Spectrum of myeloid neoplasms and immune deficiency associated with germline GATA2 mutations

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Abstract
Guanine-adenine-thymine-adenine 2 (GATA2) mutated disorders include the recently described MonoMAC syndrome (Monocytopenia and Mycobacterium avium complex infections), DCML (dendritic cell, monocyte, and lymphocyte deficiency), familial MDS/AML (myelodysplastic syndrome/acute myeloid leukemia) (myeloid neoplasms), congenital neutropenia, congenital lymphedema (Emberger’s syndrome), sensorineural deafness, viral warts, and a spectrum of aggressive infections seen across all age groups. While considerable efforts have been made to identify the mutations that characterize this disorder, pathogenesis remains a work in progress with less than 100 patients described in current literature. Varying clinical presentations offer diagnostic challenges. Allogeneic stem cell transplant remains the treatment of choice. Morbidity, mortality, and social costs due to the familial nature of the disease are considerable. We describe our experience with the disorder in three affected families and a comprehensive review of current literature.

Introduction
The guanine-adenine-thymine-adenine (GATA) family is comprised of six zinc-finger transcription factors that recognize approximately 7 million GATA motifs in the human genome [1, 2]. GATA1 is instrumental in development of erythrocytes, mast cells, eosinophils, and megakaryocytes [3–8] and is implicated in Down syndrome-related acute megakaryocytic leukemia and transient myeloproliferative disorder [9, 10]. GATA1 is also associated with X-linked thrombocytopenia and dyserythropoietic anemia (Diamond–Blackfan anemia) [75–77]. GATA2, located on 3q21 [11] is pivotal in proliferation of hematopoietic stem cells (HSC) and mutations were first described in aplastic anemia [12–15]. Pedigree studies have initially recognized two mutations in GATA2 in familial AML, p.T354M, and p.T355del, both in the second zinc finger (ZF-2) of GATA2 [16–18], while two other mutations; p.R308P and p.A350-N351ins8 are associated with de novo AML [78]. During erythropoiesis; GATA switching results in displacement of GATA2 by GATA1 from chromatin causing inhibition of GATA2, promoting downstream erythroid differentiation [5, 19]. In contrast, GATA2 overexpression induces megalakaryocytic differentiation in cell lines [20]. GATA2 exerts an inhibiting influence on the PU.1 gene which is essential for monocytic, granulocytic, and lymphoid differentiation [21]. In contrast to RUNXI, which is essential for generation of HSC, GATA2 appears to be essential for HSC generation and subsequent survival [22]. Other GATA genes perform a diverse array of functions. GATA3 promotes T-cell lymphopoesis [23–28] but deficiency has been associated only with hypoparathyroidism, deafness, and renal
GATA4 has recently been implicated in childhood onset diabetes [29]. GATA 5 CpG island hypermethylation in renal carcinoma appear to identify aggressive phenotypes with poor outcomes [30]. In animal models, GATA6 has been shown to orchestrate cardiac muscle hypertrophy in response to pressure stress and increase hepcidin expression in inflammatory states [31, 32]. In summary, GATA factors 1–3 appear to be involved in hematopoiesis, while GATA 4–6 appear to be more important for cardiac development and function [33] although expression has been demonstrated in other endodermal and mesodermal organs such as lung, liver and gonads and gut [34].

The study of germline mutations such as GATA2 provides profound insights into leukemogenesis, immune dysfunction and cross-talk of seemingly diverse genetic pathways such as CEBPA, PU.1 [35–38], and RUNX1 [39–43]. The clinical phenotype of germline GATA2 mutations include, but is not limited to, spectrum of immune deficits such as MonoMAC syndrome [44–46], dendritic cell, monocyte and lymphoid deficiency (DCML) [47], familial MDS (myelodysplastic syndrome)/AML (acute myeloid leukemia), and Emberger’s syndrome [48]. Of note, sporadic mutations in GATA2 are described and may have no familial implications as described below. Our focus in this article is the haploinsufficiency induced by spontaneous germline mutations in GATA2 resulting in an autosomal dominant inheritance of diverse phenotypes [44, 46, 49].

The differential diagnosis of GATA-2 deficiency includes other related disorders with overlapping features and are summarized in Table 1.

### Case Series

#### Family 1

The proband is a 38-year-old Caucasian male, who presented with progressive dyspnea and fatigue of 3 months duration and was found to have pancytopenia. A bone marrow biopsy revealed hypocellular marrow but demonstrated acute myeloid leukemia (AML) with the following cytogenetic abnormalities: t (1; 21) (q10; q10) [9]/+8[4]/46XY [7]. He received standard induction chemotherapy with idarubicin and cytarabine, and his course was complicated by an orbital fungal infection with Absidia litchi, medically and surgically managed, following which he underwent a reduced-intensity conditioning-matched unrelated donor allogeneic stem cell transplant (MUD-Allo-HCT). Posttransplant course was complicated by severe refractory immune-mediated thrombocytopenia requiring a splenectomy and an orbital relapse of AML. Due to history of multiple family members being affected (Fig. 2) by AML and extra genital warts (sister, son, and daughter), congenital lymphedema (son), and cytopenias (sister) a work-up for familial bone marrow failure syndromes was carried out. GATA2 mutation analysis performed at the National Institutes of Health (NIH) confirmed the presence of a missense mutation (1339A>C, p S447R) in the patient, a female sibling, a son, and a daughter. The female sibling with MDS and viral warts also underwent MUD-Allo-HSCT (hematopoietic stem cell transplant) and remains symptom-free 14 months posttransplant. The probands son and daughter also underwent MUD allogeneic HSCT and are doing very well more than 12 months posttransplant. Patient characteristics and outcomes are shown in Table 2.

#### Family 2

Family 2 was discovered by the birth of a newborn with dysmorphic features (head size larger than stomach) resulting in a cytogenetic examination in infancy with identification of deletion 3q13.2-q21.3, which includes the GATA2 gene. The child exhibited monocytopenia without lymphopenia or neutropenia. Dendritic cell activity was not assessed for. The parents were tested and did not have the same gene defect. She is being followed with monthly blood

### Table 1. Mutations/disorders in differential diagnosis of GATA2 deficiency.

| Familial MDS/AML [67] | Warts/HPV infections [51] | Mycobacterial infections [68–70] | Congenital lymphedema [71–73, 75, 76] | Pulmonary alveolar proteinosis [77] |
|-------------------|--------------------------|---------------------------------|---------------------------------|-----------------|
| TERT/TERC         | DOCK 8                   | IFNGR1                          | FLT4                            | Anti-GM-CSF Ab  |
| CEBPA             | CXCR4                    | IFNGR2                          | GJC2                            | CSF2RB          |
| RUNX1             | HIV/CD41                 | IL12RB1                         | FOXC2                           |                 |
|                   | TMC6B                    | STAT1 (loss of function; AR and AD) | SOX18                          |                 |
|                   | SPINK5/LEKT1             | IRF8                            | CCBE1                           |                 |
|                   | STK4/MST1                | CYBB (macrophage-specific mutation) | PTPN14                         |                 |
|                   |                          | TIK2                             |                                 |                 |
|                   |                          | ISG15                            |                                 |                 |
|                   |                          | IKKG (NEMO)                      |                                 |                 |

MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; HPV, human papillomavirus.
Table 2. Clinical characteristics and outcomes of patients with GATA2 mutations that underwent allogeneic stem cell transplantation.

| No. | Diagnosis       | Cytogenetics/GATA2 mutation | Associated features | Prior Rx | HCT-CI | CMV | Regimen                  | ABO/HLA | GVHD Prop | aGVHD Status | Complications                                                                 | Day 30 Chimerism/Marrow | Day 100 Chimerism/Marrow | Last follow up (Days) |
|-----|-----------------|-----------------------------|---------------------|----------|--------|-----|-------------------------|---------|------------|-------------|--------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| 1   | AML 38/M        | 46,XY, t(1;21) [9] +        | NK8-cell def        | Idarubicin| 0      | D+  | Fludarabine TBI (2010)  | ABO-mismatch HLA 9/10 | Tacrolimus Mtx | GI | Grade 1 | E. Faecalis CMV Anti-platelet antibodies/Thrombocytopenia | 100% Donor 30% Hypo-Cellular | 100% Donor 30% Hypo-Cellular | 356 (extra medullary relapse day 307) |
| 2   | MDS 35/F        | S447R                       | NK8-cell def        | Busulfan | 0      | D-  | Cytoxan                  | ABO-match HLA 10/10  | Tacrolimus Mtx | Skin | Grade 1 | 100% Donor 30% Hypo-Cellular | 100% Donor 60% Hypo-cellular | 208 |                                                                 |
| 3   | MDS 10/F        | S447R                       | NK8-cell def        | None     | 0      | D-  | Cytoxan, TBI Alemtuzumab| ABO-match HLA 9/10  | Tacrolimus Mtx | Skin | Grade 1 | 100% Donor 30% Hypo-Cellular | 100% Donor 20% Hypo-cellular | 247 |                                                                 |
| 4   | Chronic Neutropenia 7/M | S447R | NK8-cell def        | None     | 0      | D-  | Cytoxan, TBI Alemtuzumab| ABO-match HLA 10/10  | Tacrolimus – | – | – | 100% Donor 30% Hypo-cellular | Pending | NA | 31 |

MDS, myelodysplastic syndrome; AML, acute myeloid leukemia.
tests and has not demonstrated any systemic infections or signs of MDS/AML although cognitive development appears to be delayed.

**Family 3**

In Family 3, the proband is a Caucasian female who presented at age 17 years with abdominal pain, hemoptysis, and mild pancytopenia. A CT scan revealed mild diffuse thoracic and abdominal lymphadenopathy. A detailed evaluation found acute Epstein–Barr virus (EBV) infection. A bone marrow biopsy was mildly hypocellular with mild erythroid hypoplasia and megakaryocytic hyperplasia with atypia. The cytogenetics were 46, XX [20]. She had a history of recurrent episodes of hidradenitis suppurativa, skin abscesses, folliculitis, otitis media, and throat infections.
Several years later, she was initiated on therapy with pegylated G-CSF. In spite of this, otitis media and abscesses continued. Two years later, she presented with a hypercatabolic state, with progressive hepato-splenomegaly and constitutional features. A bone marrow biopsy demonstrated progressive megakaryocytic atypia. While cytogenetics were once again normal, however, a MDS-fluorescence in situ hybridization (FISH) panel identified a deletion of -3q21 in 99% of analyzed nuclei. A phytohemagglutinin-stimulated karyotyping of peripheral blood lymphocytes also demonstrated the -3q21 (RPN1 deletion) in 99% of analyzed nuclei.

**GATA2** is located within this region, Expression studies confirmed **GATA2** haploinsufficiency. She is awaiting a donor for a MUD-HSCT.

**Discussion**

**MonoMAC syndrome and DCML deficiency**

The terms MonoMAC and DCML are synonymous, in terms of the genetic etiology, and refer to a primary immunodeficiency with predisposition to MDS/AML. MonoMAC refers to a recently described syndrome of MONOcytopenia and Mycobacterium Avium Complex infections characterized by germline **GATA2** mutations [44, 46]. DCML, also caused by germline **GATA2** mutations refers specifically to the cytopenias frequently seen in most patients—DCML deficiency (both B and NK cell) [50]. Two independent groups studied 24 individuals with these syndromes and reported similar mutations noted above in familial syndromes (T354M and T355 del). The scope of immune deficiency in this group is vast and not limited to mycobacterial infections. Opportunistic viral (disseminated human papillomavirus [HPV] and HPV-associated squamous cell carcinoma) [51], parasitic and fungal infections, as well as pulmonary alveolar proteinosis (**GATA2** is known to influence the phagocytic activity of pulmonary alveolar macrophages) can be seen [52]. A majority of patients with **GATA2** mutations eventually show deficiency of B lymphocytes, NK cells, CD4 lymphocytes, and monocytes [53].

**Emberger’s syndrome**

Emberger’s Syndrome is primary lymphedema with cutaneous warts, deafness, and a propensity to develop MDS/AML. Intact **GATA2** function is required for proper lymphatic vascular development during embryogenesis in mice [54]. Ostergaard and colleagues identified eight mutations in **GATA2** in three patients with this syndrome by whole-exome sequencing identifying this mutation as the only common denominator between the group [48]. At least 1 other patient with propensity to varicella zoster and salmonella infections has been reported [48]. Complications secondary to prolonged lymphedema such as secondary cellulitis and deep vein thrombosis (DVT) are frequent [53]. Null mutations in **GATA2** appear to be associated with severe viral infections and lymphedema [52].

**Familial MDS/AML**

**GATA2** overexpression has been documented in one-third to one half of nonfamilial AML and correlates with a poor prognosis with shorter overall and event-free survival when treated with standard chemotherapy [55, 56]. Of the original four families with **GATA2** mutations, described by Hahn et al. with MDS/AML, three had the T354M mutation, and one had deletion T355. Both mutations occurred in the second zinc finger (ZF) of **GATA2** (Fig 1). In the T354 mutation families, all members had the mutation but not all had developed hematological disease at least by the time of reporting [16]. Bone marrow biopsies are typically hypocellular in contrast to the common MDS marrow picture, with abundant atypical megakaryocytes in >90% patients [53]. Some patients have also fulfilled the diagnostic criteria for CMML (chronic myelomonocytic leukemia) and LGL (large granular lymphocytic leukemia) suggesting overlap syndromes [53]. Other acquired mutations such as **ASXL1** may herald the development of AML [57]. Increased levels of FLT3 ligand have also been reported to be associated with clinical progression [58].

**Chronic myeloid leukemia**

A novel **GATA2** mutation L359V has been found in nearly 10% of patients with accelerated or blast phase CML, but not CLL or ALL [59, 60]. This is thought to be mediated through PU.1 inhibition. It is interesting to note that
GATA2 overexpression or the L359V gain-of-function mutation have been associated with AML and CML, respectively; whereas loss-of-function mutation of GATA2 such as T354M have been linked to MDS. L359 and T354 located in the same region on the second zinc finger of GATA2 thus highlighting the vital role GATA2 plays in hemostasis of myeloid precursors.

**Aplastic anemia**
Expression of GATA-2 mRNA in purified CD34-positive cells was significantly decreased in aplastic anemia compared with normal subjects when examined by immunocytochemical analysis [61]. The changes extend further to stromal cells, with lower expression of GATA2 in patients with aplastic anemia when compared to controls by RT-PCR-ELISA [62]. GATA-2 is instrumental in both hematopoiesis and adipogenesis. Overexpression of peroxisome proliferator-activated receptor-gamma (PPAR-γ), an adipogenic factor) and underexpression of GATA2 by mesenchymal stem cells may explain fatty marrow replacement in AA patients [63].

**Pediatric neutropenia**
A high frequency of GATA2 mutations has been reported in pediatric patients with mild chronic neutropenia [64]. Analysis of French Neutropenia registry data revealed chronic familial neutropenia in seven families predisposing to MDS/AML associated with GATA2 mutations that included a complete deletion of GATA2 locus as well as additional mutations (p.R396Q, R204X, R330X, E224X, A372T, and M388V) [64].

**Pulmonary disease**
Ventilation-diffusion defects can be demonstrated in about two-thirds of GATA2-deficient patients while pulmonary hypertension (PAH) and pulmonary alveolar proteinosis (PAP) are some of the rare manifestations occurring in <20% in one series [53]. PAP in GATA2 deficiency is not due to GM-CSF-(Granulocyte Monocyte- Colony Stimulating Factor) autoantibodies and is refractory to GM-CSF inhalational and subcutaneous therapy [53].

**Treatment**

**Immune deficiency**
Allogeneic HSCT remains the main therapy for GATA2-deficient patients with immunodeficiency. Timing of HSCT for immune deficiency alone is less well defined as compared to MDS/AML and should focus on risk-benefit ratios for the individual and the family. The incidence of HPV, mycobacterial, and fungal infections decreases considerably after successful allogeneic HSCT [53, 65]. Notably, it may take more than 3.5 years for reversal of phenotype and full immune reconstitution of B, NK, and monocyte populations [66]. This may be especially problematic with delayed engraftment typical of umbilical cord grafts. Both PAP and PAH also respond well to HSCT and repeated lung infections or declining lung function

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**Table 3. Suggested screening categories for GATA2 mutation.**

| Mutation type       | AA location | Phenotype                        |
|---------------------|-------------|----------------------------------|
| Non-sense           | 337(ZF1)    | Emberger syndrome                |
| Missense            | 254         | MonoMAC/DCML                     |
|                     | 354(ZF2)    | Familial MDS/AML, MonoMAC/DCML   |
|                     | 361(ZF2)    | MonoMAC/DCML                     |
|                     | 371(ZF2)    | MonoMAC/DCML                     |
|                     | 373(ZF2)    | Emberger syndrome                |
|                     | 396(ZF2)    | MonoMAC/DCML                     |
|                     | 398(ZF2)    | MonoMAC/DCML                     |
| Frameshift           | 1           | MonoMAC/DCML                     |
|                     | 78          | Emberger syndrome                |
|                     | 81          | MonoMAC/DCML                     |
|                     | 105         | Emberger syndrome                |
|                     | 194         | Emberger syndrome                |
|                     | 200         | MonoMAC/DCML                     |
|                     | 259         | MonoMAC/DCML                     |
|                     | 317(ZF1)    | MonoMAC/DCML                     |
|                     | 341(ZF1)    | Emberger syndrome                |
| In-frame insertion  | 355(ZF2)    | Familial MDS/AML, MonoMAC/DCML   |
| or deletion         | 361(ZF2)    | Emberger syndrome                |
| Large deletion      | 340–381(ZF1 & 2) | MonoMAC/DCML                  |

MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; DCML, dendritic cell, monocyte, and lymphocyte.

**Table 4. Mutations of GATA2 resulting in variable phenotypes (Fig. 3) [78].**

| Mutation type       | AA location | Phenotype                        |
|---------------------|-------------|----------------------------------|
| Non-sense           | 337(ZF1)    | Emberger syndrome                |
| Missense            | 254         | MonoMAC/DCML                     |
|                     | 354(ZF2)    | Familial MDS/AML, MonoMAC/DCML   |
|                     | 361(ZF2)    | MonoMAC/DCML                     |
|                     | 371(ZF2)    | MonoMAC/DCML                     |
|                     | 373(ZF2)    | Emberger syndrome                |
|                     | 396(ZF2)    | MonoMAC/DCML                     |
|                     | 398(ZF2)    | MonoMAC/DCML                     |
| Frameshift           | 1           | MonoMAC/DCML                     |
|                     | 78          | Emberger syndrome                |
|                     | 81          | MonoMAC/DCML                     |
|                     | 105         | Emberger syndrome                |
|                     | 194         | Emberger syndrome                |
|                     | 200         | MonoMAC/DCML                     |
|                     | 259         | MonoMAC/DCML                     |
|                     | 317(ZF1)    | MonoMAC/DCML                     |
|                     | 341(ZF1)    | Emberger syndrome                |
| In-frame insertion  | 355(ZF2)    | Familial MDS/AML, MonoMAC/DCML   |
| or deletion         | 361(ZF2)    | Emberger syndrome                |
| Large deletion      | 340–381(ZF1 & 2) | MonoMAC/DCML                  |

MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; DCML, dendritic cell, monocyte, and lymphocyte.
should be considered an indication in clinical context [53]. Earlier transplantation, before organ dysfunction ensues, results in less morbidity and mortality.

**MDS/AML**

Allogeneic HCT remains the only treatment with favorable responses in GATA2-mutated MDS/AML (Fig. 3). In the NIH experience, 21 patients were transplanted for either hematological (MDS/AML) or immunological indications (age 15–49 years) with good responses (Fig. 1). Of note, half the patients who were not transplanted passed away by age 40 [51]. A similar NIH experience further outlined use of conditioning regimens for non-myeloablative allogeneic HCT [66]. Donors included fully matched related and unrelated donors (conditioning-fludarabine + total body radiation 200 cGy) and alternative sources such as umbilical cord blood and haploidentical bone marrow (fludarabine + cyclophosphamide and total body irradiation 200 cGy, with posttransplant cyclophosphamide for T-cell replete grafts). Busulfan was later added for a more robust eradication of the body irradiation 200 cGy, with posttransplant cyclophosphamide for T-cell replete grafts). Busulfan was later added for a more robust eradication of the GATA2 clone. Azithromycin was started before and continued for 1 year posttransplant due to increased propensity to nontuberculous mycobacterial (NTM) infections, in addition to standard prophylaxis. No NTM infections during or after transplant were reported using prophylaxis. Overall survival was 57% at 36 months. Our patient characteristics and outcomes are shown in Table 2. Tacrolimus was used for graft versus host disease prophylaxis. All four patients have engrafted with 100% donor chimerisms (CD3 and CD33 fractions). One patient had CMV-Cytomegalovirus reactivation and refractory thrombocytopenia which failed to improve despite splenectomy. Three developed acute GVHD and one had chronic GVHD involving esophagus with dysphagia and strictures that improved with steroids. Two clinical trials are currently recruiting patients for myeloablative and reduced-intensity conditioning allogeneic HSCT for GATA2 mutations and enrollment is encouraged whenever feasible (NCT01861106 and NCT00923364 at www.clinicaltrials.gov).

**Genetic counseling**

Early genetic diagnosis and screening is paramount [53]. Patients and families should be seen in conjunction with a geneticist. Suggested screening categories are listed in Table 3. Variable phenotypes resulting from different GATA2 mutations are listed in Table 4.

**Conflicts of Interest**

None declared.

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