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Germline predisposition in myeloid neoplasms: Unique genetic and clinical features of GATA2 deficiency and SAMD9/SAMD9L syndromes

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ABSTRACT

Increasing awareness about germline predisposition and the widespread application of unbiased whole exome sequencing contributed to the discovery of new clinical entities with high risk for the development of haematopoietic malignancies. The revised 2016 WHO classification introduced a novel category of “myeloid neoplasms with germline predisposition” with *GATA2*, *CEBPA*, *DDX41*, *RUNX1*, *ANKRD26* and *ETV6* genes expanding the spectrum of hereditary myeloid neoplasms (MN). Since then, more germline causes of MN were identified, including *SAMD9*, *SAMD9L*, and *ERCC6L2*. This review describes the genetic and clinical spectrum of predisposition to MN. The main focus lies in delineation of phenotypes, genetics and management of *GATA2* deficiency and the novel *SAMD9/SAMD9L*-related disorders. Combined, *GATA2* and *SAMD9/SAMD9L* (*SAMD9/9L*) syndromes are recognized as most frequent causes of primary paediatric myelodysplastic syndromes, particularly in setting of monosomy 7. To date, ~550 cases with germline *GATA2* mutations, and ~130 patients with *SAMD9/9L* mutations had been reported in literature. *GATA2* deficiency is a highly penetrant disorder with a progressive course that often rapidly necessitates bone marrow transplantation. In contrast, *SAMD9/9L* disorders show incomplete penetrance with various clinical outcomes ranging from spontaneous haematological remission observed in young children to malignant progression.

Introduction: germline predisposition in myeloid neoplasms

Nearly a century ago the first classical inherited bone marrow failure (BMF) syndrome predisposing to myeloid neoplasms (MN) had been reported by the paediatrician Guido Fanconi, and later named Fanconi Anemia (FA) [1]. Since then, a number of additional inherited BMF syndromes with risk for the development of myelodysplastic syndrome (MDS) and leukemia have been discovered, including severe congenital neutropenia (SCN), Shwachman Diamond syndrome (SDS), telomere biology disorders/dyskeratosis congenita, Down syndrome, RASopathies, and DNA repair disorders [2–10]. These disorders are usually straightforward to diagnose because of preexisting dysmorphologies and haematological symptoms arising from abnormalities of haematopoietic stem and progenitor cells. The characteristics of recurrently occurring genetic syndromes are outlined in Table 1. Although BMF manifests early in

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Table 1
Germline syndromes predisposing to myeloid neoplasms.

Disease/Gene	Risk for MN	Age of MN onset, years *	Population at High Risk for MN	Reported somatic mutations	Reported karyotypes	Congenital anomalies	Immune deficiency
Germline predisposition to myelodysplastic syndromes/acute myeloid leukemia (MDS/AML)							
GATA2	High	0.4–78 (~20)	Children – Adults	SETBP1, ASXL1, RUNX1, PTPN11, NRAS, KRAS, CBL, EZH2, ETV6, STAG2, JAK3, IKZF1, CRLF2, IDH2, TP53	–7, der(1; 7), +8, +21	++	++
SAMD9, SAMD9L	Moderate	Paediatric age, not yet defined	Children	SETBP1, ASXL1, RUNX1, PTPN11, KRAS, CBL, EZH2, ETV6, BRAF, RAD21	–7, del(7q), del12p13.2, UPD7q	++	–
RUNX1	High	6–77 (~33)	Children – Adults	Somatic revertant mosaicism (cis SAMD9/9L, UPD7q) RUNX1 (trans mutation or duplication via LOH), ASXL1, BCOR, DNMT3A, PHF6, WT1, GATA2, FLI1, JMJD5, KDM6B, CDC25C	+21, +8, –7	–	–
CEBPA	High	2–50 (~25)	Children – Adults	CEBPA (trans mutation at 3' end), GATA2, WT1, EZH2, TET2, SMC3, NRAS, DDX41, CSF3R	–	–	–
ETV6	Moderate (mostly ALL)	8–82	Adults	BCOR, RUNX1, NRAS	–	–	–
DDX41	Moderate	6–93 (~55)	Adults	DDX41 (trans p.Arg525His mutation, p.Ala255Asp, p.Glu247Lys, p.Pro321Lys)	del(20q), del(7q), –7, +8	–	–
ANKRD26	Low	>30	Adults	–	–	–	–
TET2 (1 family with p.K1363fs mutation)	Not known	53–61 (60)	Adults	TET2 (p.His863fs), BRAF, ZRSR2, SRSF2, JAK2, GATA2	–	–	–
Classical inherited bone marrow failure syndromes							
Fanconi Anemia 22 FA genes	High	0.1–49 (13)	Children	Somatic revertant mosaicisms (back mutations), RUNX1	del(7q), dup(1q), dup(3q), complex	++	–
Severe Congenital Neutropenia ELANE, G6PC3, HAX1, JAGN1, GF11, VPS45A, TCRG1	High	2–49 (12)	Children – Adults	CSF3R, RUNX1, RAS genes	–7, del(7q), +21	+	–
Shwachman Diamond Syndrome SBDS, ELF1, SRP54, DNAJC21	Variable	MDS: 5–42 (8)	Children – Adults	TP53 (>50% of cases with SBDS germline mutation), EIF6, PRPF8, CSNK1A1, U2AF1, IDH1, RUNX1, SETBP1, NRAS, KRAS, BRAF, DNMT3A, TET2, ASXL1	isochromosome 7q, –7, del(20q)	++	(+)
Telomere Biology Disorders DC: TERC, TERT, DKC1, RTEL1, TINF2, ACD, CTC1, NHP2, NOP10, NPM1, PARN, WRAP53 Pulmonary fibrosis: POT1, ZCCHC8, NAF1 CLL/Melanoma: POT1	Moderate (mostly adults)	19–61 (35)	Adults	Somatic revertant mosaicism (UPD of TERT/TERC allele, or activating TERT promoter mutations – very rare); Leukemia mutations uncommon	–	+	+
Down syndrome and rasopathies Trisomy 21	Moderate	1–4 (1.5)	Children	GATA1 short, cohesin (RAD21, STAG2, NIPBL, SMC1A, SMC3), CTCF, EZH2, KANSL1, BCOR, WT1, DCAF7 TP53, NRAS, KRAS, PTPN11, JAK2, JAK3, SH2B3	MLL gene rearrangements, complex	++	(+)

(continued on next page)

Table 1 (continued)

Disease/Gene	Risk for MN	Age of MN onset, years *	Population at High Risk for MN	Reported somatic mutations	Reported karyotypes	Congenital anomalies	Immune deficiency
Rasopathies NF1, CBL, PTPN11, NRAS, KRAS	Moderate	CBL: 0.1–3.6 (1.1)	Children	Duplicaton of mutant allele (via UPD), additional RAS pathway mutations	–7	++	–
DNA repair syndromes ERCC6L2	High	14-65 (38)	Adults	TP53, IDH1	–7, +20, –18, del (5q)	+	–
Xeroderma pigmentosum C (XP-C)	Low	7-29 (25)	Adults	TP53, CSF3R, TET2, RAD21	–7, del(5q), complex	+	–
Other TP53, CMMRD, Werner/Bloom syndrome, NBS, AT, Ligase IV deficiency	MN are rare	All ages	Children – Adults	Chromothripsis	–7, complex	+	+

Abbreviations: DC, dyskeratosis congenita; CMMRD, Constitutional Mismatch Repair Deficiency; NBS, Nijmegen Breakage Syndrome; AT, Ataxia telangiectasia; MN, myeloid neoplasms.

+, present; (+), possibly present; ++, commonly present; –, absent.

*Approximate age range (median) assessed from literature reports; CLL chronic lymphocytic leukemia; ALL, acute lymphoblastic leukemia; UPD, uniparental disomy; LOH, loss of heterozygosity.

life, MDS and leukemia develop as a secondary disease after a latency of years to decades from diagnosis of the underlying condition [5, 11–16]. Clonal evolution is usually associated with a number of recurrent somatic mutations, for example *RUNX1* in FA, *CSF3R* and *RUNX1* in SCN, *TP53* in SDS, *GATA1* short and cohesin genes in Down syndrome [5,7,10,12,16–23]. Additional mutations can involve typical leukemia drivers including RAS pathway genes, *SETBP1*, *ASXL1*, *EZH2*, and others. Recurrent karyotype abnormalities are also found, particularly loss of chromosome 7 (monosomy 7 (–7), del(7q), der(1; 7), isochromosome 7q), trisomy 8 (+8), or trisomy 21 (+21). While most of the somatic mutations are known leukemia drivers (*RUNX1*, RAS pathway, *TP53*), others might represent benign adaptive responses (*EIF6*, *CSF3R*). In addition, revertant somatic events including back mutations or uniparental disomy have been reported in FA and *TERT/TERC* mutated telomere biology disorders [24–27].

The identification of germline mutations in *RUNX1* (1999) and *CEBPA* (2004) initiated a new era for the discovery of monogenic disorders predisposing to MN [28,29]. For the most part these “new” syndromes result from heterozygous mutations in haematopoietic transcription factors or regulators (*GATA2*, *RUNX1*, *CEBPA*, *ETV6*, *DDX41*, *SAMD9*, *SAMD9L*, and *TET2*, Table 1) [31–37,52,147]. These syndromes often pose unique diagnostic challenges. First, the full spectrum of clinical and genetic manifestations is not yet fully defined, forcing us to adopt the “expect the unexpected” approach for the workup of such cases. Second, unlike the classical inherited BMF syndromes which are often diagnosed based on medical history, these new entities can often manifest with MN without preceding clinical problems. And finally, many patients have negative family history (even in families with multiple mutated individuals) which can be attributed to incomplete penetrance/variable expressivity and a considerable rate of *de novo* germline mutations. Despite these challenges, there are genetic and phenotypic patterns that can serve as diagnostic red flags. These can include certain types of mutations that are identified on a somatic sequencing panel, for example variants with allelic frequency nearly 50% in a patient without significant blast increase, *DDX41* somatic hotspot mutation that co-occurs with germline *DDX41* alterations, bi-allelic *CEBPA* mutation with one mutation positioned at 3'-end, and finally the domain-specific localization such as missense *GATA2* mutations in zinc finger 2. In addition, certain clinical signs can be syndrome-specific, i.e. lymphedema, hydrocele, and congenital deafness in *GATA2*, ataxia in *SAMD9L*, adrenal hypoplasia in *SAMD9*, or preceding thrombocytopenia in individuals with *RUNX1/ETV6/ANKRD26* mutations.

GATA2 and *SAMD9/SAMD9L* (*SAMD9/9L*) syndromes are the most frequent predisposing conditions in children and adolescents with primary MDS and are associated with the development of –7 karyotype: collectively they account for at least 50% of paediatric MDS with –7 [37–39,52]. The following text will discuss in detail the clinical and genetic spectrum of *GATA2* and *SAMD9/9L* syndromes.

GATA2 deficiency

GATA2 is a key transcription factor critical for ontogenesis of haematopoietic system, including haematopoietic stem cell (HSC) activity and self-renewal, myeloid and myelo-erythroid progenitor cell differentiation, and erythroid precursor cell maintenance [40–44]. In the past decade, heterozygous germline *GATA2* mutations have been identified in a number of cohorts with cellular deficiencies (immunodeficiency syndromes initially referred to as MonoMAC syndrome, DCML deficiency, Emberger syndrome, chronic neutropenia) [45–48], and in patients with familial MDS and acute myeloid leukemia (AML), as well as paediatric MDS [47–53]. To date, approximately 150 unique *GATA2* germline mutations have been identified in roughly 550 patients (Fig. 1).

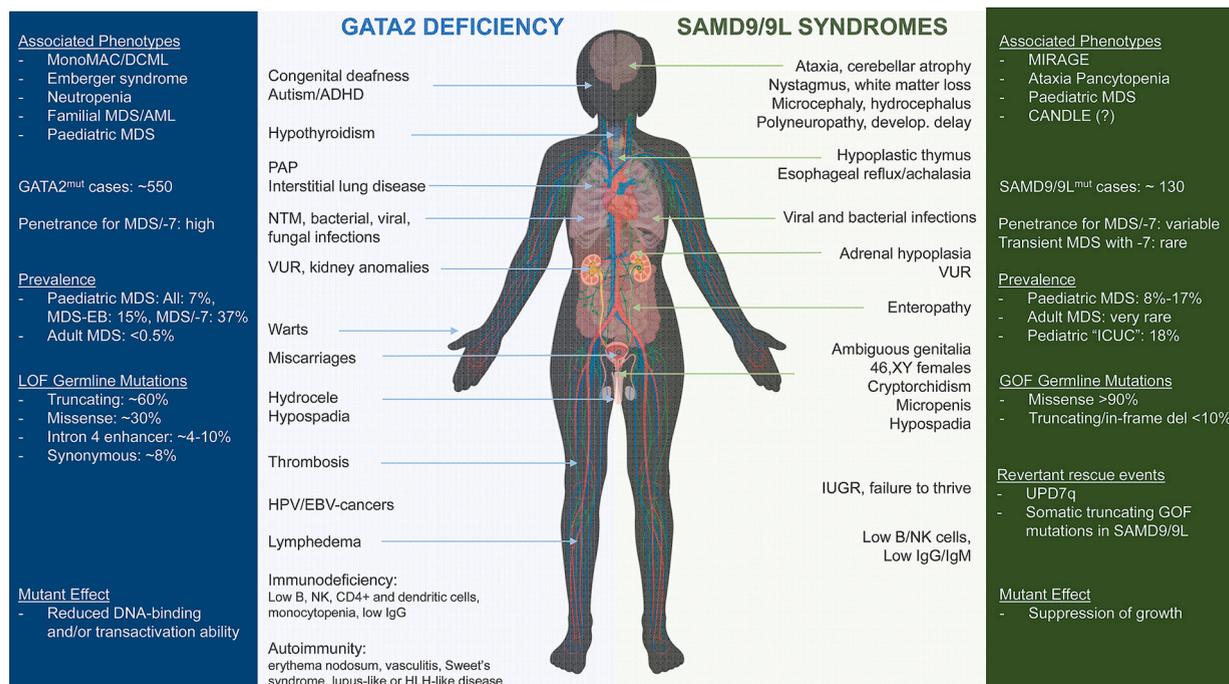


Fig. 1. Clinical characteristics of GATA2 deficiency and SAMD9/9L syndromes.

Key information referring to phenotypes, prevalence and genetics are summarized in the outside coloured boxes; clinical manifestations are depicted in the middle. Abbreviations: MonoMAC, Monocytopenia and *Mycobacterium avium* complex infection syndrome; DCML, Dendritic cell, Monocytes, B/NK Lymphocytes deficiency; MDS, Myelodysplastic Syndrome; MDS-EB, MDS with Excess of Blasts; AML, Acute Myeloid Leukemia; -7, monosomy 7; LOF, loss of function; ADHD, Attention Deficit Hyperactivity Disorder; PAP, Pulmonary Alveolar Proteinosis; NTM, Nontuberculous mycobacteria; VUR, Vesicoureteral Reflux; IUGR, Intrauterine Growth Restriction; MIRAGE, Myelodysplasia, Infection, growth Restriction, Adrenal hypoplasia, Genital phenotypes, and Enteropathy; CANDLE, Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated temperature; ICUC, idiopathic cytopenia of unknown cause (denotes children with unclear cytopenia and suspected bone marrow failure); GOF, gain of function.

Penetrance and prevalence

GATA2 deficiency follows an autosomal dominant inheritance pattern with the majority (up to 80%) of cases arising *de novo* [49, 52–55]. Although the lifetime penetrance for the development of MN is very high, incomplete penetrance is possible, as suggested by the presence of several asymptomatic mutation carriers of various ages within affected families [50,52,53,56–58]. Recently, distinct patterns of GATA2 promoter methylation leading to disbalance in allelic expression have been identified in 2 patients and proposed as a mechanism for reduced clinical expressivity [59,60].

Summarizing published cohort studies and smaller case series, approximately 75% of GATA2 mutation carriers develop MN at an estimated median age of 20 years (Table 1). The spectrum of MN includes primary paediatric MDS, AML, chronic myelomonocytic leukemia (CMML) and myeloproliferative neoplasms [47,49–55,61]. In children and adolescents with primary MDS, GATA2 deficiency is a predominant germline predisposition accounting for 7% of all MDS cases, 15% of patients with advanced MDS, and 37% of patients with MDS and -7 karyotype [52,62]. Among children, the prevalence of GATA2 deficiency increases with age, and 2/3 of adolescents with MDS and monosomy 7 carry germline GATA2 mutations. In adult MDS, GATA2 deficiency is rare and present in less than 0.5% of individuals [52], however the true prevalence in various age groups has yet to be defined.

Clinical presentation

The initial haematological presentation in patients with GATA2 deficiency can be very variable, ranging from cytopenias and hypocellular BMF-like picture, severe immunodeficiency to myeloid neoplasms. Many patients often lack family history of MDS and exhibit mild initial symptoms with preceding cellular deficiencies [49,52,62]. However, MDS can also manifest as a stand-alone diagnosis without preceding cytopenia. GATA2-deficient patients often suffer from preexisting monocytopenia, B-cell and NK-cell lymphopenia, reduction/lack of CD56^{bright} NK cells and dendritic cells, inverted ratio of CD4:CD8 cells, and chronic neutropenia [48,53,58,61–65]. Immune deficiency is typically recorded as a consequence of profound cytopenias and loss of functional stem cells [66]. When compared to other marrow failure conditions in children, reduction of progenitor and mature B-cells are the most constant feature of GATA2 deficiency [62]. Notably, monocytosis has been observed at diagnosis in GATA2 patients with MDS and is likely attributed to disease progression [52,53], although transient monocytosis in infancy has been also observed (unpublished own

observations). The immunological phenotypes are heterogeneous. Many patients can initially present with HPV-related infections (warts, generalized verrucosis, cervical intraepithelial neoplasia), disseminated nontuberculous mycobacterial, as well as systemic bacterial and fungal infections [50,53,67]. Recurrent respiratory tract infections can result in a development of pulmonary alveolar proteinosis (PAP) or interstitial lung disease [50,53]. Moreover, compromised function of the immune system may contribute to malignant transformation of HPV- or EBV-related neoplasia and increased occurrence of other solid tumors [47,50,53,68]. Furthermore, *GATA2* mutated patients have been repeatedly shown to suffer from autoimmune dysregulation such as autoimmune cytopenia, arthritis, panniculitis, erythema nodosum, psoriasis, lupus-like syndrome and autoimmune hepatitis [53,56,63,69–71].

GATA2-MDS patients demonstrate heterogeneous morphological features involving hypocellular marrow with cytopenias, or normal to hypercellular marrow in case of advanced MDS. Frequently recognized dysplasia is seen in megakaryocyte lineage, but other lineages are also affected [50,63].

Apart from haematological and immunological symptoms, at least 50% of *GATA2*-deficient patients present with constitutional abnormalities affecting different organ systems (Fig. 1). In addition to lymphedema, hydrocele and congenital deafness, abnormalities of pulmonary, cardiovascular, urogenital and neurological systems have been repeatedly observed [48,50,52,53,56,62,63]. This includes i.e. PAP, thrombosis, pulmonary embolism, vesicoureteral reflux, hypospadias, hydrocele, developmental delay, or behavioral disorders/ADHD. The presence of both immune deficiency and typical constitutional features, especially in context of MDS should trigger genetic workup for *GATA2* mutations.

GATA2 germline mutations

De novo or inherited heterozygous loss of function mutations have been identified as the genetic basis of *GATA2* deficiency. These mutations are thought to lead to loss of function of *GATA2* protein (through loss of one allele or malfunctioning protein) specifically abolishing the DNA-binding function of the C-terminal zinc finger (ZF2) [39,47,49,72–77,79]. Overall, 3 main mutation categories can be distinguished i.e. null (frameshift, nonsense, splice site and whole gene deletions) located prior or within ZF2 and accounting for around two thirds of all reported variants, missense substitutions clustered within ZF2 representing one third of *GATA2* mutations and intronic alterations affecting +9.5 kb enhancer element (EBOX-GATA-ETS) detected in ~4–10% of cases (Fig. 1). Additionally, rare changes including in-frame deletions/insertions and missense mutations downstream of ZF2 were found [39]. Most recently, we identified 5 heterozygous synonymous *GATA2* mutations (p.Thr117Thr, p.Leu217Leu, p.Gly327Gly, p.Ala341Ala, p.Pro472Pro) in 9 patients with *GATA2* deficiency that led to selective loss of mutated copy of *GATA2* mRNA [81]. The hotspot p.Thr117Thr mutation has been also described by others [77,82] and mechanistically was found to introduce a new splice donor resulting in premature translation termination associated with nonsense-mediated decay.

Experimental studies found impaired ability of mutant *GATA2* protein to bind DNA and activate transcription of target genes. This was shown for several mutations (p.Arg330X, p.Ala345delinsALLVAALLAA, p.Thr354Met, p.Thr355del, p.Thr358Asn, p.Arg361Leu, p.Cys373Arg, p.Arg396Gln, p.Arg396Leu, p.Arg398Trp) [47,49,73–76,79]. Moreover, some of the mutations were shown to affect proliferation, differentiation and apoptosis in haematopoietic cells [49,74]. Variable expressivity of *GATA2* ZF2 germline mutations is common. The most recurrent mutations p.Thr354Met, p.Arg396Gln and p.Arg398Trp all predispose to myeloid malignancies, however p.Thr354Met was shown to be associated with MDS as initial presentation, while p.Arg396Gln and p.Arg398Trp mutations were suggested to correlate with a phenotype of immunodeficiency manifesting prior to malignant transformation [75]. Although, reduced DNA-binding/transactivation ability has been shown to be causal of *GATA2* haploinsufficiency, this does not explain the genotype/phenotype correlation for individual ZF2 mutations. One possible explanation could be the altered interaction between *GATA2* and other proteins, as shown for *GATA2* p.Thr354Met and p.Cys373Arg mutations that compared to wild type *GATA2* protein bind more strongly to the haematopoietic differentiation factor PU.1 [75]. Hence, detailed mechanistic studies are paramount to understand these phenotypic differences and functional consequences of germline *GATA2* mutations. Genotype-phenotype correlative analyses have thus far been unsuccessful and potential associations seen in some studies were not validated in other cohorts. In a recent study encompassing 79 French patients with *GATA2* deficiency, patients harboring missense mutations (14 out of 38) were more likely to develop leukemia than patients with frameshift mutations (2 out of 28; $p = 0.007$) [53]. However, an analysis conducted by our group in a large cohort of paediatric MDS ($N = 137$) did not confirm this association (own unpublished observations).

Somatic *GATA2* mutations compared to germline mutations show different localization within the protein and are associated with other haematological phenotypes. Of the roughly 50 reported somatic mutations, the majority are found within the boundaries of N-terminal zinc finger (ZF1), but some mutations also occur in ZF2 [83]. These mutations are generally rare and were identified in paediatric and adult AML (predominantly accompanied by biallelic *CEBPA* mutations), chronic myeloid leukemia in blast crisis, as well as acute erythroid leukemia [84–93]. In contrast to germline variants, acquired *GATA2* mutations were characterized as either LOF (p.Pro304His, p.Leu321Val, p.Leu321Pro, p.Arg330Gln, p.Arg362Gln, p.Ala341_Gly346del) or gain-of-function (GOF; p.Gly320Asp, p.Leu359Val). It is interesting to note that certain somatic *GATA2* ZF2 mutations in adults with MN can “phenocopy” symptoms of *GATA2* germline disorder, i.e. immunodeficiency (monocytopenia, low B-/NK-cells, recurrent infections) accompanied by lymphedema or PAP [94,95].

Acquired cytogenetic and genetic aberrations

The most common karyotype abnormalities are monosomy 7 or der(1; 7) that can occur in up to 80% of *GATA2*-related MDS patients, with average estimate across all published studies of ~41% (Fig. 2) [39]. Trisomy 8 is the second most common aberration identified in up to 40% of patients in single cohorts, and an average of 15% across published studies. Additional common abnormality

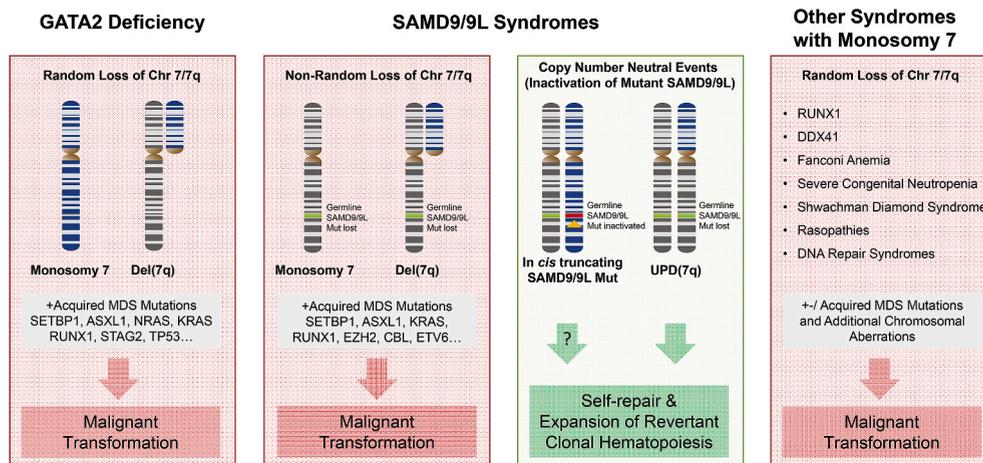


Fig. 2. Monosomy 7 driven mechanisms of clonal evolution in MDS predisposition syndromes.

Malignant transformation of GATA2 deficiency (outside left box), SAMD9/9L disorders (middle boxes) and other predisposing syndromes (outside right box) is associated with loss of whole chromosome 7 or its long (7q) arm followed by acquisition of somatic mutations in leukemia-related genes. Loss of chromosome 7 is non-random in SAMD9/9L syndromes and leads to disappearance of germline SAMD9/9L mutation. Revertant clonal haematopoietic in SAMD9/9L syndromes arise from UPD7q or acquired truncating SAMD9/9L mutation (middle right box). Abbreviations: MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; UPD, uniparental disomy.

is trisomy 21, while complex karyotypes are generally not encountered. GATA2-related MDS is also associated with acquired MDS/leukemia driver mutations (Table 1). Recurrent oncogenic alterations were identified in genes *ASXL1*, *SETBP1*, *RUNX1*, *STAG2*, *CBL*, *EZH2*, *NRAS*, *KRAS*, *JAK3*, *PTPN11*. [51,54,58,96–100] Furthermore, single GATA2-MDS cases were also reported to harbor somatic mutations in *IKZF1*, *CRLF2*, *HECW2*, *GATA1*, *GATA2*, *ATRX*, *BRCA2*, *GPRC5A*, *IDH2*, *TP53*, *WT1* [97,99,101].

Therapeutic considerations

There are no consensus guidelines on management of GATA2 deficiency and the surveillance strategies are individually tailored. Most patients are being followed by haematologists, immunologists or transplant physicians and general recommendations include periodic assessment of complete blood counts and immune status, yearly bone marrow evaluation with cytogenetics and somatic mutational testing, as well as screening for HPV-related cancers and pulmonary symptoms. Haematopoietic stem cell transplantation (HSCT) is the only curative treatment with reported outcomes ranging from 54% (4 year overall survival (OS)) in adults transplanted for MDS/AML or immunodeficiency [50], to 66% (5 year OS) in children transplanted for MDS with -7 [52], or 62% (5 year OS) in a French GATA2 cohort [53], and 86% (2 year disease-free survival) in young adults with MDS [68]. Because -7 karyotype is associated with a high risk of progression to more advanced MDS, patients with this cytogenetic category should undergo HSCT as soon as possible [102]. While myeloablative conditioning is preferred in MDS with -7 (independent of blasts) as well as advanced MDS/AML, reduced intensity conditioning might be preferred option in patients with hypocellular MDS without high risk somatic alterations, as well as patients with immunodeficiency alone. HSCT was shown to reverse HPV-related lesions as well as respiratory problems (PAP) [68, 103–105]. Patients with stable disease course, without relevant infections, bone marrow dysplasia and transfusion-dependency might qualify for a watch & wait strategy [106,107]. However, it can be assumed that most GATA2-deficient patients show progressive disease and even with careful watching the best opportunity for low risk HSCT might be missed. Currently, transplant indications include progressing immunodeficiency with recurrent infections, respiratory complications (PAP), transfusion-dependency, and MDS [50,52,104,105,108]. The optimal point in time for performing HSCT would be the stage of hypocellular MDS or immunodeficiency prior development of MDS/leukemia evolution or severe organ dysfunction.

SAMD9 and SAMD9L syndromes

Sterile alpha motif domain-containing protein 9 (*SAMD9*) and the paralogue gene *SAMD9*-like (*SAMD9L*) are located side-by-side on chromosome 7q21. Initial study describing acquired microdeletions of 7q21 in patients with MN drew preliminary attention to these poorly characterized genes [113]. *SAMD9/9L* are IFN and TNF- α responsive proteins that were shown to play a role in antiviral response [109–112], tumor suppression [113,114], inflammation [115,116], development [117–119] and endosomal fusion [118, 120]. *Samd9l*-deficient mice develop myeloid disease resembling human MDS with -7 [120]. The first link to human disease was a description of biallelic LOF *SAMD9* mutations (p.K1495E and p.R344X) in several consanguineous Jewish-Yemenite families with normophosphatemic familial tumor calcinosis (NFTC), however no further NFTC cases with *SAMD9* mutations were found [115,116]. In 2016, heterozygous missense *SAMD9* mutations with GOF effect were linked to a severe early-onset condition with Myelodysplasia, Infections, Restriction of growth, Adrenal hypoplasia, Genital phenotypes and Enteropathy (MIRAGE) [118,119]. At the same time,

missense GOF mutations in *SAMD9L* were described as a cause of a syndrome with progressive neurological phenotype, pancytopenia and hypocellular bone marrow (Ataxia Pancytopenia (ATXPC)) [117,121]. Both conditions have a unifying phenotype of early onset myelodysplasia with monosomy 7. Following the first discoveries in syndromic cohorts, a number of studies reported germline missense *SAMD9* and *SAMD9L* mutations in paediatric cohorts with MDS (often without syndromic manifestation) [122–125]. Recently, germline frameshift *SAMD9L* mutations were also discovered in several children presenting with autoinflammatory panniculitis resembling Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated Temperatures (CANDLE) syndrome [126].

Penetrance and prevalence

SAMD9/9L syndromes are autosomal dominant syndromes resulting from GOF, mostly missense mutations with variable penetrance. *SAMD9* mutations are associated with a high rate of *de novo* cases with very high penetrance especially in pedigrees presenting with MIRAGE syndrome. For *SAMD9L* mutations, the penetrance for haematological disease is incomplete and has been estimated at 70% [123]. Similarly, low penetrance for neurological phenotypes (that might increase with age) has been observed [117].

Germline *SAMD9/9L* mutations account for a large proportion of primary childhood MDS and the prevalence was shown to range from 8% (43/548) in a large multi-institutional consecutive cohort of the European Working Group of Childhood MDS (EWOG-MDS) [37] to 17% (8/46) in a single institution report [122]. Interestingly, in a French cohort of patients with idiopathic cytopenia of unknown cause (“ICUC”), 18.6% (16/86) of patients carried germline *SAMD9/9L* mutations [125].

Clinical presentation

Multiple organ systems can be affected in *SAMD9/9L* syndromes, with predominant haematologic, immunologic, endocrine, genital and neurologic involvement (Fig. 1). Initial clinical presentation is heterogeneous and can range from severe disease with high infant mortality, to transient cytopenia and immune dysfunction. Patients with MIRAGE (*SAMD9*) phenotype present with early onset adrenal hypoplasia and primary adrenal insufficiency, intrauterine growth restriction, genital phenotypes (46XY females, bifid shawl scrotum, testicular dysgenesis, intra-abdominal or inguinal testes, clitoromegaly), gastrointestinal issues (enteropathy, reflux, achalasia), severe systemic infections, as well as thrombocytopenia and anaemia at birth - which in some patients can be self-limiting during infancy [37,118,119,128–139]. Patients with *SAMD9L* mutations might show disease-specific neurological findings with very variable age of onset and dynamics of progression. Severe cerebellar ataxia is observed in some but not all cases [117]. Some patients might show cerebellar atrophy, dysmetria, nystagmus, white matter abnormalities, and loss of Purkinje cells [117,140,141].

Of note, haematological phenotype is the “common denominator” of both syndromes manifesting in the majority of patients [117, 121–123,125,142]. The haematological spectrum involves single lineage cytopenia (mostly thrombocytopenia) or pancytopenia with hypocellular marrow, and MDS with -7 or $\text{del}(7q)$. In a large paediatric MDS cohort the majority (90%) of *SAMD9/9L*-mutated patients presented with refractory cytopenia of childhood (RCC), while MDS with excess blasts was found in 10% of cases [37]. In a small subset of patients advanced leukemic disease (AML, CMML) can be diagnosed [37,122–124]. The median age at diagnosis in paediatric MDS with *SAMD9/9L* was shown to be 9.6 years (0.2–17.6) which is comparable with *GATA2*-related MDS [37]. The most widespread aberrant karyotype is $-7/\text{del}(7q)$ and shows a unique non-random pattern where the chromosome 7 with mutant *SAMD9/9L* copy is always lost, which by itself can be considered a pathognomonic sign of *SAMD9/9L* syndromes (Fig. 2).

Immune dysfunction is not well defined and shows varying phenotype and severity. Mostly in patients with MIRAGE phenotype (*SAMD9*) but also in several *SAMD9L*-mutated patients, severe invasive infections have been described. The causative organisms were bacteria (*Pseudomonas aeruginosa*, *Clostridium difficile*, *Staphylococcus*, *Serratia marcescens*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Stenotrophomonas maltophilia*, *Streptococcus pyogenes*), viruses (MRSA, CMV, EBV, rhinovirus, coronavirus, varicella), and fungi (*Aspergillus*, *Candida*) causing sepsis, meningitis, otitis, sinusitis, laryngitis, hepatitis, bronchiolitis, pneumonia, neonatal necrotizing enterocolitis, pancolitis, gastroenteritis, enteropathy, urinary tract infections, otitis media, ecthyma gangrenosum, warts, dental abscesses, and urethritis [118,119,121,124,125,128–133,136–139,141,143–145]. However, the majority of non-syndromic *SAMD9/9L*-MDS patients generally do not appear to have high risk to develop immune dysfunction and severe infections. Decreased peripheral B/NK-cells, low IgG and IgM or increased TNF-alpha and IL-6 levels were documented in cases with *SAMD9/9L* mutations [121,125,128,131,135,143]. Other rare dysmorphic features documented in single patients include skeletal abnormalities (scoliosis, joint contracture at wrist and ankles), hearing loss, dysmorphic facial features, camptodactyly, arachnodactyly, glomerular proteinuria, dysautonomia and speech delay [129,131].

SAMD9/9L genetics

Thus far 38 distinct *SAMD9* and 26 *SAMD9L* mutations have been identified in 110 symptomatic patients as mutually exclusive events [118,119,121,122,124,126,129–134,140–143,145,146]. The majority of these patients exhibit haematological phenotype with cytopenias, and/or MDS with -7 . Most germline mutations are missense and occur predominantly in the second half (C-terminus) of *SAMD9/9L* proteins, encompassing the predicted P-LOOP_NTPase domain. Six cases with truncating germline mutations in *SAMD9L* were also reported in children with CANDLE phenotype [126].

Thus far, all functionally evaluated germline missense *SAMD9/9L* mutations were shown to inhibit cell growth in 293 cellular overexpression assay [118,119,123]. Of note, many mutated amino acids show moderate or weak conservation across species, thus posing a risk of being scored as ‘likely benign’ based on *in silico* predictors. The current state-of-art for assessment of pathogenicity

includes functional validation on a research basis. However, such testing must be interpreted with caution since sensitivity and specificity have not been defined and various groups utilize different readouts [118,119,122,123].

Clonal evolution and somatic reversion

The unique aspect of *SAMD9/9L* disease mechanism is ‘adaptation by aneuploidy’ that is achieved by the non-random loss chromosome 7 (–7/del(7q)) which contains mutated *SAMD9/9L* gene copy (Fig. 2)[118,119,121–125,129,134,135,141–145]. The decrease of mutant allele in haematopoiesis poses a diagnostic challenge, since germline *SAMD9/9L* mutations show decreased variant allele frequency (VAF), with VAF even below 5% (own observations), necessitating germline validation in non-haematopoietic specimens, i.e. fibroblasts.

Several case reports documented complete disappearance of –7 clones, thus far seen exclusively in young children, a phenomenon previously referred to as transient monosomy 7 syndrome [121–124,141–143]. However, –7 is a high risk lesion with malignant propensity (i.e. due to loss of several tumor suppressor genes such as *EZH2*). Clonal evolution to advanced MDS/AML is a recurrent complication in *SAMD9/9L*-related MDS with –7 and was shown to be accompanied by somatic driver mutations in *SETBP1*, *ASXL1*, *RUNX1*, *PTPN11*, *KRAS*, *CBL*, *EZH2*, *ETV6*, *BRAF*, and *RAD21* [122–124,142].

Somatic revertant mosaicism with expansion of benign, corrected haematopoiesis represents another unique feature of *SAMD9/9L* syndromes (Fig. 2). The two mechanisms observed so far are the acquisition of truncating *SAMD9/9L* mutations or an independent uniparental disomy of 7q (UPD7q). Somatic *SAMD9/9L* mutations are acquired *in cis* (on the same allele) and are thought to exert a LOF effect and “neutralize” the GOF germline mutation, as documented in cellular growth assays [119,121,123,124,131,134,142]. Missense somatic *SAMD9/9L* are rarely encountered but were also shown to modify germline mutant function [121]. A true genetic reversion with replacement of the mutant *SAMD9/9L* allele via UPD7q has been thus far reported in 11 patients who experienced spontaneous remission [121–125,141–143]. This reversion likely arises through non-allelic homologous recombination in a del(7q) clone, where the wild type 7q arm is duplicated. Strikingly, the reversion seems to be definitive, as shown in patients who normalized their blood counts and marrow cellularity with normal findings up to over 20 years after diagnosis [123,125]. UPD7q can be considered a protective mechanism against the development of MDS, but it is not clear how it arises and how it outcompetes –7/del(7q) clones.

Therapeutic considerations

SAMD9/9L are newly described MDS predisposition syndromes where clinical outcome data is derived from retrospective studies and no guidelines exist on prospective management. The current practice for patients mild haematological phenotypes is guided by the morphological subtype (as recommended by the EWOG-MDS working group). For example, patients with RCC without severe neutropenia and no transfusion dependency can be followed with a watch & wait strategy with periodic assessment of blood counts and yearly marrow evaluation aiming at detection of high-risk somatic changes (–7, somatic driver mutations). A very careful consideration must be given to patients with *SAMD9/9L* syndromes and –7, where not enough data exists to deviate from the general recommendation for paediatric MDS with –7 where HSCT is performed in a timely manner [102]. Children with severe multi-organ involvement in context of MIRAGE syndrome who received HSCT were shown to have rather poor outcome complicated by syndrome-related comorbidities [128,145]. On the other hand, children with *SAMD9/9L* germline mutations who were transplanted for MDS had satisfactory outcomes with a 5 year OS of 85% [37]. Going forward one might speculate that young children with clinically stable disease (MDS and –7 without severe cytopenias and without somatic leukemia mutations) might benefit from careful watching with repeated molecular studies to document loss of monosomy 7 clone and emergence of revertant UPD7q clones. At the same time however, the patients might be exposed to the risk of clonal evolution to a more advanced disease where HSCT outcome might be inferior compared to initial disease state.

Practice points

- Recently described autosomal dominant syndromes predisposing to myeloid neoplasms often manifest without preexisting features or family history and show variable expressivity and incomplete penetrance
- *GATA2* and *SAMD9/SAMD9L* syndromes are most common germline drivers of paediatric MDS and account for at least half of paediatric MDS with monosomy 7
- HSCT is indicated in patients with transfusion dependency, neutropenia, immunodeficiency, morphologically advanced disease, and high-risk cytogenetic and genetic lesions
- *GATA2* deficiency is a highly penetrant disease with progressive course necessitating HSCT, while *SAMD9/SAMD9L* syndromes can show diverse outcomes ranging from spontaneous remission (in young children) to clonal progression.

Research agenda

- Prospective monitoring of patients with hereditary predisposition to MN might reveal risk factors for clonal evolution
- It remains to be answered if a careful watch & wait strategy in stable patients with *SAMD9/9L*-related MDS and monosomy 7 might identify patients with spontaneous genetic reversion and disappearance of monosomy 7, and eventually become a standard approach.

- Collaborative studies are required to address the question of incomplete penetrance in syndromes predisposing to MN.

Declaration of competing interest

The authors declare no conflict of interest.

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