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PROGRESS IN HEMATOLOGY

Familial predisposition of myeloid malignancies: Biological and clinical significances of recurrent germline mutations

Heterogeneity of GATA2-related myeloid neoplasms

Shinsuke Hirabayashi[1] · Marcin W. Wlodarski[2,3,4] · Emilia Kozyra[2,5] · Charlotte M. Niemeyer[2,3,4]

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Abstract The *GATA2* gene codes for a master hematopoietic transcription factor that is essential for the proliferation and maintenance of hematopoietic stem and progenitor cells. Heterozygous germline mutations in *GATA2* have been initially associated with several clinical entities that are now collectively defined as GATA2 deficiency. Despite pleiotropic clinical manifestations, the high propensity for the development of myelodysplastic syndromes (MDS) constitutes the most common clinical denominator of this major MDS predisposition syndrome. The immunological phenotypes can be variable and mostly include deficiency of monocytes and/or B cells. Thus far, nearly 380 GATA2-deficient patients had been reported, with a roughly estimated prevalence of myeloid neoplasia of at least 75%. The most common abnormal karyotypes associated with *GATA2*-related MDS are monosomy 7, der(1;7) and trisomy 8. The overall clinical penetrance seems to be nearly complete for this transcriptopathy disorder. The high-risk MDS subtypes and karyotypes, and the underlying immunodeficiency guide decision-making toward timely stem cell transplantation.

✉ Shinsuke Hirabayashi
hirabayashi-slh@umin.ac.jp

[1] Department of Pediatrics, St. Luke's InternationalHospital, 9-1, Akashi-cho, Chuo-ku, Tokyo 1048560, Japan

[2] Department of Pediatrics and Adolescent Medicine, Division of Pediatric Hematology and Oncology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[3] German Cancer Consortium (DKTK), Freiburg, Germany

[4] German Cancer Research Center (DKFZ), Heidelberg, Germany

[5] Faculty of Biology, University of Freiburg, Freiburg, Germany

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Introduction

Historically, familial myelodysplastic syndromes (MDS)/acute myeloid leukemia (AML) with nonsyndromic manifestation have been occasionally described in association with monosomy 7 karyotypes [1]. Germline mutations in genes coding for transcription factors CEBPA and RUNX1 were discovered as the cause of autosomal dominant familial MDS/AML syndromes, but the genetic cause remained obscure in many reported pedigrees. In 2011, loss-of-function (LOF) mutations or deletions in the *GATA2* gene were identified as the third major MDS/AML predisposition syndrome [2]. Strikingly, at almost same time, germline *GATA2* mutations were brought in association with other clinical entities, namely the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome [3], dendritic cell, monocyte, B and NK lymphoid (DCML) deficiency [4] and primary lymphedema associated with predisposition to acute myeloid leukemia (Emberger syndrome) [5]. Finally, GATA2 deficiency had been identified as the most common known genetic cause of primary childhood MDS, where the majority of affected cases had negative family history [6]. Today, it is well accepted that all these clinical manifestations belong to the broad spectrum of a single genetic disease.

Patients with inherited bone marrow failure disorders (IBMFS) such as Fanconi anemia and severe congenital neutropenia have an increased risk of MDS/AML, and a differential diagnosis of IBMFS is important for treatment stratification [7]. From this point of view, the exclusion of germline *GATA2* mutations and other familial MDS/AML

predisposition syndromes clearly also has an impact on therapy recommendations and family counseling. These aspects are now addressed in a new chapter on myeloid neoplasms with germ line predisposition, included in the 2016 revision of the WHO classification of hematological malignancies [8].

In this review, we summarize key information on myeloid neoplasms originating from germline *GATA2* mutation.

Role of GATA2 in normal and malignant hematopoiesis

The *GATA2* gene encodes a chief hematopoietic transcription factor that through its 2 zinc finger domains (ZF) can occupy GATA DNA motifs in several thousand genes [9]. While ZF1 is thought to be involved in protein–protein interaction, ZF2 can control transcription through protein-DNA binding. GATA2 plays a critical role in hematopoietic development as it controls the transition from hemogenic endothelium to hematopoietic stem cells (HCS) and is required for HSC survival and self-renewal, through cooperative processes involving other transcription factors (Fig. 1) [9]. GATA2 itself cooperates in a complex network of transcription factors (TF), and depending on the stage of hematopoiesis it can be activated or repressed by other TF, as well as control the expression of other TF crucial for lineage development. Homozygous Gata2 knock-out mice exhibit embryonic lethality due to the failure of definitive hematopoiesis [10]. Heterozygous knock-out Gata2 mice demonstrate compromised HSC longevity, leading to reduced numbers of progenitor cells, with no occurrence of MDS or leukemia [11].

Genetic causes of GATA2 deficiency

The *GATA2* gene is located the long arm of chromosome 3 at position 21.3. Retrospectively, the first report likely depicting GATA2 deficiency in context of a large interstitial microdeletion (3q21.1-q21.3) was reported in 2008 [12]. Three major types of monoallelic mutations are known to cause GATA2 deficiency: truncating or splice site mutations leading to premature translation termination prior or within ZF2, missense mutations within ZF2, and noncoding variants in the +9.5 kb enhancer region of intron 4. In addition, small in frame or whole gene deletions are encountered on single occasions. The typical mutational landscape in an exemplary cohort of patients with GATA2-related pediatric MDS [8] is depicted in Fig. 2. Overall, the mutations seem to result in haploinsufficiency. LOF-effect was demonstrated for the ZF2 mutations Thr354Met and Thr355del found in familial MDS/AML [2]; Arg361Leu and Cys373Arg in Emberger syndrome [5]. Noncoding GATA2 variants in intronic regulatory region leading to haploinsufficiency were initially reported by Holland's group [13, 14] in the +9.5 intronic region that acts as GATA2 transcriptional enhancer [15]. Notably, 10.5% of patients with pediatric MDS and *GATA2* mutation carried these noncoding variants (Fig. 2). The term GATA2

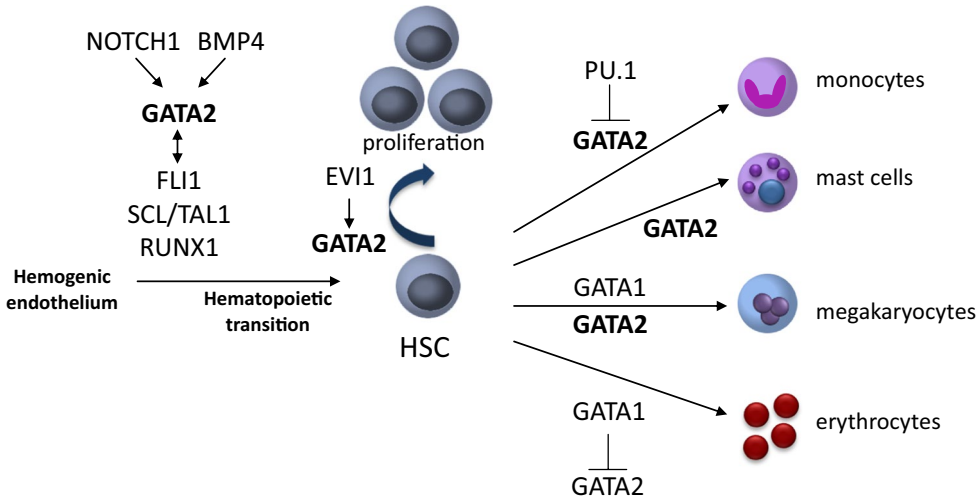

Fig. 1 GATA2 and related transcription factors in hematopoietic development. GATA2 plays a pivotal role in emergence of hematopoietic stem cells from hemogenic endothelium in the process called endothelial to hematopoietic transition (ETH). In this process GATA2 expression is regulated by NOTCH1 and BMP4, interacting with other hematopoietic players, involving FLI1, SCL/TAL1 and RUNX1. Additionally, the HSC proliferation is controlled by EVI1, which binds to the GATA2 promoter as an enhancer. While in monocytic and erythroid development, GATA2 expression is switched off or displaced by other transcription factors, GATA2 is involved in the differentiation of mast cells and megakaryocytes

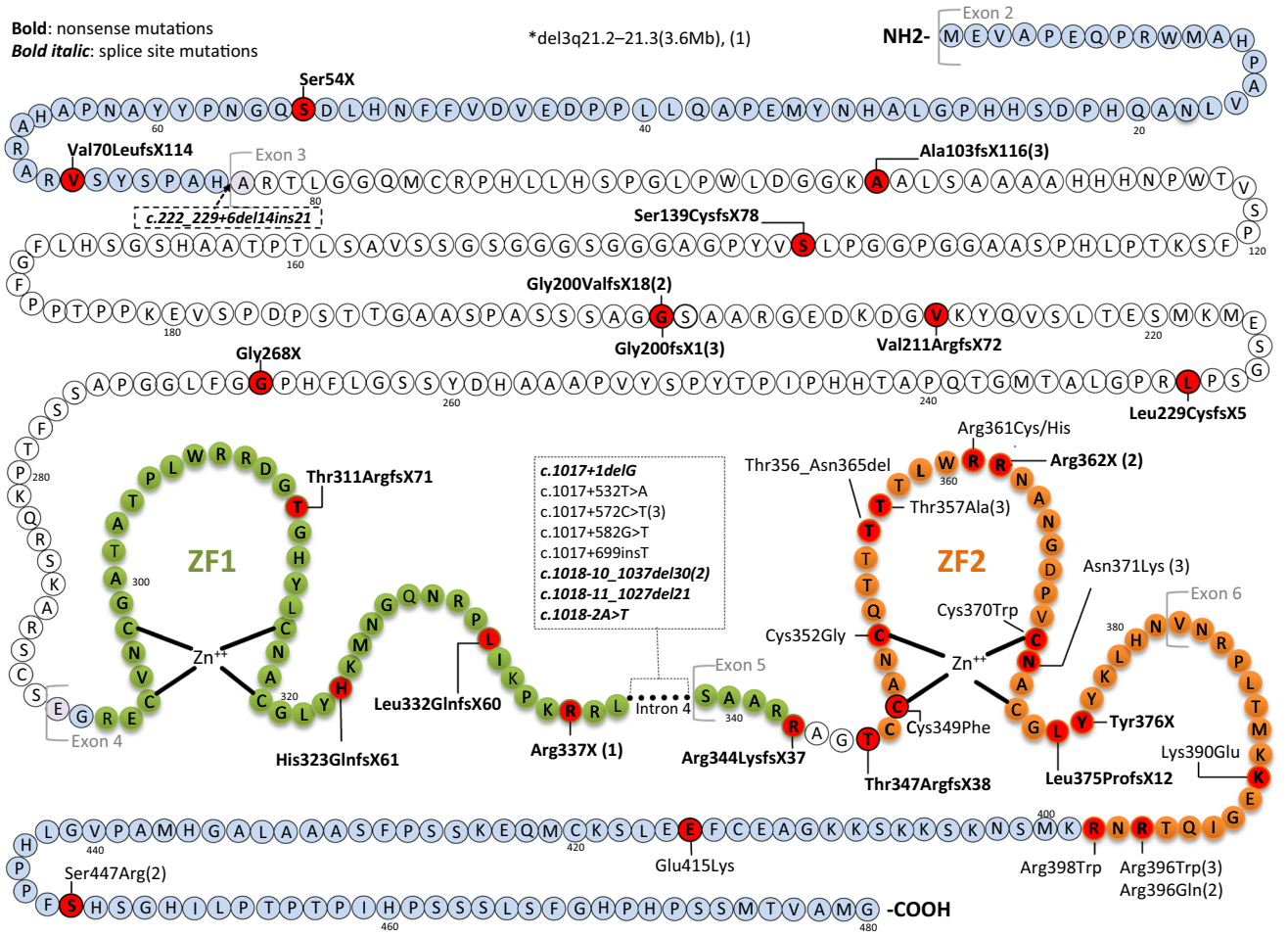

Fig. 2 *GATA2* germline mutations in children and adolescents with MDS. Structure of GATA2 protein with two functionally important zinc finger (ZF) domains marked in green (ZF1) and red (ZF2). 42 germline *GATA2* mutations are depicted, as previously reported by Wlodarski et al. [6]. *Red-color circles* represent affected amino acids. *Numbers* in *brackets* indicate the numbers of cases with a particular variant. *Bold font* denotes nonsense mutations, whereas *bold italic font* demonstrate splice site mutations

deficiency or haploinsufficiency has been widely accepted to describe GATA2-related disorders. On the other hand, somatic *GATA2* mutations in adult AML can occur in both ZF regions with preference for ZF1 [16, 17] and can exhibit both loss- or gain-of-function effects [16, 18, 19]. Generally, only one *GATA2* allele is affected in carriers and (unlike for *DDX41* or *RUNX1*) secondary somatic *GATA2* mutations are not detected. However, in one study, two heterozygous mutations Thr358Asn and Leu359Val were identified *in-cis* in an individual from a family presenting MDS/AML [20]. Interestingly, Leu359Val mutation displayed significant gain of function [21]. The current diagnostic workup for suspected GATA2 deficiency should include Sanger- or NGS-based analysis of the coding sequence, intron 4 enhancer, and copy number analysis to rule out *GATA2* gene deletion. It is important to note that for the confirmation of germline status, skin fibroblasts or hair follicles offer the optimal source for germline DNA, while the use of buccal swabs might not be valid due to contamination with blood leukocytes (and in case of a positive result does not prove if the mutation is truly germline).

Clinical phenotype of GATA2 deficiency

Long-term observation of patients and family carriers in several patient cohorts allows to construct a provisional model of GATA2 disease evolution (Fig. 3). After uneventful pregnancy, birth and preschool years, *GATA2*-mutation carriers can develop progressive cellular deficiency (e.g., of monocytes, B-, NK-cells) and cytopenias (Fig. 3; Table 1). This can continue for a few to tens of years and eventually, in the adulthood culminate in leukemic progress with the development of AML or other type of myeloid neoplasia. Notably, in children, the disease can take an "alternative" course where MDS can develop all of a sudden after

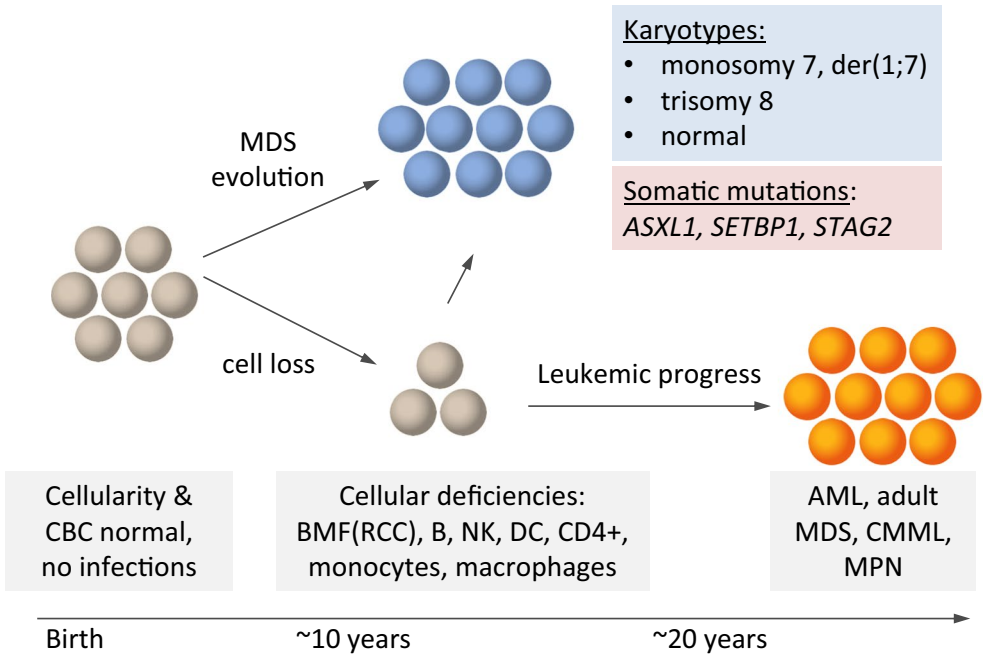

Fig. 3 Evolution of MDS in GATA2-deficient background. As a result of GATA2 haploinsufficiency, stem cell exhaustion can develop over the course of decades and result in cellular deficiencies defining the immunodeficiency phenotype. Additionally, either as an independent clinical phenotype, or during later disease stages following hypocellular stage, myeloid neoplasia can develop and be associated with accumulation of specific cytogenetic abnormalities or somatic mutations. Bone marrow cellularity in GATA2-deficient bone marrow likely changes according to disease stage

Table 1 Non-hematologic disease spectrum

Systemic infections: mycobacterial (non-tuberculous), fungal, viral (herpesviruses)
HPV-associated disease: generalized warts, intra-epithelial neoplasia
Autoimmune manifestations (i.e., lupus-like, AIHA, ITP, arthritis, hepatitis)
Pulmonary alveolar proteinosis, BOOP-like disease, abnormal lung function
Lymphedema: extremities, genital (hydrocele), cellulitis
Thrombosis (deep vein)
Congenital deafness
Hypotelorism, epicanthis folds, uni/bilateral ptosis
Urogenital malformations (VUR, kidney asymmetry, hymen imperforatum)
Behavioral problems, autism spectrum disorders, chronic headache

unremarkable clinical history. However, preexisting immunodeficiency was shown to be retrospectively present in at least 50% of GATA2-carriers who developed MDS, pointing to the possibility of preexisting immuno-cytopenias might be present in more patients [6]. Depending on the studied patient cohort, the median age at diagnosis for roughly 380 cases in the literature was shown to be in range from 12 to 35 years (average 19.7 years), with 75% of carriers developing myeloid neoplasia [22]. The most common karyotypes were monosomy 7 or der(1;7) found in 41% of all carriers (with predilection for pediatric cohorts where 75–80% of cases acquire this karyotype), and trisomy 8 detected on average in 15% of reported cases [22]. It is worth to remark that del5q and complex karyotypes are generally not encountered in GATA2 deficiency.

Dysmorphic features can be present in some but not all affected patients, and include congenital deafness, facial anomalies, urogenital malformations; behavioral problems such as autism spectrum disorders can be also present. Other non-hematologic disease manifestation is variable: some patients may develop pulmonary problems, autoimmune symptoms (e.g., lupus-like disease, immune cytopenias), thrombosis, and generalized warts and HPV-related cancers (Table 1). In summary, hematopoietic, immune, lymphatic, vascular, urogenital, and neurological systems can be affected by GATA2 deficiency. The overall penetrance for hematologic malignancy is very high, and for the occurrence of any of the specific disease symptoms is nearly complete.

MonoMAC syndrome/DCML deficiency

Immunodeficiency was the leading medical problem in the initial cohorts described with *GATA2* mutations: autosomal dominant and sporadic monocytopenia and mycobacterial

infection (MonoMAC) syndrome [3], dendritic cell, monocyte, B and NK lymphoid (DCML) deficiency [4] with predisposition to MDS/AML. Generalized warts related to HPV infection were common viral complication, in addition to severe HSV, VZV, EBV and CMV infections. Disseminated non-tuberculous mycobacteria (NTM) infections were observed in about half of cases with MonoMAC syndrome [23]. Severe bacterial or fungal infections, and pulmonary alveolar proteinosis (PAP) were also prevalent in MonoMAC syndrome. Notably, after HSCT, the rates of infections and PAP can significantly decrease [24].

Emberger syndrome

The association of primary lymphedema and predisposition to MDS/AML with or without congenital deafness by autosomal dominant inheritance was reported by Emberger et al. [25]. Germline *GATA2* mutations were identified as a single common denominator by whole exome sequencing [5]. GATA2 protein is expressed at high levels in endothelial cells and lymphatic vessel valves [26, 27] and controls the expression of PROX1 and FOXC2 genes important for programming lymphatic valve development [28]. In one study, it has been suggested that N-terminal frameshift mutations or larger deletions of *GATA2* are more likely to cause lymphedema [23]; however, this association could not be confirmed in other patient cohorts [6]. Congenital deafness is presumed to result from failure of generation of the perilymphatic space surrounding the semicircular ducts in inner ear [29].

Familial MDS/AML

Germline *GATA2* mutations were detected in four pedigrees with an autosomal dominant inheritance pattern of MDS/AML in 2011 [2]. Variable clinical manifestations were shown in large pedigrees [30]. It is not understood, however, why some patients develop MDS while carriers of identical mutations in the same family do not develop relevant hematologic symptoms.

Pediatric MDS

Our group has screened more than 600 cases of primary or secondary MDS in children and adolescents who were enrolled in the European Working Group of MDS in childhood. The overall frequency of germline *GATA2* mutations was 15% for advanced and 7% for all primary MDS cases. Surprisingly, 72% of adolescents diagnosed with MDS and monosomy 7 harbor germline mutations in *GATA2*. Conversely, mutations were absent in the group with secondary MDS that was therapy related or occurred after aplastic anemia. We propose that *GATA2* screening should be included in the workup of all children and young adults with monosomy 7, trisomy 8, or independent of karyotype if presenting with features suspicious for GATA2 deficiency [6, 31]. Interestingly, in pediatric MDS cohorts, not monocytopenia but B-cell lymphopenia (including progenitors in bone marrow) was identified as the most consistent immunological feature [32, 33]. This might be due to the fact that true functional monocytopenia might be masked by the expansion of malignant myelo-monocytic lineage in the setting of MDS with monosomy 7.

CMML/JMML

Monocytopenia has been previously proposed as a diagnostic feature of GATA2 deficiency. However, some patients with GATA2-related MDS can present with monocytosis rather than monocytopenia [6, 34]. Somatic *ASXL1* mutations are associated with the presence of monosomy 7, BM hypercellularity and CMML [35]. Furthermore, several (rare) cases of adult CMML disease were reported in germline *GATA2* mutation carriers. GATA2 deficiency seems not to play a role in the pathogenesis of JMML [36].

Aplastic anemia

GATA2 deficiency-associated bone marrow disorder can present with features overlapping with aplastic anemia. Distinguishing GATA2 patients from aplastic anemia is critical for selecting appropriate therapy. Four out of 32 patients with suspected aplastic anemia who had features suspicious for *GATA2* mutations were identified by DNA sequencing [37].

Chronic neutropenia

The analysis of patients enrolled in the French Severe Chronic Neutropenia Registry identified 7 pedigrees with germline *GATA2* mutations who presented with mild chronic neutropenia associated with immunodeficiency and subsequent MDS evolution [38].

Acquired genetic abnormalities in carriers of germline *GATA2* mutations

The mechanism of malignant clonal evolution in GATA2-deficient patients is not understood. First, recurrent karyotype abnormalities involving chromosomes 7 and 8 point to their mechanistic relevance in context of underlying GATA2 deficiency. However, these cytogenetic aberrations are not specific to GATA2 deficiency, as they also can arise in MDS originating from hereditary predisposition syndromes [39]. Second, recurrent loss-of-function

ASXL1 mutations have been described in patients with GATA2 deficiency. However, the presence of *ASXL1* mutations seems to be determined by the underlying karyotype, namely monosomy 7 [40]. This most frequent karyotype in pediatric is associated with *ASXL1* and *SETBP1* mutations, independently of germline *GATA2* mutational status [34, 41]. Similarly to *ASXL1*, the presence of somatic *SETBP1* mutations in GATA2-related MDS seems to be associated with monosomy 7 [42]. From functional perspective, the association of *SETBP1-ASXL1* mutations was postulated as a cooperative mechanism advancing leukemic transformation [43]. Finally, recurrent mutations in *STAG2* gene were identified in several cases with GATA2 deficiency; however, the functional significance is not known [41, 44, 45].

Treatment of myeloid neoplasms with germline *GATA2* mutations

Because the phenotypic heterogeneity is not only evident between different non-related carriers of the same mutation, but also within a single family, it is difficult giving advice on the individual outcomes and recommending tailored treatment strategies. Nevertheless, early diagnosis of GATA2 deficiency can help to avoid unnecessary or toxic therapies, for example, prolonged immunosuppression or AML-type chemotherapy given for advanced MDS. Overall, non-curative therapies should be limited and because of the high risk for evolution of advanced MDS with unfavorable karyotypes, timely HSCT should be suggested as a curative approach. Overall survival (OS) of GATA2-mutated patients transplanted for immunodeficiency was shown to be 54% at 4 years after transplantation in a NIH-based study [23]. In pediatric GATA2 cohorts, 5-year OS was 66% in patients transplanted for MDS with monosomy 7. Notably, OS and outcome of HSCT were not influenced by *GATA2* mutational status [6]. Our findings indicate that GATA2 deficiency itself does not increase transplant-related mortality in affected children (most of the patients received myeloablative regimen due to monosomy 7). Ideally, HSCT should be performed before the development of MDS with excess of blasts, cytogenetic clone, and oncogenic somatic mutations. These factors support the need for a close monitoring of *GATA2* mutation carriers for the occurrence of any of these events.

Concluding remarks

GATA2 deficiency belongs to the disease group of transcriptopathies predisposing to myeloid neoplasia. The heterogenous clinical manifestation, ranging from immunodeficiency, vascular phenotypes, deafness, to sporadic myeloid neoplasia illustrates the pleiotropic function of this master transcription factor. However, many important questions remain unanswered at present. For example, it is not known what drives the development of delayed onset myeloid neoplasia in GATA2-haploinsufficient background. Among many hypotheses, one could speculate that either a chronic pathogen challenge might be toxic to the BM and result in leukemic transformation, or GATA2 deficiency itself results in dose perturbation of other transcription factors such as RUNX1 or PU1 which themselves can act as oncogenes. Another question is what determines the variable clinical expressivity where in one family several affected carriers display varying phenotypes and develop MDS at different age. Thus far, there is no evidence of revertant somatic mosaicism (such as encountered in Fanconi anemia) in GATA2 deficiency; however, other mechanisms that control the rate of allelic expression might be the cause, e.g., epigenetic modulation. Several of these questions should be answered in prospective international studies.

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Author contributions SH and MWW wrote the paper, EK and CMN contributed with conception and figures.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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