



## GATA1-Related Cytopenia

Kaoru Takasaki, MD,<sup>1</sup> Melissa A Kacena, PhD,<sup>2</sup> Wendy H Raskind, MD, PhD,<sup>3</sup> Mitchell J Weiss, MD, PhD,<sup>4</sup> and Stella T Chou, MD<sup>5</sup>

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## Summary

### Clinical characteristics

*GATA1*-related cytopenia is characterized by thrombocytopenia and/or anemia ranging from mild to severe. Thrombocytopenia typically presents in infancy as a bleeding disorder with easy bruising and mucosal bleeding (e.g., epistaxis). Anemia ranges from minimal (mild dyserythropoiesis) to severe (hydrops fetalis requiring in utero transfusion). At the extreme end of the clinical spectrum, severe hemorrhage and/or erythrocyte transfusion dependence are lifelong; at the milder end, anemia and the risk for bleeding may decrease spontaneously with age. One or more of the following may also be present: neutropenia, splenomegaly, cryptorchidism, hypospadias, and rarely additional clinical features of Diamond-Blackfan anemia. Heterozygous females may have mild-to-moderate symptoms such as menorrhagia. Rarely, *GATA1*-related cytopenia can progress to myelodysplastic syndrome or aplastic anemia.

### Diagnosis/testing

The diagnosis of *GATA1*-related cytopenia is established in a male proband with cytopenia resulting from ineffective hematopoiesis by identification of a hemizygous pathogenic variant in *GATA1* by molecular genetic testing. The diagnosis of *GATA1*-related cytopenia may be established in a female proband with cytopenia by identification of a heterozygous pathogenic variant in *GATA1* by molecular genetic testing.

### Management

*Targeted therapy:* For severe disease, hematopoietic stem cell transplantation (HSCT) can be curative.

**Author Affiliations:** 1 Instructor, Department of Pediatrics, Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Email: takasakik@chop.edu. 2 Professor and Vice Chair for Research, Department of Orthopaedic Surgery, Indiana University School of Medicine, Indianapolis, Indiana; Email: mkacena@iupui.edu. 3 Professor, Departments of Medicine and Psychiatry and Behavioral Sciences, University of Washington Medical Center, Seattle, Washington; Email: wendyrun@uw.edu. 4 Member and Chairman, Department of Hematology, St Jude Children's Research Hospital, Memphis, Tennessee; Email: mitch.weiss@stjude.org. 5 Associate Professor, Department of Pediatrics, University of Pennsylvania School of Medicine; Division of Hematology, Chief, Division of Transfusion Medicine, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Email: chous@chop.edu.

*Supportive care:* Platelet transfusions for moderate-to-severe epistaxis, severe gingival bleeding, or other clinically significant bleeding; DDAVP<sup>®</sup> may be helpful for short-term management of mild-to-moderate bleeding; platelet transfusion prior to surgical or invasive dental procedures for individuals with a history of pathologic bleeding, thrombocytopenia, and/or platelet dysfunction; red blood cell transfusions for clinical manifestations of anemia (fatigue, tachycardia); iron chelation therapy as needed for chronic red blood cell transfusions; extended pre-transfusion red blood cell phenotyping and consideration of Rh and K antigen matching for those receiving frequent transfusions. Treatment for neutropenia includes counseling regarding infection risk; prophylactic antibiotics when indicated; prompt evaluation when febrile; empiric parenteral antibiotics for febrile individuals with severe neutropenia. HSCT can be curative for those with severe disease.

*Surveillance:* Complete blood count (CBC) with frequency based on disease severity; annual CBC in those with mild cytopenia(s) and monthly CBC in those with severe cytopenia(s) that require intervention such as red blood cell transfusion. Monitor for iron overload in those with frequent erythrocyte transfusions.

*Agents/circumstances to avoid:* Those with thrombocytopenia and/or platelet aggregation defects should avoid antiplatelet agents including aspirin and nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) and avoid contact sports or activities with a high risk of trauma. Individuals with severe neutropenia should avoid close contact with persons who have a communicable disease to minimize risk of infection. Individuals with significant splenomegaly should avoid contact sports, which increase the risk of traumatic splenic rupture.

*Evaluation of relatives at risk:* If a *GATA1* pathogenic variant has been identified in the family, molecular genetic testing of at-risk relatives can be offered. At-risk relatives who choose not to have molecular genetic testing should have a CBC to evaluate for thrombocytopenia, anemia, and/or neutropenia.

## Genetic counseling

*GATA1*-related cytopenia is inherited in an X-linked manner. If the mother of the proband has a *GATA1* pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygous and may have mild-to-moderate symptoms. Affected males transmit the *GATA1* pathogenic variant to all of their daughters and none of their sons. Once the *GATA1* pathogenic variant has been identified in an affected family member, identification of female heterozygotes and prenatal and preimplantation genetic testing are possible.

## Diagnosis

### Suggestive Findings

*GATA1*-related cytopenia **should be suspected** in a male or female proband with any combination of the following clinical and laboratory findings and family history.

#### Clinical findings

- Excessive bruising
- Mucosal bleeding (e.g., gingival bleeding, epistaxis)
- Petechiae
- Hydrops fetalis in some infants

#### Laboratory findings

- Complete blood count. Thrombocytopenia and/or mild-to-severe anemia; rarely neutropenia
- Peripheral blood smear examination. Platelets may be larger and more spherical; variation in erythrocyte size and shape
- Bone marrow aspirate and biopsy

- Hyper- or hypocellularity
- Evidence of ineffective hematopoiesis
- Increased or decreased numbers of megakaryocytes
- Small, dysplastic megakaryocytes with signs of incomplete maturation
- Dyserythropoiesis
- Hypocellularity of granulocytic lineages
- Mild-to-moderate reticulin fibrosis [Åström et al 2015]
- Platelet aggregation studies. Normal to abnormal platelet aggregation in response to agonists (e.g., ristocetin, adenosine diphosphate, epinephrine, collagen) in some individuals [Thompson et al 1977, Freson et al 2001, Balduini et al 2004, Hollanda et al 2006, Jurk et al 2022]
- Electron microscopy. Reduced number of platelet alpha granules in some individuals [Jurk et al 2022] and dysplastic features in megakaryocytes and platelets

**Family history** is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

Note: (1) Hematologic findings in *GATA1*-related cytopenia are variable and usually nonspecific and thus by themselves not indicative of a specific diagnosis. (2) Affected individuals are typically male; females often present with milder findings.

## Establishing the Diagnosis

**Male proband.** The diagnosis of *GATA1*-related cytopenia **is established** in a male proband with cytopenia resulting from ineffective hematopoiesis by identification of a hemizygous pathogenic (or likely pathogenic) variant in *GATA1* by molecular genetic testing (see Table 1). Note: *GATA1* pathogenic variants have been rarely identified in individuals with CEP (see Genetically Related Disorders).

**Female proband.** The diagnosis of *GATA1*-related cytopenia **may be established** in a female proband with cytopenia by identification of a heterozygous pathogenic variant (or likely pathogenic) in *GATA1* by molecular genetic testing (see Table 1). Note: *GATA1* pathogenic variants have been rarely identified in individuals with CEP (see Genetically Related Disorders).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variant" in this *GeneReview* is understood to include any likely pathogenic variant. (2) Identification of a hemizygous or heterozygous *GATA1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with cytopenia, including *GATA1*-related cytopenia, are more likely to be diagnosed using comprehensive genomic testing (see Option 2).

### Option 1

**Single-gene testing.** Sequence analysis of *GATA1* to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Although no exon or whole-gene deletions or duplications have been reported as

a cause of *GATA1*-related cytopenia, some laboratories offer gene-targeted deletion/duplication analysis if a pathogenic variant is not found.

**A multigene panel** that includes *GATA1* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

## Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by cytopenia, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

**Table 1.** Molecular Genetic Testing Used in *GATA1*-Related Cytopenia

Gene <sup>1</sup>	Method	Proportion of Probands with a Pathogenic Variant <sup>2</sup> Detectable by Method
<i>GATA1</i>	Sequence analysis <sup>3</sup>	100% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	None reported <sup>4</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single exon deletions or duplications.

## Clinical Characteristics

### Clinical Description

Individuals with *GATA1*-related cytopenia have thrombocytopenia, anemia, and/or neutropenia.

### Affected Males

**Bleeding disorder.** Males typically present in infancy with a bleeding disorder. Affected individuals have easy bruising and mucosal bleeding (e.g., gingival bleeding, epistaxis). Petechiae, ecchymoses, and/or splenomegaly may be identified on physical examination. Excessive hemorrhage and/or bruising can occur either

spontaneously or after trauma or surgery. Fetal cerebral hemorrhage with in utero demise has been reported [Bouchghoul et al 2018].

Platelet counts are usually low ( $10\text{-}100 \times 10^3/\mu\text{L}$ ) but can vary considerably. Normal platelet counts have also been reported ( $150\text{-}400 \times 10^3/\mu\text{L}$ ), including in individuals with a germline pathogenic variant resulting in a truncated protein (GATA-1s; see Molecular Genetics) causing congenital anemia [Hollanda et al 2006, Sankaran et al 2012]. The platelets are typically larger than normal (macrothrombocytopenia) and more spherical than the typical discoid morphology [Crispino & Horwitz 2017, Bouchghoul et al 2018]. Platelets may be pale, reflecting reduced granularity.

**Anemia.** Individuals with anemia may present with fatigue or pallor; anemia may also be incidentally identified on a complete blood count (CBC) obtained for other reasons. Hematocrit ranges from 16% to 35% (normal: 35%-45%). Red cell indices on CBC typically show normochromic cells that may be mildly microcytic (75-79 fL) or macrocytic (101-103 fL) (normal: 80-99 fL). On peripheral blood smear there is variation in erythrocyte size and shape and hypochromia, reflecting low hemoglobin content.

The severity of anemia ranges from mild dyserythropoiesis to severe hydrops fetalis requiring in utero transfusions [Crispino & Horwitz 2017, Bouchghoul et al 2018, Abdulhay et al 2019].

*GATA1* pathogenic variants affecting p.Arg307 (c.919C>T [p.Arg307Cys] and c.920G>A [p.Arg307His]) were identified in four male probands with hemolytic anemia, mild thrombocytopenia, and reticulocytosis, with elevated adenosine deaminase and bone marrow erythroid hyperplasia [Hetzer et al 2022, Ludwig et al 2022]. A beta-thalassemia-like phenotype with globin chain imbalance has been reported in association with the *GATA1* variant p.Arg216Gln, but the anemia and reticulocytosis were accompanied by thrombocytopenia and a coagulopathy, suggesting that this is a distinct disease from beta-thalassemia [Yu et al 2002].

*GATA1* pathogenic variants have been identified in individuals previously diagnosed with **Diamond-Blackfan anemia** (see Nomenclature). Pathogenic frameshift or nonsense variants in *GATA1* that result in the exclusive production of an amino terminus-truncated protein termed GATA-1 short (GATA-1s) (e.g., c.2T>C, c.3G>A) have been identified in several unrelated probands with pure red cell aplasia and additional clinical features of Diamond-Blackfan anemia [Sankaran et al 2012, Klar et al 2014, Ludwig et al 2014, Parrella et al 2014, Zucker et al 2016, Chen et al 2022, Hasle et al 2022, van Dooijeweert et al 2022]. Diamond-Blackfan anemia is typically associated with heterozygous pathogenic variants in ribosomal protein-encoding genes and is characterized by profound normochromic and usually macrocytic anemia with normal leukocytes and platelets, congenital malformations in up to 50% of affected individuals, and growth deficiency in 30% of individuals. For individuals with *GATA1* pathogenic variants the accurate diagnosis is *GATA1*-related cytopenia.

Rarely, *GATA1*-related cytopenia can progress to myelodysplasia and myelodysplastic syndrome or aplastic anemia [Kratz et al 2008; Authors, unpublished data].

**Neutropenia.** Persistent neutropenia ( $0.5\text{-}1.0 \times 10^3/\mu\text{L}$ ; normal:  $1.9\text{-}8.0 \times 10^3/\mu\text{L}$ ) with abnormal neutrophil morphology was observed in some affected males in one family [Hollanda et al 2006]; variable neutrophil counts have been reported in other affected individuals [Hollanda et al 2006, Sankaran et al 2012, Zucker et al 2016, Svidnicki et al 2021]. Individuals with severe neutropenia may be predisposed to severe bacterial infections [Hollanda et al 2006].

**Splenomegaly** has been reported in some individuals with *GATA1*-related cytopenia (see Genotype-Phenotype Correlations).

*Cryptorchidism* and *hypospadias* have been reported [Bouchghoul et al 2018, Kobayashi et al 2022]. Typically, no other congenital anomalies are present in individuals with *GATA1*-related cytopenia.

## Course and prognosis

- At the extreme end of the clinical spectrum, severe hemorrhage and/or erythrocyte transfusion dependence are lifelong. However, improvement in anemia with age, despite a severe presentation in utero and/or early infancy, has also been reported [Abdulhay et al 2019].
- At the milder end, the risk for bleeding may spontaneously decrease with age, despite continued thrombocytopenia [Mehaffey et al 2001, Del Vecchio et al 2005].
- Some affected individuals are recognized through incidental findings of mild-to-moderate cytopenia on routine blood count analysis. These individuals have a good prognosis.

## Heterozygous Females

Females may have menorrhagia or easy bruising [Svidnicki et al 2021, Camargo et al 2022]. Platelet counts may be normal or mildly to moderately decreased [Nichols et al 2000, Svidnicki et al 2021]. Two distinct platelet morphologies can be observed on peripheral blood smear, reflecting mosaicism secondary to random X-chromosome inactivation [Nichols et al 2000; Raskind et al 2000; Balduini et al 2004; Del Vecchio et al 2005; Raskind, unpublished observations]. Morphologic abnormalities of platelets can be detected by electron microscopy [White 2007, Jurk et al 2022].

## Genotype-Phenotype Correlations

*GATA1* pathogenic variants that result in truncation of the first 83 amino acids of erythroid transcription factor (GATA-1) (i.e., GATA-1 short [GATA-1s]) are associated with macrocytic anemia of varying severity. Findings that have only been reported in association with GATA-1s are neutropenia, thrombocytosis, and progression to myelodysplastic syndromes and acute myeloid leukemia.

*GATA1* missense variants affecting either the amino- or carboxy-terminus zinc finger domain that affect its ability to bind either *GATA1* sites in DNA, the cofactor friend of GATA (FOG)-1, or both are associated with macrothrombocytopenia and dyserythropoiesis but not necessarily anemia. Findings that have only been reported in association with *GATA1* missense variants are hydrops fetalis, hypospadias, cryptorchidism, and chronic hemolysis.

**c.2T>C, c.3G>A, c.220+2T>C.** These *GATA1* variants have been identified in several unrelated probands with macrocytic anemia and either thrombocytopenia or megakaryocyte dysplasia and clinical features of Diamond-Blackfan anemia without an associated pathogenic variant in a ribosomal protein-encoding gene.

**c.220+1delG.** This *GATA1* variant has been identified in two related individuals with pure red cell aplasia and a clinical diagnosis of Diamond-Blackfan anemia without an associated pathogenic variant in a ribosomal protein-encoding gene.

To date, only limited genotype-phenotype correlations have been identified. However, the authors have compiled a comprehensive table of *GATA1* variants and reported phenotypes in order to contribute to future understanding of genotype-phenotype correlations (see [Table 2](#)).

## Nomenclature

Until pathogenic variants in *GATA1* were shown to underlie this heterogeneous disorder, a variety of terms were coined for the different clinical presentations. The first term used was X-linked thrombocytopenia with thalassemia (XLTT) [Raskind et al 2000]. Other terms used in the past and still used in the current literature are:

- "Familial dyserythropoietic anemia and thrombocytopenia" [Nichols et al 2000, Del Vecchio et al 2005];
- "X-linked macrothrombocytopenia" [Freson et al 2001]; and
- "X-linked anemia with or without neutropenia and/or platelet abnormality" (XLANP) [Ogura et al 2016].

The diagnosis of "GATA1-related Diamond-Blackfan anemia" was primarily made before GATA1-related cytopenia was recognized as a distinct entity. Based on the underlying disease etiology, the appropriate diagnostic term for individuals with this phenotype is "GATA1-related cytopenia" [Author, personal observation].

## Prevalence

GATA1-related cytopenia is rare; the prevalence is not known. To date, hematopoietic disease caused by inherited pathogenic variants in GATA1 has been reported in at least 36 families.

GATA1 pathogenic variants may be more common than previously appreciated, particularly in persons with mild, unexplained thrombocytopenia present since birth [Tubman et al 2007] or individuals with congenital hypoplastic anemia and other clinical features of Diamond-Blackfan anemia with no pathogenic variants affecting ribosomal proteins identified [Sankaran et al 2012].

## Genetically Related (Allelic) Disorders

"Gray platelet syndrome" (GPS) has been used to describe a genetically heterogeneous group of congenital disorders in which the platelets are large and have a gray appearance on light microscopy (Wright-stained slides) and the platelet alpha granules are either absent or reduced in numbers on electron microscopy. Males with GPS from one family were found to have the GATA1 pathogenic variant c.647G>A (p.Arg216Gln) [Tubman et al 2007]; GPS is most often associated with pathogenic variants in NBEAL2 (see Differential Diagnosis).

**Congenital erythropoietic porphyria (CEP).** GATA1 pathogenic variant c.646C>T (p.Arg216Trp) was identified in one affected individual with moderately severe anemia and bullous skin lesions associated with CEP; no UROS pathogenic variants were identified [Phillips et al 2007]. In two additional probands with CEP, anemia, and thrombocytopenia, a pathogenic variant in UROS or SEC23B was detected in addition to GATA1 variant p.Arg216Trp [Di Pierro et al 2015].

**Acquired (somatic) GATA1 pathogenic variants** can occur in neonates with Down syndrome with transient abnormal myelopoiesis; up to 30% of these neonates will develop acute megakaryoblastic leukemia by age four years [Wechsler et al 2002, Alford et al 2011, Garnett et al 2020].

## Differential Diagnosis

GATA1-related cytopenia must be distinguished from other acquired and hereditary thrombocytopenias (e.g., Wiskott-Aldrich syndrome, which is also X-linked), platelet function abnormalities, and anemias [Bury et al 2021, Groarke et al 2021]. Algorithms exist to help differentiate among these disorders [Bury et al 2021, Groarke et al 2021]. However, the clinical phenotypes of GATA1-related cytopenias vary greatly and overlap considerably with other genetic causes of cytopenia. Hence, a genetic diagnosis is almost always required for confirmation. A multigene panel is often used to establish the diagnosis of a hereditary thrombocytopenia and thereby facilitate appropriate surveillance (some types of hereditary thrombocytopenia are associated with increased malignancy risk) and genetic counseling.

Of note:

- Numerous congenital thrombocytopenias may be considered in the differential diagnosis [Noris & Pecci 2017, Almazni et al 2019, Perez Botero & Di Paola 2021]. In GATA1-related thrombocytopenia, platelets are usually large and may be hypogranular. There may be associated platelet aggregation defects and/or a prolonged bleeding time. Relatively common congenital causes of macrothrombocytopenia that could be confused with GATA1-related disorders are described in Table 3.

- Thrombocytopenia may be the initial manifestation of bone marrow failure in individuals with a telomere biology disorder (e.g., [dyskeratosis congenita](#)).
- Cryptorchidism and/or hypospadias may suggest the involvement of *GATA1* but are not always present.
- Congenital causes of anemia that could potentially be confused with *GATA1*-related disorders are described in Table 3.

**Table 3.** Selected Genes of Interest in the Differential Diagnosis of *GATA1*-Related Cytopenia

Gene	Disorder	MOI	Clinical Characteristics
<b>Thrombocytopenia</b>			
<i>ETV6</i>	<a href="#">ETV6 thrombocytopenia &amp; predisposition to leukemia</a>	AD	Mild-to-moderate thrombocytopenia w/platelet function defects; ↑ risk of hematologic malignancy
<i>RUNX1</i>	<a href="#">RUNX1 familial platelet disorder w/assoc myeloid malignancies</a>	AD	Mild-to-moderate thrombocytopenia w/platelet function defects; ↑ risk of hematologic malignancy
<i>WAS</i>	Wiskott-Aldrich syndrome (See <a href="#">WAS-Related Disorders</a> .)	XL	Small platelets, eczema (~80%), & immunodeficiency; persons may have isolated microthrombocytopenia.
<b>Congenital macrothrombocytopenia</b>			
<i>GP1BA</i> <i>GP1BB</i> <i>GP9</i>	Bernard-Soulier syndrome (BSS) (OMIM 231200)	AR	Severe bleeding disorder w/severely defective ristocetin-induced platelet agglutination; heterozygotes may have mild disease.
<i>GP1BA</i> <i>GP1BB</i>	Mediterranean thrombocytopenia (OMIM 153670)	AD	Phenotype typically milder than BSS; dysmegakaryo-cytopenia <sup>2</sup>
<i>MYH9</i>	<a href="#">MYH9-related disease</a>	AD	Platelet macrocytosis, thrombocytopenia, & neutrophil inclusions; most persons have extrahematologic manifestation(s) (e.g., hearing loss, cataract, renal defects).
<i>NBEAL2</i> <sup>2</sup>	Gray platelet syndrome (OMIM 139090)	AR <sup>3</sup>	Pale platelets &/or absent alpha granules.
<b>Anemia</b>			
<i>BRCA1</i> <i>BRCA2</i> <i>BRIP1</i> <i>ERCC4</i> <i>FAAP100</i> <i>FANCA</i> <i>FANCB</i> <i>FANCC</i> <i>FANCD2</i> <i>FANCE</i> <i>FANCF</i> <i>FANCG</i> <i>FANCI</i> <i>FANCL</i> <i>FANCM</i> <i>PALB2</i> <i>RAD51</i> <i>RAD51C</i> <i>REV7</i> <i>RFWD3</i> <i>SLX4</i>	Fanconi anemia	AR XL AD <sup>4</sup>	↑ chromosome breakage; onset of cytopenias typically at early school age; short stature, café au lait macules, & characteristic limb abnormalities may be present; ↑ risk of malignancy



Table 3. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics
<i>UBE2T</i> <i>XRCC2</i>			
<i>EFL1</i> <i>DNAJC21</i> <i>SBDS</i> <i>SRP54</i>	Shwachman-Diamond syndrome	AR AD <sup>5</sup>	Normocytic anemia & neutropenia are most common cytopenias; exocrine pancreatic dysfunction
<b>Macrocytic anemia</b>			
<i>RPL11</i> <i>RPL15</i> <i>RPL18</i> <i>RPL26</i> <i>RPL27</i> <i>RPL31</i> <i>RPL35</i> <i>RPL35A</i> <i>RPL5</i> <i>RPL9</i> <i>RPS10</i> <i>RPS15A</i> <i>RPS17</i> <i>RPS19</i> <i>RPS24</i> <i>RPS26</i> <i>RPS27</i> <i>RPS28</i> <i>RPS29</i> <i>RPS7</i> <i>TSR2</i>	Diamond-Blackfan anemia	AD <sup>7</sup> XL <sup>8</sup>	Pure red cell aplasia w/normocellular marrow; growth deficiency, limb abnormalities, cardiac defects, & characteristic facies may be present; ↑ risk of malignancy

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

1. Sivapalaratnam et al [2017]

2. One person with gray platelet syndrome (GPS) had a *GATA1* pathogenic variant (see Genetically Related Disorders).

3. GPS can be inherited in an autosomal recessive manner (*NBEAL2*-related GPS); apparent autosomal dominant or X-linked transmission have been reported (reviewed in Nurden & Nurden [2007]).

4. Fanconi anemia (FA) can be inherited in an autosomal recessive manner, an autosomal dominant manner (*RAD51*-related FA), or an X-linked manner (*FANCB*-related FA).

5. Shwachman-Diamond syndrome (SDS) caused by pathogenic variants in *DNAJC21*, *EFL1*, or *SBDS* is inherited in an autosomal recessive manner. SDS caused by pathogenic variants in *SRP54* is inherited in an autosomal dominant manner; most such affected individuals reported to date have a *de novo* *SRP54* pathogenic variant.

7. Approximately 40%-45% of individuals with autosomal dominant Diamond-Blackfan anemia (DBA) inherited the pathogenic variant from a parent; approximately 55%-60% have a *de novo* pathogenic variant.

8. DBA is most often inherited in an autosomal dominant manner; *TSR2*-related DBA is inherited in an X-linked manner.

### Relatively common contiguous gene deletions associated with congenital macrothrombocytopenia

- Paris-Trousseau thrombocytopenia (OMIM 188025) and Jacobsen syndrome (OMIM 147791). Associated features include cardiac and facial abnormalities and intellectual disability.
- [22q11.2 deletion syndrome](#). Affected individuals can present with a wide range of highly variable features. The major clinical manifestations include congenital heart disease, palatal abnormalities, immune deficiency, characteristic facial features, and learning difficulties.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *GATA1*-related cytopenia, the following are recommended:

- Complete blood count (CBC) and examination of the peripheral blood smear to assess the degree of cytopenia(s) and morphologic abnormalities
- Detailed history of the disease course, including the age at which hematologic disease was detected and the associated symptoms
- Documentation of abnormal/unexpected bleeding episodes and platelet counts obtained at the time of the episodes to help determine whether platelet function is abnormal and whether disease severity has changed over time

Note: Platelet aggregation studies may identify functional abnormalities that predict a greater risk of bleeding for any given platelet count, but studies can be difficult to interpret when platelet counts are lower than 100,000/ $\mu$ L.

- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of *GATA1*-related cytopenia for medical and personal decision making

### Treatment of Manifestations

#### Targeted Therapy

*In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED*

For those with severe disease, hematopoietic stem cell transplant (HSCT) can be curative [Hollanda et al 2006, Phillips et al 2007, Parrella et al 2014].

- HSCT should be considered in individuals with severe *GATA1*-related cytopenia, particularly if a human leukocyte antigen (HLA)-matched donor is available. Molecular genetic testing for the known familial *GATA1* pathogenic variant is critical to allow identification of an unaffected potential donor.
- While HSCT may offer a cure, clinical experience with HSCT treatment in those with *GATA1*-related cytopenia is limited and families must be counseled on the significant risks and morbidity associated with HSCT, particularly for non-HLA-matched donors.

#### Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended.

#### Thrombocytopenia and/or platelet dysfunction

- Individuals with moderate-to-severe epistaxis, severe gingival bleeding, or other clinically significant bleeding should receive platelet transfusions. Transfusion requirements vary, as bleeding can be related to quantitative and/or qualitative platelet defects.
- For individuals with thrombocytopenia and/or platelet aggregation defects, DDAVP<sup>®</sup> treatment may be helpful for short-term management of mild-to-moderate bleeding.

- Platelet transfusion prior to surgical or invasive dental procedures is recommended for individuals with a history of pathologic bleeding, thrombocytopenia, and/or platelet dysfunction.
- Individuals who are only mildly symptomatic (easy bruisability without mucosal or more severe bleeding) do not require specific treatment.
- There is no evidence that splenectomy is beneficial in people with *GATA1*-related cytopenia, although this treatment may be considered if splenomegaly is severe. Although cytopenias may improve after splenectomy, platelet dysfunction will not improve.

### Anemia

- Red blood cell transfusions for clinical manifestations of anemia (e.g., fatigue, tachycardia)
- Iron chelation therapy may be needed in those with iron overload secondary to chronic red blood cell transfusion therapy.
- Extended pre-transfusion red blood cell phenotyping and consideration of Rh and K antigen matching for individuals receiving frequent transfusions can facilitate antibody detection if alloimmunization occurs.

### Neutropenia

- Individuals with neutropenia should be counseled regarding their increased risk of infection.
- Treatment with prophylactic antibiotics should be based on the history of infections and overall clinical picture.
- Individuals with neutropenia who present with fever should be evaluated promptly with a physical examination, CBC, and blood culture.
- Febrile individuals who are severely neutropenic (absolute neutrophil count  $<500/\mu\text{L}$ ) are typically treated with empiric parenteral antibiotics to avoid the possibility of life-threatening sepsis.

## Surveillance

The frequency of CBCs should be tailored to disease severity.

- Individuals with mild cytopenias should have annual CBCs.
- Individuals with severe cytopenias who require transfusions should have monthly CBCs or as indicated by clinical signs and symptoms.
- Additional surveillance with bone marrow aspirate and biopsy may be indicated in those with a phenotype similar to [Diamond-Blackfan anemia](#).
- Individuals undergoing repeated erythrocyte transfusions should be monitored for iron overload.

## Agents/Circumstances to Avoid

Individuals with thrombocytopenia and/or platelet aggregation defects should avoid antiplatelet agents including aspirin and nonsteroidal anti-inflammatory drugs (e.g., ibuprofen).

Individuals with thrombocytopenia and/or platelet aggregation defects should avoid contact sports or activities with a high risk of trauma.

Individuals with severe neutropenia should avoid close contact with persons who have a communicable disease to minimize risk of infection.

Individuals with significant splenomegaly should avoid contact sports, which increase the risk of traumatic splenic rupture.

## Evaluation of Relatives at Risk

**For early diagnosis and treatment.** Both male and female relatives of an affected individual, including those who are apparently asymptomatic, should be offered molecular genetic testing for the familial *GATA1* pathogenic variant. This helps identify as early as possible those who would benefit from prompt evaluation and treatment for cytopenia.

Note: Evaluation of at-risk relatives can include a CBC to evaluate for thrombocytopenia, anemia, or neutropenia. However, platelet, erythrocyte, and neutrophil counts can vary significantly in individuals with *GATA1* pathogenic variants and normal results do not rule out the possibility that the relative has a *GATA1* pathogenic variant and is at risk for developing complications of the disorder.

**For HSCT donor evaluation.** Any relative who is a potential HSCT donor should undergo molecular genetic testing to clarify genetic status; only those relatives who do not have the *GATA1* pathogenic variant should be evaluated further.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Correction of the *GATA1* pathogenic variant by genome editing of autologous hematopoietic stem cells may offer a viable cure in the future, although this will require individualized "n-of-few" therapy since there is no single common pathogenic variant [Voit et al 2022].

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

## Other

Unlike immune-mediated platelet disorders such as immune thrombocytopenic purpura, *GATA1*-related thrombocytopenia does not respond to steroid or immunoglobulin therapy.

Supplemental erythropoietin therapy is unlikely to be effective because the anemia is secondary to ineffective erythropoiesis, not erythropoietin deficiency.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

*GATA1*-related cytopenia is inherited in an X-linked manner.

## Risk to Family Members

### Parents of a male proband

- The father of an affected male will not have the disorder, nor will he be hemizygous for the *GATA1* pathogenic variant; therefore, he does not require further evaluation/testing.

- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *GATA1* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism (evidence of germline mosaicism has not been observed to date).
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote, the affected male may have a *de novo* *GATA1* pathogenic variant (in which case the mother is not a heterozygote), or the mother may have somatic/germline mosaicism. Because very few families with *GATA1* pathogenic variants have been described to date, the frequency of *de novo* pathogenic variants is not known.
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

**Sibs of a male proband.** The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a *GATA1* pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected.
  - Females who inherit the pathogenic variant will be heterozygous and may manifest platelet abnormalities and/or mild anemia with mild-to-moderate symptoms such as menorrhagia or easy bruising (see Clinical Description, Heterozygous Females).
- If the proband represents a simplex case and if the *GATA1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of maternal germline mosaicism.

**Offspring of a male proband.** Affected males transmit the *GATA1* pathogenic variant to all of their daughters, who will be heterozygotes (see Clinical Description, Heterozygous Females), and none of their sons.

**Other family members.** The maternal aunts and maternal cousins of a male proband may be at risk of having a *GATA1* pathogenic variant.

## Heterozygote Detection

Identification of female heterozygotes typically requires prior identification of the *GATA1* pathogenic variant in the family so that targeted testing can be performed.

Note: Females who are heterozygotes for this X-linked disorder may develop clinical findings related to the disorder (see Clinical Description, Heterozygous Females).

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are heterozygous, or are at risk of being heterozygous.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *GATA1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for *GATA1*-related cytopenia are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **Platelet Disorder Support Association**  
**Phone:** 877-528-3538  
**Email:** [pdsa@pdsa.org](mailto:pdsa@pdsa.org)  
[www.pdsa.org](http://www.pdsa.org)
- **MedlinePlus**  
[Thrombocytopenia](#)

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** *GATA1*-Related Cytopenia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<a href="#">GATA1</a>	<a href="#">Xp11.23</a>	<a href="#">Erythroid transcription factor</a>	<a href="#">GATA1 @ LOVD</a>	<a href="#">GATA1</a>	<a href="#">GATA1</a>

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for *GATA1*-Related Cytopenia ([View All in OMIM](#))

<a href="#">300367</a>	THROMBOCYTOPENIA, X-LINKED, WITH OR WITHOUT DYSERYTHROPOIETIC ANEMIA; XLTTA
<a href="#">305371</a>	GATA-BINDING PROTEIN 1; GATA1
<a href="#">314050</a>	THROMBOCYTOPENIA WITH BETA-THALASSEMIA, X-LINKED; XLTT

## Molecular Pathogenesis

*GATA1* belongs to the GATA-binding family of transcription factors that is highly expressed in hematopoietic lineages, including erythrocyte, megakaryocyte, mast cell, and eosinophil lineages. Erythroid transcription factor (GATA-1) recognizes and binds to a target site conforming to the consensus nucleotide motif WGATAR present in noncoding regulatory regions of many hematopoietic genes. The modular protein contains two zinc finger domains and an acidic N-terminal domain that can promote transcriptional activation [Ferreira et al 2005, Lowry & Mackay 2006]. The C-terminal zinc finger (C-f) domain is required for DNA binding activity at most or all target sites, and the N-terminal zinc finger (N-f) domain stabilizes GATA-1 binding to DNA at a subset of sites containing duplicated or palindromic GATA-1 motifs [Ohneda & Yamamoto 2002]. The N-f domain also

binds numerous partner proteins, including friend of GATA (FOG)-1, an essential factor required for many GATA-1 functions [Tsang et al 1997, Fox et al 1999]. Many germline *GATA1* variants associated with cytopenias occur in exons 4 or 5, resulting in missense variants within or near the N-f or C-f domains and resulting in altered DNA binding or impaired interaction with FOG-1 [Nichols et al 2000, Freson et al 2001, Mehaffey et al 2001, Freson et al 2002, Yu et al 2002, Balduini et al 2004, Del Vecchio et al 2005]. Germline pathogenic variants in exon 2 of *GATA1* can also cause *GATA1*-related cytopenias, including macrothrombocytopenia, dysplastic megakaryocytes, anemia, and neutropenia [Hollandia et al 2006, Sankaran et al 2012, Klar et al 2014, Zucker et al 2016, Abdulhay et al 2019, Hasle et al 2022, Kobayashi et al 2022, van Dooijeweert et al 2022]. Notably, similar variants have been identified in several families with clinical findings suggestive of **Diamond-Blackfan anemia** who did not have pathogenic variants in ribosomal protein-encoding genes [Sankaran et al 2012, Ludwig et al 2014, Klar et al 2014, Parrella et al 2014, Zucker et al 2016, Chen et al 2022, van Dooijeweert et al 2022]. These variants usually result in the exclusive production of an amino-truncated isoform of GATA-1, termed GATA-1 short (GATA-1s) that is missing the first 83 amino acids of the 143-amino acid protein.

**Mechanism of disease causation.** Loss of function

**Table 4.** Notable *GATA1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_002049.4 NP_002040.1	c.2T>C	p.Met1Thr <sup>1</sup>	Pathogenic variants identified in some persons w/ features of Diamond-Blackfan anemia [Chen et al 2022, Hasle et al 2022, van Dooijeweert et al 2022]
	c.3G>A	p.Met1Ile <sup>1</sup>	
NM_002049.4	c.220+1delG	--	See Genotype-Phenotype Correlations.
	c.220+2T>C	--	
NM_002049.4 NP_002040.1	c.647G>A	p.Arg216Gln	Assoc w/beta-thalassemia-like phenotype [Yu et al 2002]
	c.919C>T	p.Arg307Cys	Pathogenic variants identified in probands w/hemolytic anemia, mild thrombocytopenia, & reticulocytosis, w/↑ adenosine deaminase & bone marrow erythroid hyperplasia [Hetzer et al 2022, Ludwig et al 2022]
	c.920G>A	p.Arg307His	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

1. Pathogenic variant affects initiation codon resulting in lack of full-length DNA.

## Cancer and Benign Tumors

In children with Down syndrome (DS, trisomy 21), somatic variants resulting in the production of GATA-1s exclusively are associated with transient myeloproliferative disorder (TMD) and acute megakaryoblastic leukemia (M7 subtype, DS-AMKL) [Roberts et al 2013, Garnett et al 2020, McNulty & Crispino 2020]. TMD, found in up to 10% of infants with DS, usually resolves spontaneously; however, TMD confers a markedly increased risk for DS-AMKL [Garnett et al 2020, McNulty & Crispino 2020]. The acquired exon 2 variants lead to premature arrest of translation and reinitiation of protein synthesis at the downstream methionine codon at position 83, and result in the production of GATA-1s, which lacks the amino-terminal activation domain. Some splice site variants also result in generation of GATA-1s. The mechanisms by which *GATA1* variants in conjunction with trisomy 21 promote DS-AMKL pathogenesis are currently unknown.

Further, similar germline protein-truncating *GATA1* variants usually cause cytopenia without leukemia in individuals who do not have DS. However, these individuals, including heterozygous females, can develop myeloproliferative disorder, myelodysplastic syndrome (MDS), and/or myeloid leukemia associated with acquired trisomy 21 and other chromosomal abnormalities [Camargo et al 2022, Hasle et al 2022].

One individual with severe anemia and thrombocytopenia caused by the *GATA1* pathogenic missense variant c.613G>A (p.Val205Met) developed MDS 18 years after a failed bone marrow transplantation. It is not clear whether the MDS with a clonal deletion of 20q was due to the underlying disease caused by the pathogenic variant of *GATA1*, bone marrow transplant-associated toxicity, or both [Authors, unpublished data].

## Chapter Notes

### Author Notes

Drs Kaoru Takasaki (takasakik@chop.edu), Mitchell Weiss, (mitch.weiss@stjude.org), and Stella Chou (chous@chop.edu) are actively involved in research regarding individuals with *GATA1*-related cytopenias. They would be happy to communicate with persons who have any questions regarding diagnosis of *GATA1*-related cytopenias or other considerations.

Contact Drs Takasaki, Weiss, or Chou to inquire about review of *GATA1* variants of uncertain significance.

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### Author History

Stella T Chou, MD (2006-present)

Melissa A Kacena, PhD (2006-present)

Jessica Kirk, BS; Yale University School of Medicine (2006-2011)

Wendy H Raskind, MD, PhD (2006-present)

Kaoru Takasaki, MD (2023-present)

Mitchell J Weiss, MD, PhD (2006-present)

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