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GATA2 Deficiency

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Abstract

Purpose of Review—GATA2 deficiency is a germline disease which causes a wide spectrum of phenotypes including viral and bacterial infections, cytopenias, myelodysplasia, myeloid leukemias, pulmonary alveolar proteinosis and lymphedema. The age of clinical presentation ranges from early childhood to late adulthood, with most occurring in adolescence to early adulthood. We review the expanding GATA2 deficient phenotype, molecular genetics of disease, and developments in treatment.

Recent Findings—GATA2 mutations have been found in up to 10% of those with congenital neutropenia and/or aplastic anemia. Heterozygous mutations appear to cause haploinsufficiency due either to protein dysfunction or uniallelic reduced transcription. Disease-associated mutations in intronic regulatory elements or variations within the 5' leader exons indicate that regulation of GATA2 is critical. Those with GATA2 mutations are at high risk for myelodysplasia (MDS), cytogenetic abnormalities, acute myeloid leukemia (AML) or chronic myelomonocytic leukemia (CMML). Bone marrow transplantation has been successful for both hematopoietic and pulmonary alveolar proteinosis repair.

Summary—GATA2 is a zinc finger transcription factor essential for embryonic and definitive hematopoiesis as well as lymphatic angiogenesis. GATA2 deficiency is caused by a variety of mutations in the GATA2 gene and can have variable presentation, onset and outcome. Patients are susceptible to mycobacterial, viral and fungal infections and can develop MDS, acute or chronic leukemias, lymphedema and pulmonary alveolar proteinosis. Hematopoietic stem cell transplantation (HSCT) reverses most of the clinical phenotype with good long-term outcomes.

Keywords

GATA2; haploinsufficiency; myelodysplastic syndrome; lymphedema; nontuberculous mycobacteria; pulmonary alveolar proteinosis

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Introduction

The constellation of disseminated nontuberculous mycobacterial (NTM) infections, susceptibility to viral infections, especially human papillomavirus (HPV) and Epstein-Barr virus (EBV), and fungal infections, coupled with profound monocytopenia, B-cell and NK-cell lymphopenias was syndromically described as MonoMAC [1] and dendritic cell, monocyte, B and NK lymphoid (DCML) deficiency [2]. This immune deficiency, now known to be due to heterozygous mutations in *GATA2*, presents in older children or adults, later than the classic immunodeficiencies. Patients have an increased risk of myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and chronic myelomonocytic leukemia (CMML). The disease follows an autosomal dominant mode of inheritance as well as a large number of sporadic cases.

Within just a few months in the summer of 2011 *GATA2* was reported to be the cause of MonoMAC [3], DCML [4*], familial AML [5], and Emberger syndrome (lymphedema and myelodysplasia or leukemia) [6]. *GATA2* is a hematopoietic transcription factor, which when mutated in the germline, predisposes to MDS/AML similar to *RUNX1* and *CEBPA* [7, 8*]. Screening the French Severe Chronic Neutropenia Registry identified a subgroup of 14 patients with recurrent infections, lymphedema, warts or progression to MDS/AML, 6 of whom had *GATA2* mutations [9]. The unification of so many phenotypes under one genotype shows how complex the effects of this transcription factor are and suggests that there may be more phenotypes to emerge.

Molecular Genetics

Mutational studies in the mouse had identified several regulatory regions critical for *Gata2* expression, including upstream as well as one intronic [10]. Johnson et al. reported almost identical deletions within the intronic enhancer region in mice and in a patient with clinical features of *GATA2* deficiency [11]. The deletion affects conserved transcription factor binding sites for Tal1/SCL and *GATA2*, causing reduced transcription of the mutant allele. Homozygous deletion of the enhancer element resulted in embryonic lethality around day 13.5 due to loss of vascular integrity. Heterozygous mice were viable but had reduced expression of *Gata2* and its target genes. Lim et al. also found gestational lethality with edema and hemorrhage due to a lack of lymphatic endothelial cells [12]. Some *GATA2* mutations are full gene deletions or are predicted to cause nonsense-mediated decay. Hsu et al. screened patients with the *GATA2* deficiency phenotype who were lacking coding mutations [13**]. They identified four patients with point mutations in the same intronic enhancer region leading to reduced levels of the mutant allele and reduced overall levels of *GATA2* transcript. Three additional patients had uniallelic *GATA2* expression: loss of transcript from one allele despite the presence of two genomic alleles. Despite having several kinds of mutations (missense, nonsense, deletion, uniallelic) most aspects of the clinical phenotype were not clearly associated with mutation type except for lymphedema in the nonsense and deletion mutations [14**]. Therefore, *GATA2* deficiency is most consistent with a disease of haploinsufficiency, a trait shared by other transcription factor deficiencies, reviewed by Seidman and Seidman [15].

Patient presentation

Age of symptom onset ascribed to *GATA2* deficiency varies: the earliest is a 5-month-old with lymphedema [14**]. Infections are the most frequent initial symptom with severe viral or nontuberculous mycobacterial [NTM] infections accounting for 60% of patients, while an initial diagnosis of MDS/AML occurred in 21% of patients [14**]. While some of those with cytopenias and hypocellular bone marrow findings initially diagnosed as aplastic anemia [16] have been shown to have *GATA2* mutations similar to those observed in other settings (missense or intronic regulatory mutations), the majority of changes seen in aplastic anemia have been in the *GATA2* 5' leader sequence. How these mutations cause disease is unresolved but 5' leader sequence mutations affect translational efficiency in other inherited bone marrow failure syndromes, such as Diamond-Blackfan anemia [17].

Germline *GATA2* mutations have been found in pediatric hypoplastic MDS patients, especially those with associated somatic monosomy 7 [18, 19]. With rates of *GATA2* mutation ranging up to 50% in these groups of patients it seems wise to screen all aplastic anemia and bone marrow failure patients being considered for transplant and their family donors for *GATA2* mutations.

The variability in disease presentation was highlighted by a three-generation, *GATA2*-mutated family in which members had various presentations including mild pancytopenia, MDS with monosomy 7, non-Hodgkin lymphoma, mucocutaneous candidiasis, Emberger syndrome and acute leukemias. The ages of disease presentation ranged from 14 to 74, illustrating both the necessity of genetic screening in the setting of bone marrow donation as this disease is the potential cause of adult onset immunodeficiency and malignancy [20*].

Disease course

Clinical courses are mostly tracked in patients with recognized associated syndromes. Spinner et al. found B-cell, NK-cell lymphopenia or monocytopenia in greater than 75% of patients [14**]. Bone marrow biopsies showed MDS in 84% of patients, demonstrating hypocellular marrow with multilineage dysplasias, especially megakaryocytic dysplasias and micromegakaryocytes [14**]. Reflecting the recruitment bias of their study, 82% of patients had major infections (nontuberculous mycobacteria, warts, fungal infections). Warts may be the first symptom in *GATA2* deficiency, but since warts are so common they are often not recognized as a sign of immunodeficiency until later in life or unless they are severe. Pulmonary alveolar proteinosis (PAP) was diagnosed in 18%, but 79% had pulmonary diffusion defects.

Peripheral blood obtained after clinical disease onset consistently shows monocytopenia, along with B, NK and dendritic cell cytopenia [1, 21*]. Decline in peripheral blood monocytes and dendritic cells was accompanied by an increase in circulating CD34+ progenitors and serum Flt3 ligand. Serum Flt3 ligand has been shown to reflect hematopoiesis at the progenitor cell level, increasing with the severity of bone marrow failure and normalizing as patients recover; it inversely correlated with colony forming ability in patient bone marrow cells [22]. Flt3 ligand may be a surrogate marker of decreased bone marrow hematopoietic potential as the hematopoietic stem cells (HSCs) are depleted,

similar to the elevated Flt3 ligand levels seen after bone marrow irradiation [23], continued exploration of Flt3 ligand levels in the setting of GATA2 deficiency may help track or predict disease evolution [21*].

Ganapathi et al. [24, 25**] performed flow cytometric evaluations on 28 patients with GATA2 mutations with hypocellular bone marrow and compared them to hypocellular marrows from aplastic anemia patients with wild-type GATA2. Similar to peripheral blood, GATA2 deficient patient marrows had fewer monocytes and B cells and an increased percentage of total T cells. Additionally, they had nearly absent hematogones (precursor B cells), inverted CD4:CD8 ratios and abnormal megakaryocytes. T cell receptor rearrangement studies in 10 GATA2 patients demonstrated that 5 had apparently clonal T cell populations, the significance of which is unknown.

Mechanism of GATA2 deficiency

In 1994 Tsai et al. [26] developed a *Gata2* knockout (KO) mouse. Homozygous mice died of severe anemia by embryonic day 10.5, when HSCs in the aorta-gonad-mesonephros (AGM) region become active. Conditional knockout models of *Gata2* under the control of *Vec-Cre* (endothelial specific) and *Vav-Cre* (hematopoietic specific) showed that *Gata2* is required for HSC generation and survival in the AGM [27].

Heterozygous *Gata2* KO mice are born healthy without overt phenotype in the expected Mendelian ratios [26] and adults have normal hematologic profiles. However, heterozygotes have reduced numbers of HSCs in the AGM and the HSCs show reduced ability to repopulate secondary recipients in serial transplants, demonstrating both quantitative and qualitative deficiencies of HSCs at birth [28]. *Gata2* heterozygous KO cells produce fewer monocytes, T cells and B cells when transplanted into an irradiated host. There is also a decreased number of granulocyte-macrophage progenitor cells in the *Gata2* KO heterozygotes, particularly in the setting of stress hematopoiesis [29, 30]. Whether these features apply to the human bone marrow compartment in GATA2 deficiency remains to be seen.

With the advent of high throughput, next generation sequencing, there has been a flurry of work on GATA2 as a regulator of hematopoiesis, reviewed by Bresnick et al. [31] and Vicente et al. [32]. In 2010, Wilson et al. [33] demonstrated that *Gata2* acts as part of a heptad of transcription factors (TF) in mouse HSCs. Binding of *Gata2*, *Scl*, *Runx1*, *Ly11*, *Lmo2*, *Erg* and *Fli-1* occurred at regulatory elements of key hematopoietic genes including *Gata2* and *Runx1*. These findings were recently extended to human CD34⁺ HSCs by Beck et al. [34*], implicating the same core heptad of TFs binding at sites with H3K4me3 histone marks, a sign of active transcription. These TFs form a dense autoregulatory core which drives not only the key TFs, but miRNAs such as miR-146a that have a direct impact on HSC survival and differentiation [35, 36]. Deletion of miR-146a leads to a decline in the number of HSCs and bone marrow failure [37]. Beck et al. [34*] extended the analysis, constructing a regulatory network model of the coding and non-coding RNAs controlled by the GATA2 heptad and demonstrating that several of the miRNAs form a negative feedback loop with the TFs. This suggests that the feedback loop is key to fine-tuning the

transcriptional program of the HSCs. Therefore, decreased GATA2 levels in human GATA2 deficiency is intrinsically associated with poor regulation.

The human disease progression of GATA2 deficiency is reminiscent of other bone marrow failure syndromes, suggesting that the reduced number of HSCs at birth may not be able to maintain normal hematopoiesis against all insults throughout life. Clonal hematopoiesis, elevation of Flt3 ligand [21*], oligoclonal T cell receptor rearrangement and the loss of precursor B cells and monocytes in the bone marrow [24, 25**] all indirectly support this hypothesis. Patients likely have lower HSCs at birth, exacerbated by bone marrow stress due to infection, which then may lead to marrow exhaustion with possible development of malignancy (Figure 1).

GATA2 and malignancy

GATA2 deficient patients are at an increased risk of developing MDS and leukemia. MDS was identified in 84% of the NIH cohort [14**]: AML in 14% and CMML in 8%. MDS in GATA2 deficiency is typically hypocellular with increased reticulin and megakaryocytic dysplasia [38] and identified as WHO “Myelodysplastic syndrome, Refractory cytopenias with myelodysplasia” [39], or refractory anemia with excess blasts. The most common cytogenetic abnormality identified was monosomy 7, followed by trisomy 8 [14**]. West RR et al. [40] screened the NIH cohort and found that 29% carried somatic mutations in *ASXL1*. Patients with *ASXL1* mutations were younger, predominantly female and more likely to develop CMML, different than the *ASXL1* mutations seen in *de novo* MDS [41]. Bödör et al. [42] identified a family with *GATA2* germline mutation in which two first-degree cousins developed monosomy 7 and *ASXL1* mutations with associated MDS.

Somatic mutations in *GATA2* have been associated with leukemia, particularly normal karyotype AML (NK-AML). Celton et al. [43**] examined *GATA2* expression levels in 49 NK-AML blast samples as well as a *GATA2* mutated cell line. RNA-Seq found *GATA2* transcript levels to be decreased compared to healthy control CD34+ cells. More relevant for understanding the syndrome of GATA2 deficiency, they found > 80% of samples had expression from only one allele, similar to patients with germline uniallelic expression and regulatory mutations [13**]. They linked this pattern to hypermethylation of the *GATA2* promoter. In pediatric *de novo* AML, Shiba et al. [44] screened 157 AML patient samples and found 8 (5%) had somatic and one had germline *GATA2* mutations. Gröschel et al. [45**] and Yamazaki et al. [46**] recently showed that the chromosomal rearrangement in inv(3)/t(3;3) AML leads to repositioning of the distal *GATA2* enhancer, causing activation of *EVII* and effectively silencing *GATA2*, thus conferring functional *GATA2* haploinsufficiency.

Treatment of GATA2 Deficiency

Initial treatment of GATA2 deficiency must focus on control of infections and management of pulmonary disease, while recognizing that the underlying defect is bone marrow dysfunction. Cuellar-Rodriguez et al. [47] reported on six GATA2 deficient patients who received non-myeloablative HSCT, which corrected monocyte, B-cell, and NK counts as well as the clinical phenotype. Confirming the central role of marrow-derived alveolar

macrophages, lung function in patients with severe PAP also improved. Grossman, et al. [48**] have cumulated the NIH experience with 14 transplants in GATA2 deficiency, finding merit in the use of myeloablative conditioning for the elimination of preleukemic host cells. Haploidentical marrow donors using post-transplant cyclophosphamide have been successful as well.

The timing of transplant for a congenital disease with variable onset and expression is hard to prescribe. Monosomy 7, *ASXL1* mutations, and excess blasts all portend worse outcomes, although the timeframe for evolution to either overt bone marrow failure or leukemia is variable. However, acute leukemia can appear with very little prodrome, indicating that there is no substitute for vigilance. Dickinson et al. [21*] found elevated Flt3 ligand and cytopenias in 50% of their asymptomatic affecteds, which is likely a marker of disease progression due to loss of hematopoietic potential. In view of the general uncertainty surrounding the causes, rates and overall likelihood of progression to severe bone marrow dysfunction, we introduce bone marrow transplantation with all patients at the initial interview.

There are no clear guidelines regarding the wisest course of monitoring or the advisability of prophylaxis for those who are *GATA2* mutated and asymptomatic. However, it seems prudent to vaccinate children against HPV, to be vigilant for HSV infections, and to use azithromycin prophylaxis to prevent mycobacterial and routine bacterial infections. We monitor peripheral blood counts every 3–6 months and bone marrow biopsy with cytogenetics every 1–2 years. Because the transition from MDS to more aggressive dysplasia can be abrupt, we prefer to transplant before the development of severe end organ damage or leukemia.

Conclusion

GATA2 deficiency is a germline transcription factor defect variably characterized by HPV, NTM and fungal infections; multi-lineage cytopenias and MDS/AML; lymphedema; and pulmonary alveolar proteinosis. *GATA2* haploinsufficiency is caused by many different types of mutations, ranging from nonsense (stop codons and deletions), to missense (amino acid substitutions), to regulatory (intronic changes leading to uniallelic expression). In addition, there are clear examples of uniallelic expression for which mutations have not been identified but which must be in *cis* to the affected allele. The complete picture of *GATA2* deficiency is being filled in, but we already know that it is scientifically and medically complex and involved in an expanding array of pathways. It is also more common than any of the initial descriptions anticipated, suggesting that there may well be more manifestations to identify.

Acknowledgments

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Glossary

HSC	Hematopoietic stem cell
CMP	Common myeloid progenitor
CLP	Common lymphoid progenitor
MEP	Megakaryocyte-erythroid progenitor
GMP	Granulocyte-macrophage progenitor
DC	Dendritic cell

B	B lymphocyte
T	T lymphocyte
NK	Natural killer cell
PAP	Pulmonary alveolar proteinosis
NTM	Non-tuberculous mycobacteria
HPV	Human papilloma virus
MDS/AML	Myelodysplastic syndrome/Acute myeloid leukemia
CMML	Chronic myelomonocytic leukemia

Key Points

- GATA2 deficiency has variable presentations including infections, multi-lineage cytopenias, MDS/AML, lymphedema, aplastic anemia and pulmonary alveolar proteinosis.
- GATA2 mutations occur throughout the gene (exons, introns, regulatory) leading to haploinsufficiency and dysregulation of a critical transcription factor network.
- HSCT reverses the infectious, hematopoietic and pulmonary disease seen in GATA2 deficiency.

Effects of GATA2 deficiency

Figure 1.

GATA2 deficiency affects both quantity and quality of hematopoietic stem cells [28]. At the endothelial cell level, GATA2 deficiency patients have lymphedema secondary to effects on the vasculature [49]. PAP is thought to be secondary to dysfunctional alveolar macrophages. As hematopoiesis occurs over the course of a patient's life, specific lineage cytopenias including dendritic cell, B-cell, NK-cell, and monocyte are seen. Infections such as NTM and HPV are often present. The combination of continued HSC depletion, infections, and cytopenias stress the bone marrow as evidenced by elevation of Flt3 ligand and clonal hematopoiesis. This creates an environment conducive to development of MDS, which may lead to AML or CMML. Bold, black lines indicate cellular defects with clinical readouts.