


# Case Report of an Adolescent Male With Unexplained Pancytopenia: *GATA2*-Associated Bone Marrow Failure and Genetic Testing

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## Introduction

The approach to the patient with new-onset pancytopenia is complex and includes an extensive clinical and laboratory evaluation with bone marrow examination.<sup>1</sup> Causes of pancytopenia include cytotoxic therapies, autoimmune disorders, infection, and congenital and acquired bone marrow failure syndromes.<sup>1</sup> The congenital bone marrow failure syndromes include Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond syndrome, and other genetic conditions.<sup>1-3</sup> The accurate diagnosis of these congenital disorders is essential to inform clinical monitoring, family counseling, and hematopoietic stem cell transplantation planning, including donor selection and preparatory regimen choice.<sup>4</sup> With the advent of multi-gene panels, pediatric and adolescent cases of bone marrow failure previously categorized as idiopathic are being reclassified. The use of targeted capture gene panels in the workup of these disorders has improved our diagnostic accuracy,<sup>5</sup> and we report here one example of the clinical utility of this unbiased genetic screening in a community hospital setting.

## Case Report

A 12-year-old, previously healthy, African American male with no significant past medical history presented to his primary care physician with a 2-week history of fever, cough, and 7-kg weight loss. Review of systems was negative for any warts or lymphedema. He was diagnosed with a right upper lobe pneumonia and treated with a 10-day course of azithromycin. He was subsequently admitted to the pediatric intensive care unit with bilateral pneumonia. Physical examination was notable for an acutely ill appearing adolescent in moderate

respiratory distress; growth parameters at the time of admission were 49th percentile for height and 17th percentile for weight.

Laboratory studies at admission showed a normochromic, normocytic underproduction anemia with a hemoglobin of 9.7 g/dL (0.73%; mean normal 14 g/dL). White blood cell count/differential and platelet count were normal. Chemistries were notable for an alanine aminotransferase of 256 U/L (normal 10-40 U/L), aspartate aminotransferase of 186 U/L (normal 15-40 U/L), lactate dehydrogenase 544 U/L (normal 119-295 U/L), and C-reactive protein of 23.1 mg/dL (normal 0-0.5 mg/dL). Lymphocyte subset enumeration was performed and showed essentially normal count with the exception of a low CD4/CD8 ratio of 0.5. Blood cultures were all negative. Chest X-ray and computed tomography scan of the chest showed extensive bilateral multilobar pneumonia. He was treated with broad spectrum antibiotics and ultimately recovered and was discharged to home. Of note, he remained anemic (8.4 g/dL) and was also noted to have monocytopenia at discharge. Over the next 6 months he developed progressive pancytopenia (hemoglobin 9.4 g/dL, white blood cell count  $2.9 \times 10^9/L$ , absolute neutrophil count  $0.4 \times 10^9/L$ , absolute lymphocyte count  $2.4 \times 10^9/L$ , absolute monocyte count 0, and platelets  $197 \times 10^9/L$ ; Table 1).

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**Table 1.** Hematological Parameters Over 6 Months.

Features	Initial	3 Months	6 Months
Hemoglobin (g/dL)	8.4	9.5	9.4
White blood cells (median, 10 <sup>9</sup> /L)	7.4	4.1	2.9
Platelets (median, 10 <sup>9</sup> /L)	234	181	197

**Table 2.** Evaluation of the Adolescent With Pancytopenia.

Infectious disease	
Parvo B19	Negative
HIV 1, HIV 2	Negative
Mycoplasma	Negative
Influenza	Negative
CMV	Negative
EBV	Negative
Immunology	
ANA	Negative
Cold agglutinin	Negative
Direct coombs	Negative
Total IgG (mg/dL)	847
Total IgM (mg/dL)	69
Other	
B <sub>12</sub> (pg/mL)	427
Folate (ng/mL)	>20
T-cell subset	Negative
PNH screen	negative
Chromosomal breakage (DEB, mitomycin C)	Within normal limits
Karyotype	46, XY
Hemoglobin electrophoresis	A1 97.7% A2 1.4% F 0.9%

Abbreviation: CMV, cytomegalovirus; EBV, Epstein-Barr virus; ANA, antinuclear antibody; IgG, immunoglobulin G; IgM, immunoglobulin M; PNH, paroxysmal nocturnal hemoglobinuria; DEB, diepoxybutane.

Bone marrow aspirate and biopsy showed a hypocellular marrow for age (60% to 70% cellular) with mildly elevated myeloid to erythroid ratio with no morphologic or immunophenotypic dysplasia and no dysplastic megakaryocytes. Routine karyotype was normal. Additional testing to determine the etiology of his bone marrow failure was unrevealing (Table 2). Targeted gene capture and massively parallel sequencing were performed as previously described using a capture assay targeting mutations in known inherited and acquired bone marrow failure and MDS genes<sup>5</sup> on DNA isolated from peripheral blood.

This revealed a novel, heterozygous, nonsense mutation in *GATA2* at the +3 splice acceptor position of exon 3 (of 6 exons total): *GATA2* p.S290X Chr3: 128204572

G>T (GRCh37/hg19 assembly). The result most likely represents a nonsense variant leading to nonsense-mediated decay and haploinsufficiency for *GATA2*. However, as it disrupts a semiconserved splice acceptor site, it may also lead to an exon-skipping variant. Moreover, the serine at this position is phosphorylated, and if the latter could similarly disrupt transcriptional activity.<sup>6</sup> The *GATA2* mutation was also confirmed through a second laboratory test. This mutation is therefore consistent with *GATA2* deficiency syndrome. Family studies indicated neither parents nor siblings have the *GATA2* mutation, indicating this is a de novo mutation in our patient.

Additionally, the patient was heterozygous for a variant in *ASXL1* (p.D741V; chr20: 31022373 A>T). This variant is predicted to be nondamaging by in silico modeling and is reported 48 times on the Exome Aggregation Consortium browser and therefore considered likely to be a benign change.

## Discussion

This case illustrates the utility of broad unbiased genetic screening in the workup of pediatric marrow failure in a community hospital setting. Our patient had remained without a diagnosis after marrow examination, telomere length testing, chromosome fragility, and paroxysmal nocturnal hemoglobinuria testing in addition to other extensive tests outlined. The elucidation of a novel *GATA2* mutation and the diagnosis of *GATA2* deficiency syndrome in our patient was a direct result of utilization of this panel.

Mutations in *GATA2*, characterized first in 2011, have been implicated in several syndromes including familial myelodysplastic syndrome/acute myeloid leukemia, Emberger syndrome, monocytopenia and mycobacterial infection syndrome (monoMAC), and dendritic cell, monocyte B, and natural killer lymphoid deficiency.<sup>7-9</sup> MonoMAC syndrome is characterized by nontuberculosis mycobacterial infections with *Mycobacterium avium* complex being the most common, but also may have *M kansasii*, *M scrofulaceum*, *M bovis*, and *M szulgai*. Patients may suffer viral infections such as human papillomavirus, herpesvirus infection, and also have fungal infections such as disseminated histoplasmosis, cryptococcal meningitis, and invasive aspergillosis. Beside

infections, these patients can have complications including primary lymphedema and cytopenias.<sup>10</sup>

Emberger syndrome was first described in 1979, by Emberger, who described a family with 3 individuals over 2 generations who had severe congenital deafness, and suffered limb lymphedema and hematologic abnormalities of pancytopenia in 2 individuals and acute myeloblastic leukemia in 1 individual.<sup>11</sup> Patients with these conditions may present at any age and may present with a spectrum of features including leukemia to life threatening infections.<sup>12</sup>

In addition to the GATA2 mutation, a benign variant was identified in the *ASXL1* gene of our patient. Somatic *ASXL1* mutations are found in 10% to 30% of patients with myeloid malignancies and associated with worse outcomes including myeloid transformation.<sup>13</sup> Germline *ASXL1* mutations occur in Bohring-Opitz syndrome, in which patients have severe intrauterine growth retardation, poor feeding, trigonocephaly, and nevus flammeus of the face. In addition, patients have been described to have flexion of the elbows and wrists with deviation of the wrists and metacarpophalangeal joints.<sup>14</sup> The patient described in this report did not have these features, and given this the variant is likely an incidental finding.

## Conclusion

In conclusion, the accurate diagnosis of GATA2 deficiency has guided our patient's immediate and long-term care. The patient will be getting a human papillomavirus vaccination and has received evaluation for a bone marrow transplant at a local academic institution. This testing additionally allowed for appropriate screening of potentially affected family members: all were negative for this mutation. This is one of the first instances of previously diagnosed idiopathic pancytopenia being reclassified as a specific syndrome as a direct result of a genetic bone marrow failure screening panel performed through a community hospital in concert with a tertiary institution, thereby providing clinically important information to the patient, family, and care team.

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## Author Contributions

LA: Contributed to conception; drafted manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AJ: Contributed to conception; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AL: Contributed to conception and design; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

SK: Contributed to acquisition and analysis; critically revised manuscript; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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HS: Contributed to conception and design; critically revised manuscript; critically revised manuscript; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

## Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Abraham is a consultant for Shire.

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## References

- Weinzierl EP, Arber DA. The differential diagnosis and bone marrow evaluation of new-onset pancytopenia. *Am J Clin Pathol*. 2013;139:9-29.
- Alter BP. Diagnosis, genetics, and management of inherited bone marrow failure syndromes. *Hematology Am Soc Hematol Educ Program*. 2007:29-39.
- Shimamura A. Inherited bone marrow failure syndromes: molecular features. *Hematology Am Soc Hematol Educ Program*. 2006:63-71.
- Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. *Blood Rev*. 2010;24:101-122.
- Zheng DQ, Zhang K, Wu XC, Mieczkowski PA, Petes TD. Global analysis of genomic instability caused by DNA replication stress in *Saccharomyces cerevisiae*. *Proc Natl Acad Sci U S A*. 2016;113:E8114-E8121.
- Katsumura KR, Yang C, Boyer ME, Li L, Bresnick EH. Molecular basis of crosstalk between oncogenic Ras and the master regulator of hematopoiesis GATA-2. *EMBO Rep*. 2014;15:938-947.
- Tsai FY, Orkin SH. Transcription factor GATA-2 is required for proliferation/survival of early hematopoietic

- cells and mast cell formation, but not for erythroid and myeloid terminal differentiation. *Blood*. 1997;89:3636-3643.
8. Horwitz MS. GATA2 deficiency: flesh and blood. *Blood*. 2014;123:799-800.
  9. Dickinson RE, Milne P, Jardine L, et al. The evolution of cellular deficiency in GATA2 mutation. *Blood*. 2014;123:863-874.
  10. Camargo JF, Lobo SA, Hsu AP, Zerbe CS, Wormser GP, Holland SM. MonoMAC syndrome in a patient with a GATA2 mutation: case report and review of the literature. *Clin Infect Dis*. 2013;57:697-699.
  11. O'Neill MJF. Lymphedema, primary, with myelodysplasia. <https://omim.org/entry/614038>. Accessed November 13, 2017.
  12. Spinner MA, Sanchez LA, Hsu AP, et al. GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity. *Blood*. 2014;123:809-821.
  13. West RR, Hsu AP, Holland SM, Cuellar-Rodriguez J, Hickstein DD. Acquired ASXL1 mutations are common in patients with inherited GATA2 mutations and correlate with myeloid transformation. *Haematologica*. 2014;99:276-281.
  14. McKusick VA. Bohring-Opitz syndrome; BOPS. <https://omim.org/entry/605039>. Accessed November 13, 2017.