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Research paper

MDS-associated mutations in germline *GATA2* mutated patients with hematologic manifestations

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ABSTRACT

Germline mutation in *GATA2* can lead to GATA2 deficiency characterized by a complex multi-system disorder that can present with many manifestations including variable cytopenias, bone marrow failure, myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), and severe immunodeficiency. Penetrance and expressivity within families is often variable. There is a spectrum of bone marrow disease in symptomatic cytopenic patients ranging from hypocellular marrows without overt dysplasia to those with definitive MDS, AML, or chronic myelomonocytic leukemia. Relatives of probands with the same mutations may demonstrate minimal disease manifestations and normal marrows. A comprehensive clinical, hematological and genetic assessment of 25 patients with germline *GATA2* mutation was performed. MDS-associated mutations were identified in symptomatic GATA2 patients both with overt MDS and in those with hypocellular/aplastic bone marrows without definitive dysplasia. Healthy relatives of probands harboring the same germline *GATA2* mutations had essentially normal marrows that were overall devoid of MDS-associated mutations. The findings suggest that abnormal clonal hematopoiesis is a common event in symptomatic germline mutated *GATA2* patients with MDS and also in those with hypocellular marrows without overt morphologic evidence of dysplasia, possibly indicating a pre-MDS stage warranting close monitoring for disease progression.

1. Introduction

GATA2 is a zinc finger transcription factor important for the production and maintenance of hematopoietic stem cells both in the embryo and during adult definitive hematopoiesis. It activates its own expression and thus hematopoietic cells are extremely sensitive the levels of GATA2 [1]. GATA2 binds to several downstream targets including *SPI1* (PU.1), *LMO2*, *TAL1*, *FLI1* and *RUNX1* [2]. In humans, germline mutations have been shown to be the cause of the disorder known as GATA2 deficiency. Mutations across the gene, including missense, frameshift, nonsense, deletions, and regulatory variants lead to haploinsufficiency and disease state [3].

Germline mutations in *GATA2* are associated with widespread defects in the immune, pulmonary and vascular systems [1]. Hematological manifestations, in particular myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and chronic myelomonocytic leukemia

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Table 1
Patient Characteristics.

Patient #	Sex	Mutation Type	GATA2 Genotype	Age at Sample Collection	Bone Marrow Pathology	Cytogenetics	HPV	NTM	Lymphedema	PAP	W	F
1	F	Missense	p.R398W	23	MDS	Normal	+	+	+	-		1p
2	F	Missense	p.R398W	37	MDS	tri1q,-x,tri8	+	+	-	-		U
3	M	Missense	p.R361H	23	MDS	Normal	+	+	-	+		U
4	F	Missense	p.T372A	44	MDS	Trisomy 8	+	-	-	-		U
5	M	Unknown	Unknown#	25	MDS	Trisomy 8	+	-	-	-		U
6	M	Missense	p.R396Q	32	MDS	Normal	+	-	-	-	*	U
7	F	Stop Gain	p.R330*	27	MDS	Trisomy 8	+	-	-	-	*	2p
8	F	Stop Gain	p.R330*	27	MDS	Trisomy 8	+	-	-	-	*	2p
9	F	Stop Gain	p.G268*	53	MDS	13q deletion	+	-	+	+		U
10	F	Frameshift	p.G199Lfs21	49	MDS	9q deletion	+	+	-	-	*	U
11	F	Missense	p.R396W	28	MDS	Normal	+	+	+	-		U
12	F	Missense	p.R396Q	15	G2BMID	Normal	-	-	-	-	*	U
13	F	Frameshift	p.V140Cfs*44	26	G2BMID	Normal	+	-	-	-		U
14	M	Stop Gain	p.R362*	17	G2BMID	Normal	+	-	-	-		U
15	F	Stop Gain	p.R362*	23	G2BMID	Normal	+	-	-	-		U
16	M	Missense	p.A341P	25	G2BMID	Normal	+	-	-	-		U
17	M	Regulatory	intron 5 c.1017 + 572C > T	41	G2BMID	Trisomy 8	+	+	-	-		U
18	M	Missense	p.G346S	20	G2BMID	Normal	-	-	-	-		U
19	F	Regulatory	intron 5 c.1017 + 572C > T	60	Normal	Normal	-	-	-	-		3
20	F	Regulatory	intron 5 c.1017 + 572C > T	31	Normal	Normal	-	-	-	-		3
21	F	Regulatory	intron 5 c.1017 + 572C > T	51	Normal	Normal	-	-	-	-		3
22	M	Missense	p.R398W	54	Normal	Normal	-	-	-	-		1
23	M	Regulatory	intron 5 c.1017 + 572C > T	61	Normal	Normal	+	-	-	-		U
24	M	Regulatory	intron 5 c.1017 + 572C > T	81	CMML	Normal	+	-	-	-	*	U
25	M	Missense	p.T354M	7	Hypocellular	Normal	-	-	-	-		U

NTM = non-tuberculous mycobacterial infection.
PAP = pulmonary alveolar proteinosis.
# = GATA2 mutation in patient 5 was not determined by CLIA Sanger sequencing, alternative method used (manuscript in preparation).
W = *Reported in West et al., new specimen for this study.
F = Unique (U) or part of a family 1, 2, 3; p indicates the proband, family 2 probands are monozygotic twins, family 3 proband was not included in this cohort.
G2BMID = GATA2 deficiency related bone marrow and immunodeficiency disorder.
CMML = chronic myleomonocytic leukemia.

(CMML) are common. Indeed, some early GATA2 deficiency cohorts were first identified as familial MDS/AML [4]. It has been described as Emberger syndrome (MDS with lymphedema) [5], DCML deficiency (dendritic cell, monocyte, B, and natural killer (NK) lymphoid deficiency) [6] and as an immunodeficiency with bone marrow failure [7]. A subset of patients with germline *GATA2* mutations may present with hypocellular marrows that have features overlapping with aplastic anemia and bone marrow failure syndromes [8].

Both *de novo*, idiopathic, and GATA2-associated MDS, are characterized by dysplasia, ineffective hematopoiesis and a variable risk of progression to AML. We sought to characterize the hematological abnormalities seen in GATA2 patients who presented with infections and immunodeficiency without overt marrow dysplasia, and compare to those who presented at the MDS stage. We identified that patients had a range of hematological abnormalities including MDS, but also an intermediate borderline dysplastic state we termed GATA2 deficiency related bone marrow and immunodeficiency disorder (G2BMID). Patients with both MDS and G2BMID had similar MDS-like cytogenetic changes and mutational events, however cytogenetic abnormalities were primarily seen in MDS.

2. Methods

2.1. Patients and Sample Collection

Twenty-five sequential patients who presented to the National Institutes of Health (NIH) for evaluation on the "Natural History of GATA2 Deficiency" (NCT01905826) protocol were studied. Clinical meta-data was obtained from the NIH electronical medical record system. CLIA certified Sanger sequencing was used for *GATA2* mutation confirmation. Bone marrow biopsy and aspirate samples were evaluated by histopathology, immunohistochemistry and flow cytometry, and reviewed by board certified hematopathologists. Standard clinical cytogenetic analysis was performed on bone marrow aspirates. Genomic DNA was isolated from bone marrow, skin fibroblasts and buccal cell samples using Qiagen DNA/RNA AllPrep Mini Kit.

2.2. Sequencing

DNA sequencing of genes commonly mutated in MDS and/or AML was performed on 100 ng of genomic DNA extracted from bone marrow aspirate samples using the ThunderBolts™ Myeloid Panel (RainDance Technologies, MA) which covers 49 gene regions using 548 amplicons (Supplemental Table 1). Libraries from 16 samples were barcoded and sequenced as paired-end 300bp on a MiSeq using reagent kit v3 (Illumina, CA). Results were analyzed with NextGENe version 2.4.2.1 (SoftGenetics, PA) aligning to Human reference genome GRCh37.p10, referencing Human RefSNPs dbSNP135, removing known panel artifacts and restricting to variants with likely missense, in-frame, frameshift, and nonsense functional consequence. The filtered variants were nonsynonymous, SNP/Indel with a CADD phred score > 15 and minimum coverage depth of 700 reads. Likely heterozygous inherited single nucleotide polymorphisms (variants with allele frequency 40-60%) were removed if found within 1000 Genomes > 1% or > 5% if the variant was also in the COSMIC database (cancer.sanger.ac.uk/cosmic) (see Supplemental Table 2). Variants were annotated using ANNOVAR [9]. Sanger sequencing of buccal or skin fibroblast DNA was also used in some cases to remove likely SNPs. Thirty percent of the variants were Sanger sequenced and all, but one were confirmed (24%) (see Supplemental Table 2). The unconfirmed variant was removed from the analysis.

3. Results

3.1. Patient characteristics

We performed comprehensive hematological assessment and mutational analysis in 25 consecutive subjects with germline *GATA2* mutations who presented to the NIH Clinical Center due to a personal or family history of primary immunodeficiency, and/or cytopenias (Table 1). All patients were evaluated on an IRB-approved protocol. Patients ranged in age from 7-81 years at the time of assessment with most being in the third and fourth decade of life. Fifty-seven percent of the patients were female. Germline *GATA2* mutations were determined by CLIA (Clinical Laboratory Improvement Amendments)-certified Sanger sequencing in 24 patients. Mutations included missense (11/24, 46%), frameshift (2/24, 8%), stop gain (5/24, 21%) and regulatory (6/24, 25%) mutations; all mutations cause haploinsufficiency of GATA2. Patients had a variety of clinical phenotypes including GATA2-related human papilloma virus (HPV) (72%) and non-tuberculous mycobacterial (NTM) infections (24%) (Table 1). Three families are included in this study. The six patients with familial relationships are noted in Table 1 and shown by pedigrees in Supplemental Fig. 1.

3.2. Hematological manifestations in this cohort with germline GATA2 mutation

Peripheral blood cytopenias were common including monocytopenia (72%), lymphopenia (72%), neutropenia (40%), anemia (32%), and thrombocytopenia (8%) (Fig. 1). Bone marrow examinations were performed on all patients. Bone marrow hematological abnormalities were found in 80% of patients including 48% who met the criteria for diagnosis of MDS (n = 11) or CMML (n = 1). Patients, all with germline *GATA2* mutations, were classified into three main groups based on bone marrow histopathology and peripheral blood counts. The groups where comprised of those patients meeting World Health Organization criteria (WHO) for MDS (44%); those subjects without any dysplastic features (“normal”) (20%); and those patients with abnormal bone marrow findings but not meeting WHO MDS diagnostic criteria [10] or having hypocellular marrows with features that overlapped with aplastic anemia (28%). For the purposes of this study we termed this intermediate bone marrow status between normal and MDS as GATA2 deficiency related bone marrow and immunodeficiency disorder (G2BMID) (Table 2, Fig. 2). For G2BMID, the majority of bone marrows showed hypocellularity, atypical megakaryocytes with separated nuclei, and minimal morphologic dyspoiesis in myeloid and erythroid lineages. Micromegakaryocytes were predominantly seen in GATA2 deficiency patients with overt MDS [11]. One patient had CMML and another had hypocellular marrow with no dysplasia (other, 8%). Flow cytometric analysis of the bone marrow aspirates revealed several unusual features in a subset of patients including abnormal myeloid maturation patterns, atypical T-cell populations, CD56 expression on monocytes and plasma cells, as well as abnormal immunophenotype of CD34 + myeloblasts (e.g. CD7 expression or absence of CD38 expression). As a group those subjects with MDS or G2BMID were statistically more likely ($p < 0.05$) to have low NK, DC, hematogones and mature B cells in the bone marrow. These findings are similar to that previously reported by Novakava et al., who showed, in children, that low hematogones and mature B-cells is a consistent feature of GATA2 deficiency [12].

Those identified with germline *GATA2* mutations who appeared unaffected hematologically were, on average, older (median: 54 years, range 31-61) than those with G2BMID (median: 23 years, range: 15-41) or MDS (median: 28 years, range: 23-53). These hematologically unaffected subjects shared a germline *GATA2* mutation with a family member with immunodeficiency and hematological abnormalities. Of note, 3 of 5 individuals classified as unaffected were from the same family pedigree (Table 1, Supplemental Fig. 1). No abnormal cytogenetics were observed amongst the unaffected subjects who had bone marrow with normal morphology, and only one subject in this group had overt HPV infection.

In contrast, MDS and G2BMID patients had clear clinical phenotypes, including the well described GATA2 related infections HPV (100% of MDS and 78% of G2BMID) and NTM (45% of MDS and 14% of G2BMID). Both MDS and G2BMID patients had profound deficits in absolute monocyte, NK cell and lymphocyte counts (Fig. 1). For other lineages, a spectrum of hematological deficiency was observed. Anemia in the MDS group was more common (64% vs. 14% had hemoglobin less than 10 g/dL) and slightly more severe (median: 8.7 g/dL, range 7.3-14.7 vs. median: 11.3 g/dL, range: 8.5-15) than in G2BMID

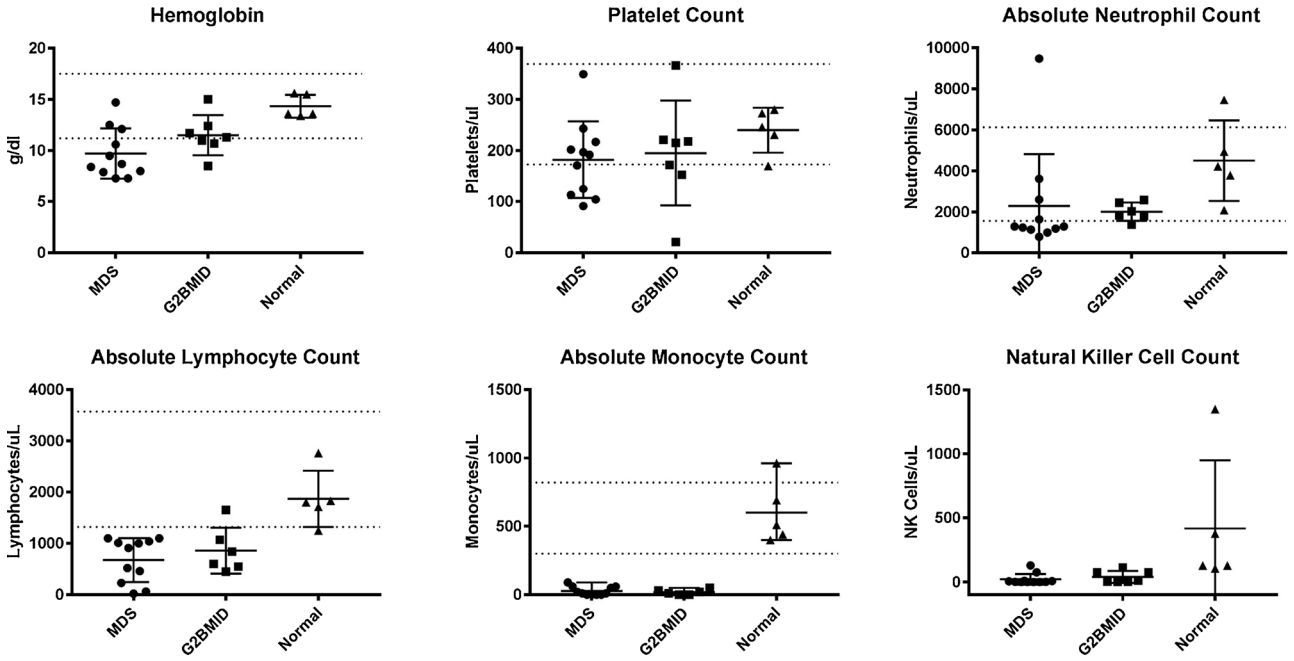

Fig. 1. Peripheral blood parameters for the all GATA2 patients included in this cohort. CBC and lymphocyte subset data shown here was taken the day of the bone marrow aspirate collection. Dotted lines represent laboratory normal values. Standard deviation error bars as shown.

Table 2
Pathology.

Bone Marrow Histopathological Categories	
Category	Major Findings
Normal	Trilineage hematopoiesis at age appropriate cellularity
GATA2 deficiency related bone marrow and immunodeficiency disorder (G2BMID)	Hypocellular a typical megakaryocytes minimal dyspoeisis
MDS	WHO diagnostic criteria met MDS- SLD, MLD or U with germline predisposition

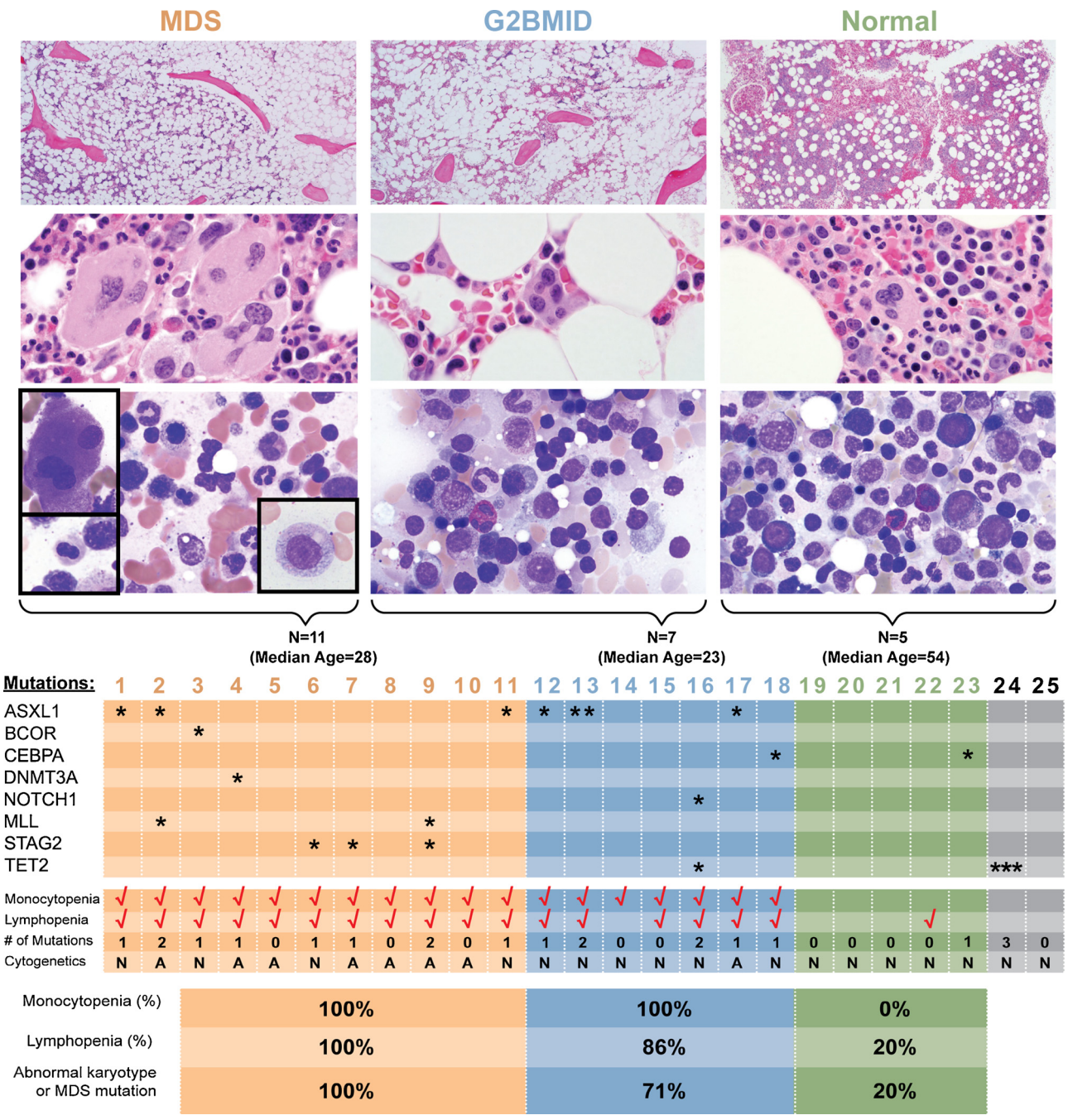

Fig. 2. GATA2 deficiency patients show significant bone marrow abnormalities, peripheral cytopenias, cytogenetic changes, and the presence of MDS-associated mutations in the bone marrow. GATA2 deficiency patients in this cohort where divided by bone marrow pathology- MDS (orange labels), G2BMID without overt dysplasia (blue labels), or normal (green labels). Representative histology for each category is shown. Grey labels are patients with other hematological abnormalities (see Table 1). ★= variant identified, number of stars corresponds to the number of variants identified. Variant details in Supplemental Table 2. √=cytopenia identified, monocytes < 300/μl or lymphocytes < 1320/μl. N = normal bone marrow cytogenetics A = abnormal cytogenetics (see Table 1 for details).

patients. Neutropenia was also more common (73% vs. 29%) and slightly more severe (median: 1290, range: 790-9480 vs. median: 1930, range: 1380-2590 cells/μl) in MDS than in G2BMID patients (Fig. 1). The rates of HPV and NTM in this cohort is higher than reported in the French/Belgian GATA2 cohort recently published by Donadieu and colleagues [13]. While the rates of cytopenias are similar between the two studies, more monocytopenia and NK cell cytopenia are seen in our cohort.

3.3. MDS-associated mutations are common in GATA2 deficiency patient bone marrow

Most patients had normal bone marrow cytogenetics (68%, 17/25) (Fig. 2). The most common abnormality in this cohort was isolated trisomy 8 (5/8) (Table 1). This is in contrast to other cohorts in which monosomy 7 was the most common cytogenetic abnormality [1]. This may represent a bias to less severe hematological phenotype in this cohort. Cytogenetic abnormalities were most common amongst patients with MDS (7/11) and only one G2BMID patient had an abnormality (1/7).

Sequencing of regions within 49 genes commonly mutated in MDS and/or AML (Supplemental Table 1), was performed on DNA extracted from bone marrow aspirate samples. Variants were found in 73% (8/11) of patients with MDS and 71% (5/7) of G2BMID patients, but only in one subject with normal bone marrow histology and without cytopenia (1/5) (Fig. 2). Variants predicted to be deleterious were found in DNA modification, chromatin regulation, transcriptional regulation, cohesion, and cell signaling genes (Supplemental Table 2). *ASXL1* mutations were seen in 33% (6/18) of MDS and G2BMID patients, consistent with previous reports [14]. *STAG2* mutations were common (3/11) in the MDS group. Two patients had *CEBPA* mutations and two had *MLL* mutations identified. The *MLL* variants identified were missense, and not the more typical fusions seem in AML. Two patients with *TET2* mutations were identified, and one with CMML had three distinct *TET2* mutations identified. Most patients (89%, 16/18) with bone marrow abnormalities had either an MDS-associated mutation and/or an abnormal karyotype regardless of whether the patient had WHO defined MDS or G2BMID.

4. Discussion

We have shown that hematological abnormalities and MDS-associated mutations are common in GATA2 deficiency, even when there is no overt morphologic evidence of dysplasia and/or primary immunodeficiency is the predominate presenting clinical manifestation. Germline mutated *GATA2* patients not meeting morphologic criteria for MDS despite cytopenias, hypocellular bone marrows and/or mild dysplasia had a mutation profile and lymphopenia/monocytopenia similar to those with GATA2-associated-MDS and may represent a transitional or equivalent state which we have termed G2BMID. Subjects harboring the fewest MDS-associated mutations were the apparently healthy germline *GATA2* mutated relatives of probands, suggesting that the acquisition of additional mutations may be associated with symptomatic disease. Recent work has shown that the variable penetrance observed in families may be due to the addition of somatic mutations such as *ASXL1*, and dynamic epigenetic reprogramming which leads to changes in the expression of the mutated allele [15].

The detection of mutations in the bone marrow of G2BMID and hypocellular MDS patients likely represents a combination of disease progression in the context of an oligoclonal bone marrow. The kinetics of stem cell exhaustion occurring due to the deficiency of GATA2 and its known requirement for proper stem cell maintenance versus clonal expansions due to accumulation of MDS-related mutations, or other factors, in the progression to MDS/AML has yet to be elucidated. Additional studies will be needed to determine if the mutations identified change over time, and if they are ultimately prognostic for progression to AML.

There are several limitations to our study. First, we were unable to follow these patients over time to see if the G2BMID pathology evolved over time to MDS based on WHO criteria or if MDS evolved to AML and if additional variants were acquired. This was due to lack of sample availability as most patients in the study proceeded to hematopoietic cell transplantation [16]. We were able to review clinical bone marrow biopsy/aspirate pathology reports for 20/25 patients that occurred within two years of the sample included in this study and in all cases confirmed stability of pathological category (MDS, G2BMID or normal). Second, we were able to definitively characterize variants identified here as somatic in only a subset due to lack of non-hematological germline tissue samples (Supplemental Table 2). Thirdly, *in silico* prediction tools were used to assess the likely pathogenicity of these variants, rather than validation with functional assays. Lastly, our cohort has recruitment bias, as most patients and family members were recruited to the NIH cohort based on a history of infections/immunodeficiency. Very few of the patients had lymphedema or pulmonary alveolar proteinosis, which skews the cohort away from Emberger syndrome phenotype.

Overall, 72% of patients in our cohort had either MDS-associated mutations, cytogenetic abnormalities or both. Patients with normal bone marrow morphology did not have variants identified, with one exception. MDS-associated mutations were identified in 15 of 25 patients. These were identified similarly in patients with both MDS and G2BMID. Unlike *de novo* MDS, no splicing factor mutations nor ringed sideroblasts were identified. No cases of AML or late mutational drivers were identified in this cohort. The additional somatic genetics events required for the development of AML remain incompletely understood in germline mutated *GATA2* patients.

Others have identified mutations in *SETBP1, ASXL1, STAG2, RUNX1, CBL, EZH2, NRAS/KRAS, JAK3,* and *PTPN11* in a cohort of pediatric GATA2-related MDS cohort [17]. Fisher et al. identified *RUNX1, SETBP1, IKZF1* and *CRLF2* variants in two pediatric GATA2-associated MDS cases [18] Ding et al. described a father-son pair with *GATA2* germline mutation and MDS who both had *STAG2* mutations, but in different genomic locations [19]. Bödör et al. described a patient with MDS, a somatic *ASXL1* mutation and monosomy 7 with poor outcome [20]. Wang et al. identified four GATA2-related MDS patients with additional somatic events including *RUNX1, STAG2, IDH2, TP53, SETBP1* and *NRAS* [21].

The development of MDS in GATA2 deficiency patients is common and occurs at a significantly younger age (median age of 29 years) when compared to idiopathic MDS with typical onset over 60 years of age. The lifetime risk of MDS is estimated at 90%, with 30-50% having MDS at the time of presentation [1]. GATA2 associated MDS is a high-risk pre-leukemic condition with the potential for rapid evolution to AML. Clonal and dyspoietic hematopoiesis with infectious and inflammatory stress seen in these patients, may contribute to the development of marrow failure, dysplasia and malignancy. In this cohort we show that, despite cytomorphological differences in the marrow, that patients with GATA2 related MDS and those with G2BMID have a similar pattern of MDS-associated mutations in the bone marrow. The MDS-associated mutations and karyotypic abnormalities identified here may play a role in driving dysmyelopoiesis and contribute to the potential for leukemic transformation. It is possible that G2BMID represents an evolving or pre-MDS like state, but the rate of progression to MDS or AML in G2BMID patients is currently undefined. We suggest that the combination of clonal and dyspoietic hematopoiesis with infectious and inflammatory stress seen in these patients, contributes to the development of marrow failure, dysplasia and malignancy.

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LJM, YY, HYW, JT, YZ, MM, JD, CP, LF, QL, JZ, APH, WW, RWW and MEY performed the research and data analysis. DDH, DMT, SMH, KRC and CSH supervised the research. LJM, KRC and CSH wrote the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2018.11.013.

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