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GATA2 deficiency and related myeloid neoplasms

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Abstract

The *GATA2* gene codes for a hematopoietic transcription factor that through its two zinc fingers (ZF) can occupy GATA-DNA motifs in a countless number of genes. It is crucial for the proliferation and maintenance of hematopoietic stem cells. During the past 5 years, germline heterozygous mutations in *GATA2* were reported in several hundred patients with various phenotypes ranging from mild cytopenia to severe immunodeficiency involving B cells, natural killer cells, CD4⁺ cells, monocytes and dendritic cells (MonoMAC/DCML), and myeloid neoplasia. Some patients additionally show syndromic features such as congenital deafness and lymphedema (originally defining the Emberger syndrome) or pulmonary disease and vascular problems. The common clinical denominator in all reported cohorts is the propensity for myeloid neoplasia (myelodysplastic syndrome [MDS], myeloproliferative neoplasms [MPN], chronic myelomonocytic leukemia [CMML], acute myeloid leukemia [AML]) with an overall prevalence of approximately 75% and a median age of onset of roughly 20 years. Three major mutational types are encountered in *GATA2*-deficient patients: truncating mutations prior to ZF2, missense mutations within ZF2, and noncoding variants in the +9.5kb regulatory region of *GATA2*. Recurrent somatic lesions comprise monosomy 7 and trisomy 8 karyotypes and mutations in *SETBP1* and *ASXL1* genes. The high risk for progression to advanced myeloid neoplasia and life-threatening infectious complications guide decision-making towards timely stem cell transplantation.

Keywords

Genetic predisposition; GATA2 deficiency; Familial MDS; MonoMAC; Emberger syndrome; Monosomy 7; Bone marrow failure

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1. Introduction

Since its initial description in 2011, GATA2 deficiency has been recognized as a major myelodysplastic syndrome (MDS) predisposition syndrome, with nearly 400 patients reported in several case series (Table 1). The phenotypic bias of the reported cohorts with GATA2-related disease exemplifies the clinical heterogeneity of this transcriptopathy disorder. Previously established clinical entities known to be caused by GATA2 mutations include monocytopenia and Mycobacterium avium complex (MonoMAC)/den-dritic cell, monocyte, B and NK lymphoid deficiency (DCML) (MIM #614172) [1–4], Emberger syndrome (MIM #614038) [5,6], and familial MDS/acute myeloid leukemia (AML) (MIM 601626 and 614286) [7]. Additional recurrent manifestations include primary pediatric MDS [8] and chronic neutropenia [9]. However, due to considerable phenotypic overlaps in affected patients these entities are now recognized as a single disorder with pleiotropic manifestations and high risk for myeloid neoplasia [8,10–12]. Experimental and clinical evidence implicates that loss of function of GATA2 leads to aberrant hematopoiesis with resulting myeloid neoplasia, often associated with acquisition of certain cytogenetic aberrations or somatic gain of function mutations.

2. Mechanistic principles

GATA2 is a nuclear regulatory protein, a member of evolutionary conserved family of transcription factors that regulate the expression of multiple target genes by binding to the consensus DNA sequence T/A(GATA)A/G located in numerous promoters and enhancers [13]. GATA1, GATA2, and GATA3 are primarily expressed in hematopoietic cells [1], whereas GATA4, GATA5, and GATA6 are mainly restricted to tissues of mesodermal and endodermal origin, eg, heart and gut [14].

The human *GATA2* gene is positioned on the long arm of chromosome 3 at position 21.3 (3q21.3) and depending on the isoform, it consists of 6 or 7 exons. Its transcription is initiated from the first two exons. The proximal IG exon is exploited in all tissues expressing GATA2, while the distal IS exon is specific for hematopoietic and neuronal cells [15–17]. GATA2 protein contains two highly conserved zinc finger domains (C-ZnF and N-ZnF) responsible for its DNA-binding ability and interaction with other proteins [13]. Additionally, other non-finger domains are distinguished: two transactivation domains, a nuclear localization signal, and a negative regulatory domain [18,19].

GATA2 is highly expressed in immature hematopoietic cells and declines with blood cell maturation. It is crucial for the proliferation and maintenance of hematopoietic stem cells (HSCs) [13,20]. High GATA2 expression was observed in hematopoietic progenitor cells, early erythroid cells, mast cells, and megakaryocytes [20,21]. However, it is not limited to the hematopoietic lineage, as it can be expressed in endothelial cells, fetal liver, fetal heart, placenta, and central nervous system [15,22–24]. *GATA2* gene expression is controlled by a variety of *cis*-regulatory elements including -77kb (human -110kb), -3.9kb, -2.8kb, -1.8kb, and +9.5 kb (containing E-box regulatory site). Those sites can be occupied by multiple factors affecting gene transcription. GATA2 can bind itself to the sites upstream the gene locus leading to positive autoregulation. It selectively occupies -2.8kb site in the

transcriptionally active state in HSCs and progenitor cells, whereas its displacement by GATA1 in erythromyeloid progenitors results in repression of *GATA2* transcription [25,26]. It has been observed that -1.8kb site is required to restrain *GATA2* expression in late-stage erythroblasts in vivo [27]. This dynamic transition of GATA factors expression referred as the “GATA switch” plays a critical role in differentiation of hematopoietic cells. It is responsible for the maintenance of erythroid homeostasis by the transcriptional regulation of multiple erythroid genes [28].

3. Role in leukemic transformation

GATA2 plays a pivotal role in HSCs emergence from hemogenic endothelium in the process called endothelial to hematopoietic transition (Fig. 1) [29]. Subsequently, it is essential for the maintenance and proliferation of HSCs by the complex interactions with a network of other hematopoietic transcription factors, eg, RUNX1, SCL/TAL1, MYB, GFI1, FLI1, LYL1, or PU.1 [21,29]. Balanced expression of GATA2 is essential for proper hematopoiesis and the disruption of its structure and/or activity can contribute to leukemogenesis. GATA2 overexpression is associated with development of AML and correlates with poor prognosis [30]. Among the cases with normal karyotype, GATA2 overexpression coincided with FLT3-ITD, *NPM1* mutations and with *WT1* or *EVII* over-expression [31]. Somatic GATA2 mutations GATA2 are frequent (~10%) in intermediate-risk karyotype AML with biallelic CEBPA mutations and are associated with favorable prognosis. Most of the reported somatic mutations are located within ZF1, with p. Leu321Phe being the most prevalent [32,33]. Confirmed gain-of-function mutation p. Leu359Val (ZF2) had been identified in 10% of cases with chronic myelogenous leukemia (CML) during blast transformation [34]. Furthermore, it has been reported that rearrangement of *GATA2* distal enhancer -77kb, resulting from chromosomal aberrations inv(3)(q21q26.2) or t(3;3)(q21;q26.2) promotes leukemic transformation [35,36]. Through structural repositioning the regulatory element is displaced into close proximity of *EVII*, resulting in its misexpression in hematopoietic stem and progenitor cells (HSPC). This disengagement leads to “somatic” GATA2 haploinsufficiency, consequently disrupting homeostasis of hematopoietic progenitors.

Complete deficiency of GATA2 in a knockout mouse model results in embryonic lethal phenotype due to failure in initial blood cell production [21]. Notably, haploid dose of GATA2 in a haploinsufficient mouse model results in defective HSC production with a 50% reduction of definitive HSC compartment, without the development of MDS or leukemia [37,38]. In the setting of human GATA2 deficiency, it is unclear how germline loss-of-function mutations result in myeloid neoplasms.

4. Hematological presentation of GATA2-related disease

While the common denominator of clinical phenotype are cytopenias and myeloid neoplasms, the initial presentation can be variable. Some patients present early in life with cytopenias, immunodeficiency and hypocellular bone marrow failure, and can experience severe bacterial and viral infections [4,9,11,39-42]. In other patients MDS with excess of blasts (MDS-EB) can develop sporadically without preexisting clinical features or accessory non-hematological phenotypes pointing towards GATA2 deficiency, and without family

history of MDS, possibly attributed to the fact that the initial presentation in such cases might be mild and preceding cytopenias undetected. [7,8,43]. The incidence of *GATA2* deficiency is unknown, however due to the high disease penetrance and intolerance to deleterious mutations in *GATA2* gene (ExAC database: 12 expected, 0 observed loss-of-function mutations), it can be assumed that the majority of mutation carriers will develop hematologic or immunologic problems throughout life (in one study the penetrance was estimated at 90% by the age of 60 years) [12].

Initial hematologic symptoms can include single lineage cytopenias or pancytopenia; however, in contrast to the MonoMAC phenotype, monocytosis can be the initial presenting sign in patients who develop *GATA2*-related MDS [1,8,9,11,12,40-42,44]. In some cases there is evidence of immune dysregulation with respective manifestations such as autoimmune hemolytic anemia or immune thrombocytopenia-like manifestation. Morphological features are also heterogeneous and can involve marrow hypocellularity in patients with cytopenias, and normo- to hypercellular marrow in patients presenting with MDS-EB. Multilineage dysplasia is present in most cases. Other features observed are reticulin fibrosis, reduced numbers of bone marrow B and natural killer (NK) cells, and increased numbers of T-cell large granular lymphocytes. Most patients develop MDS (refractory cytopenia of childhood, refractory cytopenia with multilineage dysplasia, MDS-EB) with high risk of evolution to AML or chronic myelomonocytic leukemia (CMML), while rather small subset presents with de novo AML [7,8,12,45,46]. The prevalence of myeloid neoplasia can be estimated at approximately 75% of mutation carriers, according to the numbers provided in published case series with approximately 378 mutation carriers (Table 1) [6-9,11,12,39,41-43, 45-51]. The median age at onset of myeloid neoplasia ranges between 12 and 35.5 years and on average equals 19.7 years (Table 1). In children and adolescents with primary MDS, *GATA2* deficiency accounts for 7% of all cases, and 15% of patients with MDS-EB. The most common cytogenetic aberrations are monosomy 7 or der(1;7)(q10;p10) leading to a monosomy 7q and a trisomy 1q. Depending on the screening cohort these aberrations can be present in up to 80% of *GATA2*-related MDS patients, with average estimate of ~41% (Table 1). Concurrent cytogenetic lesions in patients with monosomy 7, include trisomy 8, or trisomy 21, while complex karyotypes are generally not observed. Isolated trisomy 8 is the second most common cytogenetic category, with prevalence rates up to 40% and a roughly estimated average of 15% (Table 1). Notably, when investigating consecutive primary MDS cohorts in children and adolescents, 37% of patients with monosomy 7 and 16% of patients with trisomy 8 had an underlying *GATA2* deficiency. In conclusion, monosomy 7 and trisomy 8 karyotypes are associated with *GATA2* deficiency and their presence can serve as diagnostic “red flag” pointing towards underlying *GATA2* deficiency.

5. Immunological features of *GATA2* deficiency

The immunodeficiency phenotypes initially reported in association with *GATA2* mutation included warts, atypical mycobacterial infection, herpes virus infection and fungal disease [3,4,11,12,40,48]. In addition, GM-CSF antibody negative pulmonary alveolar proteinosis autoimmune cytopenias, panniculitis, arthritis and hepatitis and may affect up to 10% of patients. Death from infection or human papillomavirus (HPV) and Epstein-Barr virus

(EBV)-related neoplasia may occur. These presentations have been referred to as MonoMAC or DCML deficiency to describe the immunodeficiency arising from a profound mononuclear cytopenia that can occur in the absence of MDS or AML, or antecedent by decades. Key features include a dendritic cell deficiency and monocytopenia, loss of transitional B cells, absence of CD56bright NK cells, inverted CD4:CD8 ratio and abundance of terminally differentiated CD45RA⁺ CD8⁺ Tcells (so-called T-effector memory RA⁺ or TEMRA cells). Overall, the cellular phenotype is remarkably close to that seen in chronic infection or age-related immunosenescence [70]. Generally, immunoglobulin (Ig) is preserved, although patients can become markedly hypogammaglobulinemic and be treated as common variable immune deficiency (CVID). Even those with apparently normal Ig levels may suffer frequent sinopulmonary infections and derive benefit from Ig infusion therapy, suggesting that their humoral responses are of poor quality.

Prior immune deficiency in a patient with MDS is a very strong indicator that *GATA2* mutation may be present [3,4,40]. However, immune dysfunction is not an invariable feature of *GATA2* mutation. Several cohorts of children and young adults with a high rate of *GATA2*-associated MDS have been described who do not have clinical manifestations of immune dysfunction at the time of diagnosis [7,8]. The question remains open as to whether silent mononuclear cytopenia preceded hematological transformation in these cases or whether abrupt transformation to MDS/AML is possible without any prodromal signs. It is apparent that long-lived plasma cells, memory T cells and stable immunoglobulin affords a significant level of protection to common pathogens, even when bone marrow function is significantly declining. Therefore, it is not surprising that many patients remain without infectious complications unless they are exposed to mycobacterium, H1N1 influenza or other virulent pathogen. Moreover, prospective study of healthy family members carrying *GATA2* mutation, indicates that marked and progressive DCML deficiency can be revealed by immunophenotyping whilst the peripheral blood count remains normal [11]. One study reported that the loss of B cells and their precursors is the most constant feature of *GATA2* deficiency, especially in patients who develop MDS when monocytopenia might be masked by progenitor cell expansion and total lymphocyte counts are maintained by expanding memory T cells [43].

Prospective immunophenotyping of more healthy relatives carrying familial *GATA2* mutation will be required to answer this question definitively. It is possible that declining mononuclear cells may prove a useful adjunct for monitoring such unaffected ‘carriers’. The value of progressively elevated Flt3 ligand and clonal dominance in the bone marrow have also been evaluated in this context. When a relatively healthy individual is identified with *GATA2* mutation, it is desirable to avoid exposure to corticosteroids and immunosuppressive drugs, and suggest regular monitoring of pulmonary function.

6. Extra-hematopoietic manifestations

There is a wide range of dysmorphic features associated with *GATA2* deficiency [1,4-9,11,12]. These include deafness due to congenital sensorineural defect, hypotelorism, epicanthic folds, long tapering fingers, neck webbing, behavioral disorder/ADHD, hypothyroidism, urogenital malformations, uni-/bilateral ptosis or hydrops fetalis. Primary

lymphedema is a common feature and can generally manifest with delayed onset on the limbs or as testicular hydrocele; however, atypical manifestations can also be expected, eg, occurring in the face (Fig. 2). As with immunodeficiency, the occurrence of these features in young patients with MDS should arouse a suspicion of *GATA2* mutation.

7. Mutational background

To date more than 100 different germline mutations in *GATA2* gene had been identified in roughly 400 reported cases [6-9,11,12,39,41-43,45,47-52]. The mutations are scattered throughout the gene but essentially three main types can be specified (Fig. 3). Truncating mutations (stop gain, indel, splice site) prior or within ZF2 are encountered in roughly 60% of reported cases, followed by missense mutations within ZF2 detected in ~30% of patients. Thirdly, noncoding variants within intron 4 (*NM_032638.4*) affecting the +9.5kb regulatory site containing E-box and GATA and ETS elements are detected in up to 10% of patients. Rare aberrations reported in single cases are whole-gene deletions, in-frame deletions, and missense mutations C-terminal of ZF2. Additional reported germline variants of unknown significance (p.Pro41Ala, p.Pro250Ser, p.Pro250Ala) are located outside relevant protein domains. Thus far, only a handful of mutations were functionally studied, including p.Thr354Met, p. Thr355del, p.Ala318Thr, p.Leu321Phe, p.Arg396Gln, p.Thr358Asn, p.Ala350_Asn351ins8, p.Arg361Leu, p.Cys373Arg, p.Leu321Pro, p.Pro304His, and p.Arg330X, which are supposed to be loss-of-function mutations with reduced DNA binding ability and/or transactivation activity [6,7,33,53–55]. Conversely, somatic *GATA2* mutations p.Leu359Val (ZF2) and p.Gly320Asp (ZF1) identified in adult myeloid malignancies were described as gain-of-function mutations [33,56]. Considering these findings, there is an urgent need to perform more mechanistic studies to elucidate the functional consequences of germline *GATA2* mutations.

To date, no significant genotype–phenotype association has been established. Although one study reported a possible association of null mutations with lymphedema and severe infections [39], this association could not be confirmed in other cohort studies [8,57]. It can be estimated that approximately 20%–30% of all germ-line mutations are inherited while others occur de novo [8,10].

8. Clonal evolution and acquired genetic changes

While roughly 75% of *GATA2*-deficient patients develop myeloid neoplasia (Table 1), the drivers of myeloid transformation are not entirely known. Concurrent *ASXL1* mutations have been reported in a number of patients with *GATA2*-related MDS and were postulated as a collaborating event in the development of myeloid neoplasia [47,50,58]. However, this association seems to arise from the bias of monosomy 7, which is the most frequent karyotype in *GATA2*-related MDS. When investigating larger cohorts of patients primary MDS and monosomy 7, there was no difference in the frequency of *ASXL1* mutations between patients with or without germline *GATA2* mutation [59–61]. Other mutations recurrently encountered in *GATA2*-related MDS are gain-of-function hotspot *SETBP1* mutations [60]. These mutations are common in AML, CMML, and atypical CML, and they are thought to act as strong oncogenic drivers [62,63]. Interestingly, analysis of bone marrow

of patients with GATA2-related MDS at the single-cell level revealed a nonrandom nature of clonal evolution, with monosomy 7 developing as an early somatic event that seems to be followed by the acquisition of *SETBP1* and *ASXL1* mutations (Pastor and Wlodarski, unpublished observations).

9. Therapy and prognostic considerations

Early diagnosis of GATA2-deficiency should help limiting the use of non-curative therapies specifically avoiding immunosuppression. It is evident that AML-type chemotherapy should be avoided in GATA2-related advanced MDS due to the underlying immunodeficiency and stem cell defect. The high risk for progression to advanced disease with high-risk karyotypes guides the decision-making towards timely HSC transplantation (HSCT); however, there is no clear evidence to advocate for early an HSCT in *GATA2* mutation carriers who are phenotypically silent. However, it is well accepted that HSCT should be performed before the patients develop MDS-EB with karyotypic abnormalities, severe immunodeficiency with systemic infections, or severe lung disease. The ideal time window for HSCT in GATA2-deficient patients is considered to be during the phase with marrow hypocellularity and before manifestation of severe complications (ie, invasive infections) or development of monosomy 7 and/or blast increase [64–68].

No reliable estimates exist on the outcomes GATA2-deficient patients within prospective cohorts. The National Institutes of Health reported a survival rate of 54% at 4 years after HSCT in 21 GATA2-deficient patients transplanted for myeloid neoplasia or immunodeficiency [12]. Notably, in pediatric consecutive MDS cohorts, when examining *GATA2* mutational status according to MDS subtypes, *GATA2* mutational status did not confer poor prognosis [8]. The comparably favorable 5-year overall survival of 66% in GATA2-deficient children transplanted for MDS with monosomy 7 likely results from the younger age and the lower rate of systemic complications. The preparative regimen for HSCT in GATA2-related MDS can be guided by the known MDS risk factors such as cytogenetic evolution, severity of cytopenias, and advanced disease. These considerations support the need for a close monitoring of patients at risk for the occurrence of any of these complications, with individually tailored surveillance strategies.

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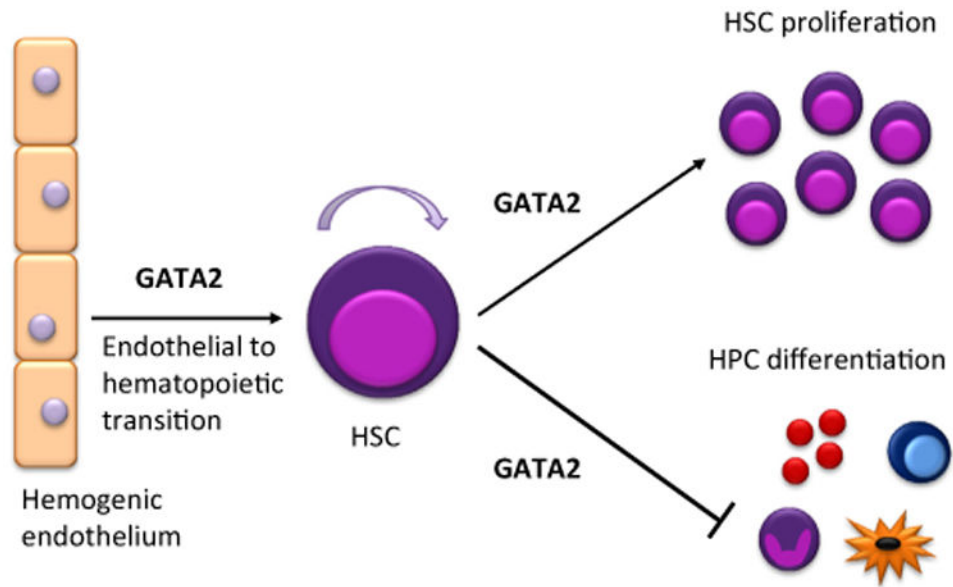


Fig. 1. Mechanistic principles. GATA2 is involved in the emergence of hematopoietic stem cells from hemogenic endothelium. Later, it is essential for the home-ostasis and proliferation of HSCs, at the expense of proliferation of hematopoietic progenitor cells (HPCs).

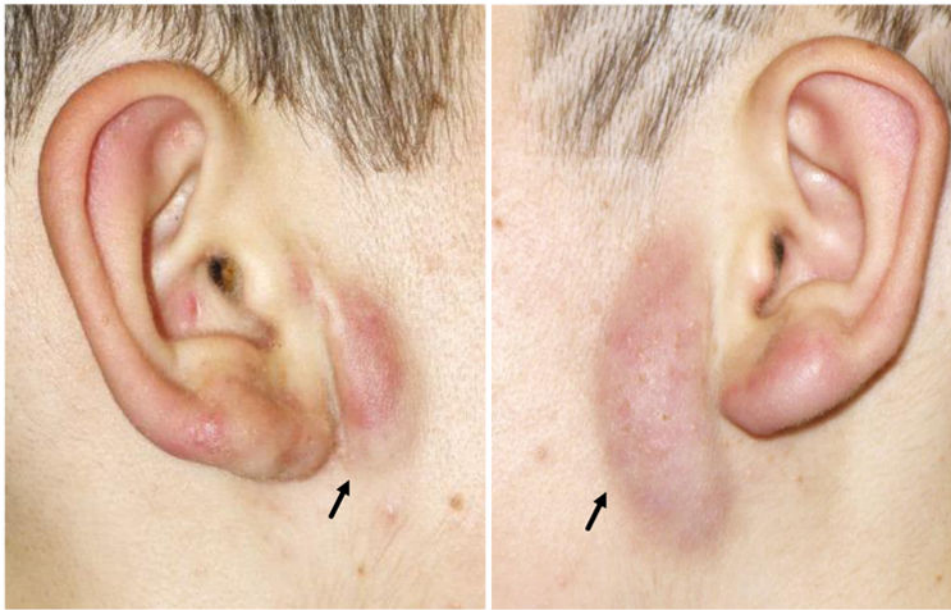


Fig. 2. Atypical lymphedema manifestation in the preauricular region on the face of a teenage patient diagnosed with GATA2 deficiency.

Table 1

Prevalence of GATA-related myeloid neoplasia.

Year reported	Author	PMID	Screening cohort	No. of GATA2-mutated cases	No. of cases with myeloid neoplasia	Age at Dx of myeloid neoplasia; median (range), years	Monosomy 7 & der(1;7), %	Trisomy 8, %
2011	Hahn ⁷	21892162	Familial MDS/AML	28	15	10–53 (20.5)	50	10
2011	Ostergaard ⁶	21892158	Emberger syndrome	14	8	9–53 (12)	75	0
2012	Bodor ⁴⁷	22271902	Familial MDS	5	2	18–23 (20.5)	2/2	0
2012	Kazenwadel ³⁹	22147895	MDS/AML	10	9	10–33 (16)	44	11
2012	Holme ⁴⁵	22533337	Familial MDS	4	4	12–48 (20)	25	0
2013	Pasquet ⁹	23223431	Chronic neutropenia	14	10	6–35 (15)	70	0
2013	Hsu ⁴⁸	23502222	MonoMAC	32	20	3–78 (21.5)	n.a.	n.a.
2014	Spinner ¹²	24227816	GATA2 deficiency	57	42	0.4–78 (19)	21	24
2014	West ⁵⁰	24077845	GATA2 deficiency	48	42	12–78 (35.5)	20	22.5
2014	Dickinson ⁴¹	24345756	GATA2 deficiency	30	11	4–40 (25)	18	18
2015	Mir ⁴²	25619630	Myeloid neoplasms	5	3	7–38 (22.5)	0	0
2015	Ganapathi ⁴¹	25359990	GATA2 deficiency	28	28	14–60 (30)	23	23
2015	Churpek ⁶⁹	26492932	Familial MDS	7	6	13–68 (16.5)	0	25
2015	Wang ⁵¹	26022708	Pediatric MDS	6	5	n.a.	80	20
2015	Zhang ⁵²	25239263	Pediatric MDS	5	5	12–22 (16)	0	40
2016	Wlodarski ⁸	26702063	Pediatric MDS	60	57	3–19 (12)	75	9
2016	Novakova ⁴³	27013649	Pediatric MDS	12	10	4.4–17 (14.5)	80	10
2017	Schlums ⁴⁹	28209719	GATA2 deficiency	13	5	7–60 (18)	n.a.	n.a.
Total/avg				378	282 (75%)	19.7 (12–35.5)	41%	15%

Dx = diagnosis; N.a. = data not available.

* Not included in summary statistics for karyotypes due to low number of reported cases.