplay between germline predisposition and somatic alterations is essential for risk stratification, treatment planning (including HSCT donor selection), and surveillance. Here, we discuss factors based on genetic findings that should be considered in the context of disease management.

Individuals with MDS predisposing syndromes require regular hematologic monitoring (CBC and typically bone marrow evaluations) and assessment of immune parameters to detect early signs of MDS evolution or immunodeficiency which would trigger a decision for timely HSCT.[28] Patients with GATA2 deficiency and monosomy 7, complex karyotype, or high-risk somatic mutations (*SETBP1, RUNX1, EZH2, ETV6, RAS* pathway genes) represent high-risk disease requiring urgent HSCT evaluation.

SAMD9/9L syndromes present unique age-dependent considerations: young children with monosomy 7 may experience spontaneous remission and thus might benefit from watchful waiting (given the potential for life-long spontaneous cure without monosomy 7 recurrence), while older patients with monosomy 7 typically require upfront HSCT for progressive disease.[72]

Patients without known germline predisposition but with high-risk features (excess blasts, monosomy 7, leukemia driver mutations) require timely HSCT. In contrast, patients independent of germline predisposing mutations who do not fulfill criteria for HSCT, including: i) absence of transfusion dependency or severe neutropenia; ii) no severe immunodeficiency; and iii) no advanced / transformed MDS, are generally followed with watchful waiting and close surveillance. However, even in stable patients, HLA typing should be generally performed upfront to identify potential HSCT donors (family members, matched unrelated donors) should transplantation become necessary.

Hematopoietic stem cell transplantation is the only curative option for pediatric MDS; however, there is ongoing debate regarding the role of pre-transplant cytoreduction chemotherapy in patients with elevated blast count and/or somatic oncogenic mutations. Collaborative clinical trials will be able to determine which patients would benefit from cytoreduction before HSCT. Given their complexity, we recommend referring patients with these disorders to specialized centers with expertise in MDS and germline predisposition where multidisciplinary care is provided and long-term surveillance protocols are established.

Disclosures

MWW reports consulting for Retro Bio (not relevant to the work in this manuscript). All of the other authors have no conflicts of interest to disclose.

Contributions

LK and MWW designed the figures. MWW is responsible for the review concept and supervision. All authors carried out the literature review and wrote the manuscript.

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