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GATA1-Related X-Linked Cytopenia

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Summary

Disease characteristics. *GATA1*-related cytopenia is characterized by thrombocytopenia and/or anemia ranging from mild to severe and one or more of the following: platelet dysfunction, mild β-thalassemia, neutropenia, and congenital erythropoietic porphyria (CEP) in males. Thrombocytopenia typically presents in infancy as a bleeding disorder with easy bruising and mucosal bleeding, such as 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 life long; at the milder end, anemia and the risk for bleeding decrease spontaneously with age. Females carriers may have mild to moderate findings, such as menorrhagia.

Diagnosis/testing. Diagnostic laboratory findings usually include macrothrombocytopenia (low number of platelets that are larger than normal) and anemia with red cell indices that are usually normochromic. Defects in platelet aggregation in response to agonists may be seen. In some cases electron microscopy reveals reduced numbers of platelet alpha granules and dysplastic features in platelets and megakaryocytes. *GATA1* is the only gene known to be associated with *GATA1*-related cytopenia. Molecular genetic testing is available on a clinical basis.

Management. *Treatment of manifestations:* platelet transfusions for moderate to severe epistaxis, gingival bleeding, or gastrointestinal bleeding; no specific treatment for mild symptoms (easy bruisability only); erythrocyte transfusions when anemia is symptomatic (fatigue, tachycardia). *Prevention of primary manifestations:* For severe cases, bone marrow transplantation (BMT) can be curative. *Surveillance:* monitoring complete blood counts (with frequency depending on disease severity) to inform re: supportive care; monitoring those undergoing repeated erythrocyte transfusions for iron overload. *Agents/circumstances to avoid:* Those with thrombocytopenia should avoid antiplatelet agents including aspirin and nonsteroidal anti-inflammatory agents (NSAIDs) (e.g., ibuprofen). Those with thrombocytopenia and/or platelet aggregation defects should avoid contact sports or activities with a high risk of trauma. *Testing of relatives at risk:* screen with complete blood count to evaluate for thrombocytopenia, anemia, or neutropenia.

Genetic counseling. *GATA1*-related cytopenia is inherited in an X-linked manner. If the mother of an affected male has a *GATA1*-disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Affected males pass the disease-causing mutation to all of their daughters and none of their sons. Prenatal testing using molecular genetic techniques is available for families in which the *GATA1* mutation has been identified.

Diagnosis

Clinical Diagnosis

The diagnosis of *GATA1*-related cytopenia is suggested in males with the following:

- Thrombocytopenia and/or anemia ranging from mild to severe (including fetal hydrops)
- One or more of the following:
  - Platelet dysfunction
  - Mild β-thalassemia
  - Neutropenia
  - Congenital erythropoietic porphyria (CEP)
- Family history consistent with X-linked inheritance
- No evidence of Wiskott-Aldrich syndrome (WAS), an X-linked disorder of microthrombocytopenia that can present with or without immunodeficiency

The diagnosis of *GATA1*-related cytopenia is established when a *GATA1* disease-causing mutation detected in a research laboratory is confirmed in a clinical laboratory.

Note: (1) Hematologic findings in *GATA1*-related cytopenia are variable and usually nonspecific (i.e., seen in numerous conditions and thus by themselves not indicative of a specific diagnosis). (2) Females may be affected but usually have milder symptoms.

Testing

Diagnostic laboratory findings in males with *GATA1*-related cytopenia include the following:

- **Complete blood count**
  - Platelet counts are usually low (11-82 x 10^3/μL), but vary considerably with specific mutations. Normal counts have also been reported (150-400 x 10^3/μL). The platelets are typically larger than normal (macrothrombocytopenia).

- Anemia (hematocrit 16%-35%; normal: 35%-45%) may be present; the severity is associated with the specific mutation. Red cell indices are normochromic but may be mildly microcytic (75-79 fl) or macrocytic (101-103 fl) (normal: 80-99 fl).
- Significant persistent neutropenia (0.5-2.8 x 10^3/μL; normal 1.9-8.0 x 10^3/μL) was observed in one family with a specific *GATA1* mutation [Hollanda et al 2006].

Note: Thrombocytopenia, anemia, and neutropenia are usually defined as two standard deviations below values observed in the normal population.

- **Peripheral blood smear** may show the following:
  - Some platelets that are larger and more spherical than the typical discoid morphology. Platelets may be pale, reflecting reduced granularity.
  - Variation in erythrocyte size and shape and hypochromia, reflecting low hemoglobin content.
  - Decreased neutrophils with abnormal morphology; this rare finding was reported in one family with an unusual germline mutation that results in exclusive production of truncated GATA-1 (erythroid transcription factor) protein (GATA-1s) [Holanda et al 2006].
- **Bone marrow biopsy** may show the following:
  - Hyper- or hypocellularity
  - Increased or decreased numbers of megakaryocytes
  - Small, dysplastic megakaryocytes with signs of incomplete maturation
  - Dyserythropoiesis
  - Hypocellularity of erythroid and granulocytic lineages
- **Platelet function abnormalities.** Defects in platelet aggregation in response to agonists, such as ristocetin, adenosine diphosphate, epinephrine or collagen occur in some cases [Thompson et al 1977, Freson et al 2001, Balduini et al 2004, Hollanda et al 2006]. These studies can be normal in some affected individuals.
- **Electron microscopy.** Findings in some cases include reduced numbers of platelet alpha granules and dysplastic features in megakaryocytes and platelets.
- **In subtypes associated with globin chain imbalance,** findings consistent with mild hemolysis, including mild reticulocytosis, elevated LDH, and low haptoglobin, may be present. In addition, HbA2 and HbF may be elevated.

Note: (1) In female carriers, two distinct platelet morphologies can be observed on peripheral blood smear, reflecting mosaicism secondary to random X chromosome inactivation. (2) Bleeding time is usually prolonged in *GATA1*-related thrombocytopenia.

Definitions of Terms Used to Describe this Disorder

Thrombocytopenia: reduced platelet count
Macrothrombocytopenia: thrombocytopenia with large platelets
Dyserythropoiesis: impaired production and maturation of erythrocytes (red blood cells)
Thalassemia: an inherited form of anemia associated with unbalanced globin chain synthesis
Hemoglobin: the oxygen-carrying compound of red blood cells, made up of heme, α-globin, and β-globin. β-thalassemia is associated with decreased β-globin synthesis in red blood cells.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *GATA1* is the only gene known to be associated with *GATA1*-related cytopenia.

Clinical testing

- **Sequence analysis.** Most *GATA1* mutations identified in *GATA1*-related cytopenias have been missense mutations. One germline mutation predicting a splicing abnormality that results in the loss of the first 83 coding amino acids of GATA-1 has been reported [Hollanda et al 2006].

Table 1 summarizes molecular genetic testing for the heterogeneous inherited *GATA1*-related disorders.

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

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	*GATA1* exonic and splice site mutations	Unknown	Clinical Testing

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Initial testing should include complete blood count, examination of the blood smear, and bone marrow aspirate and biopsy to confirm that cytopenia results from ineffective hematopoiesis rather than peripheral destruction or sequestration. The diagnosis can be confirmed by molecular testing.

Platelet function studies or electron microscopy may also be informative, as specific abnormalities are reported in some affected individuals.

Genetically Related (Allelic) Disorders

Two hematopoietic disorders in children with Down syndrome (DS) associated with acquired (somatic) mutations in exon 2 of *GATA1* are transient myeloproliferative disorder (TMD) and acute megakaryoblastic leukemia (M7 subtype, DS-AMKL) [Wechsler et al 2002, Muntean et al 2006].

Transient myeloproliferative disorder (TMD), found in up to 10% of infants with DS, usually resolves spontaneously; however, TMD confers a markedly increased risk for DS-AMKL [Wechsler et al 2002, Hitzler & Zipursky 2005]. The acquired exon 2 mutations 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-1 short isoform (GATA-1s) that lacks a previously defined amino-terminal activation domain. Some splice site mutations also result in generation of GATA-1s. How *GATA1* mutations synergize with trisomy 21 to promote DS-AMKL is unknown.

"Grey platelet syndrome" is a term that has been used to describe a genetically heterogeneous group of congenital disorders in which the platelets are large and have a grey appearance on

light microscopy (Wright-stained slides) and the platelet alpha granules are either absent or reduced in numbers on electron microscopy. Although autosomal dominant inheritance predominates, a mutation in *GATA1* was found in at least one family with an X-linked variant of grey platelet syndrome [Tubman et al 2005].

Clinical Description

Natural History

Males. *GATA1*-related thrombocytopenia typically presents in infancy as a bleeding disorder. Affected individuals have easy bruising and mucosal bleeding, such as epistaxis. Physical examination may reveal petechiae, ecchymoses, or splenomegaly. Excessive hemorrhage and/or bruising can occur either spontaneously or after trauma or surgery. Some affected individuals may be recognized only after incidental findings of mild to moderate cytopenias on blood count analysis.

Anemia, the other major clinical problem in males with *GATA1*-related cytopenia, ranges from minimal with only mild dyserythropoiesis [Freson et al 2001] to severe hydrops fetalis requiring in utero transfusions [Nichols et al 2000]. Anemia can be so severe that affected males are red blood cell transfusion-dependent after birth [Freson et al 2002].

Variable mild to moderate neutropenia with macrocytic anemia and normal platelet counts were reported in one extended family (with a germline mutation leading to exclusive GATA-1s production) in which those individuals with severe neutropenia were predisposed to infection [Hollanda et al 2006].

In one family, moderately severe anemia was associated with congenital erythropoietic porphyria (CEP) [Phillips et al 2005]. The affected individual also had bullous skin lesions associated with porphyria.

The long-term course depends on disease severity. At the extreme end of the clinical spectrum, severe hemorrhage and/or erythrocyte transfusion dependence are life long. At the milder end, the risk for bleeding decreases spontaneously with age, despite continued thrombocytopenia [Mehaffey et al 2001, Del Vecchio et al 2005]. The anemia may also improve with age [author, personal observation].

Splenomegaly is commonly present in one form of *GATA1*-related disease (see Genotype-Phenotype Correlations).

Typically, no other physical anomalies are present.

Carrier females. Females who carry a *GATA1* mutation may manifest mild to moderate symptoms such as menorrhagia, presumably related to the proportion of relevant cells that contain the mutant *GATA1* allele on the active X chromosome [Raskind et al 2000; Balduini et al 2004; Raskind, unpublished observations].

Genotype-Phenotype Correlations

To a large extent, disease severity depends on the nature of the *GATA1* mutation. GATA-1 (erythroid transcription factor) is a transcription factor containing two zinc fingers. The carboxyl terminal finger (C-f) is essential for binding to DNA at most or all target genes. The amino terminal finger (N-f) stabilizes GATA-1 binding to a subset of DNA target sites and also participates in critical protein interactions. Most importantly, the N-f is required for interaction with the critical essential GATA-1 cofactor FOG-1.

Most *GATA1* mutations associated with inherited thrombocytopenia/anemia occur within the N-f and affect DNA binding, FOG-1 interactions, or perhaps both. The extent to which these functions are impaired can be linked to clinical severity.

For example, two different amino acid substitutions occur at GATA-1 amino acid position 218:

- An aspartic acid-to-glycine missense mutation (i.e., p.D218G) results in a mild phenotype characterized by macrothrombocytopenia without anemia [Freson et al 2001].
- A tyrosine substitution at the same position (i.e., p.D218Y) results in a severe phenotype with profound anemia and thrombocytopenia [Freson et al 2002].

In four families, two different mutations are described at amino acid position 216, which forms part of the DNA binding face of GATA-1. The phenotypic variability observed between different families illustrates how different mutations in GATA-1 protein could selectively impair its ability to recognize specific elements in cis configuration.

- Substitution p.R216Q causes macrothrombocytopenia with mild anemia and mild β-thalassemia [Raskind et al 2000, Yu et al 2002, Balduini et al 2004].
- The missense mutation p.R216W causes more severe symptoms, including anemia and CEP [Phillips et al 2005]. Apparently, this particular mutation causes porphyria by impairing transcription of the gene encoding the heme synthetic enzyme uroporphyrinogen III synthase, a known GATA-1 target gene [Solis et al 2001].

Specific genotype-phenotype correlations are illustrated further by the family described by Hollanda et al (2006), in which a germline splice mutation results in the exclusive production of the amino terminal truncated GATA-1s protein. Affected individuals exhibit a unique phenotype that includes macrocytic anemia, variable neutropenia, and trilineage dysplasia in the bone marrow. Hence, generation of the neutrophil lineage appears to be selectively affected (directly or indirectly) by loss of the GATA-1 amino terminus.

Table 2. Genotype-Phenotype Correlations

Mutation	FOG-1 Binding	DNA Binding	Platelet Phenotype [1]	Red Cell Phenotype	Platelet Aggregation	Other Features	Reference
p.V205M	↓↓	Normal	↓ Large	↓ Dyserythro-poietic, fetal hydrops	Not studied	Cryptorchidism [2]	Nichols et al 2000
p.G208S	↓	Normal	↓ Large	Normal	Decreased		Mehaffey et al 2001 [3, 4]
p.G208R	Not studied	Not studied	↓↓ Large	↓ Dyserythro-poietic	Not studied	Cryptorchidism in proband but also in two sibs with wild type *GATA1*	Del Vecchio et al 2005 [3, 4]
p.R216Q	Normal	↓	↓ Large	Mild β-thalassemia	Normal, but prolonged bleeding time	Splenomegaly	Thompson et al 1977, Raskind et al 2000, Yu et al 2002, Balduini et al 2004
p.R216W	Not studied	Not Studied	↓	Mild β-thalassemia	Not reported	Congenital erythropoietic porphyria	Phillips et al 2005
p.D218G	↓	Normal	↓ Large	Dyserythro-poiesis without anemia	Decreased		Freson et al 2001
p.D218Y	↓↓	Normal	↓↓ Large	Severe anemia	Not studied	Platelets in carrier female expressed only wild type allele	Freson et al 2002
p.G332C	Not studied	Not studied	Normal counts, but dysplastic megakaryocytes	Macrocytic anemia of variable severity	Decreased	Neutropenia	Hollanda et al 2006

1. Decreased platelet alpha granules are observed in all affected males studied.
2. Cryptorchidism in another family did not cosegregate with *GATA1* mutation [Del Vecchio et al 2005].
3. No response to splenectomy and/or steroids
4. Decreased bleeding episodes with age, despite persistence of thrombocytopenia

Nomenclature

Until *GATA1* mutations 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 in the current literature are "familial dyserythropoietic anemia and thrombocytopenia" [Nichols et al 2000, Del Vecchio et al 2005] and "X-linked macrothrombocytopenia" [Freson et al 2001].

Prevalence

GATA1-related cytopenia is rare; the prevalence is not known. To date, hematopoietic disease caused by inherited mutations in *GATA1* has been reported in ten families [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; Phillips et al 2005; Hollanda et al 2006; Raskind, unpublished observation].

GATA1 mutations may be more common than previously appreciated, particularly in persons with mild, unexplained thrombocytopenia/"grey platelet syndrome" present since birth [Tubman et al 2005].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

GATA1-related thrombocytopenia must be distinguished from other acquired and inherited thrombocytopenias [Balduini & Savoia 2004, Drachman 2004] (see Table 3). Algorithms exist to help differentiate among these disorders [Drachman 2004, Noris et al 2004].

Acquired thrombocytopenia can be categorized by immune causes, such as immune thrombocytopenic purpura (ITP) and lupus-associated thrombocytopenia or nonimmune causes, associated with decreased platelet life span or decreased platelet production.

Inherited thrombocytopenias, including those that are *GATA1*-related, are generally rare and frequently misdiagnosed as acquired. Inherited thrombocytopenias are generally classified on the basis of platelet size and functional abnormalities, pattern of inheritance, and associated features.

In *GATA1*-related disorders, platelets are usually large and may be hypogranular. Relatively common congenital causes of **macrothrombocytopenia** that could potentially be confused with *GATA1*-related disorders are described in Table 3.

Inherited syndromes of **small or normal-sized platelets** include congenital amegakaryocytic thrombocytopenia, amegakaryocytic thrombocytopenia with radio-ulnar synostosis, thrombocytopenia and absent radii, chromosome 10-linked thrombocytopenia, and *CBFA2 (RUNX1)*-related familial platelet disorder with predisposition to acute myeloid leukemia (FPD-AML).

Because of its X-linked mode of inheritance and association with thrombocytopenia, Wiskott-Aldrich syndrome (WAS) can be confused with *GATA1*-related disorders. Distinguishing features of WAS include small platelets, eczema (~80%), and immunodeficiency, although milder mutations may only manifest with microthrombocytopenia.

GATA1 mutations are often associated with anemia because GATA-1 controls genes that participate in both megakaryocyte and erythrocyte development. This association may be useful in differentiating *GATA1*-related disorders from other inherited macrothrombocytopenias. *GATA1* mutations are also more likely than the acquired platelet disorders to exhibit thrombocytopenia and platelet function abnormalities.

Table 3. Etiology and Characteristics of Other Inherited Syndromes of Macrothrombocytopenia

Name	Gene Symbol (Chromosome Location)	Mode of Inheritance	Features	Reference / OMIM Number
Bernard-Soulier syndrome	*GP1BA* (17p13) *GP1BB* (22q11) *GP9* (3q21)	AR [1]	Severely defective ristocetin-induced platelet agglutination Severe bleeding disorder	Lopez et al 1998 OMIM
MYH9-related syndromes	*MYH9* (22q12-13)	AD	Neutrophil inclusions May have hearing loss, cataract, or renal defects	Seri et al 2003 May-Hegglin anomaly OMIM Sebastian syndrome OMIM Fechtner syndrome OMIM Epstein syndrome OMIM
Mediterranean thrombocytopenia	*GP1BA*	AD	Dysmegakaryo-cytopoiesis	OMIM
Paris-Trousseau thrombocytopenia	*FLI1*, *ETS1* (11q23)	Microdeletion	Cardiac and facial abnormalities Mental retardation	OMIM
Jacobsen syndromes				Grossfeld et al 2004 OMIM
Velocardiofacial/ DiGeorge syndrome	(del22q11.2)	Microdeletion	Facial and cardiac abnormalities Mental retardation Psychiatric disorders	Sullivan 2004 OMIM
Gray platelet disorder [2]		Heterogeneous	Pale platelets Reduced or absent α-granules	OMIM

1. Heterozygotes may have mild disease.
2. One person with an X-linked form of this syndrome was found to have a mutation in *GATA1* [Wechsler et al 2002, Tubman et al 2005].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with *GATA1*-related cytopenia:

- Complete blood count and examination of the peripheral smear to assess the degree of cytopenia(s)
- Detailed history of age at which hematologic disease was manifest
- 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 also be useful to identify functional abnormalities that predict a greater risk of bleeding for any given platelet count, but can be difficult to interpret when platelet counts are lower than 100,000.

Treatment of Manifestations

Individuals with *GATA1*-related cytopenia are treated supportively.

Thrombocytopenia. Individuals with moderate to severe epistaxis, gingival bleeding, or gastrointestinal bleeding should receive platelet transfusions. Transfusion requirements vary

from person to person as bleeding can be related to both quantitative and/or qualitative platelet defects.

For individuals with thrombocytopenia and/or platelet aggregation defects, DDAVP treatment may be helpful for short-term management of mild to moderate bleeding.

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 cases of *GATA1*-related disease, although this treatment may be considered if splenomegaly is severe. Although splenectomy may improve the cytopenias, platelet dysfunction will not be improved.

Anemia. Erythrocyte transfusions are indicated when anemia is symptomatic (fatigue, tachycardia). Iron overload and the development of alloantibodies may limit chronic transfusion therapy. Extensive pretransfusion typing and matching for minor erythrocyte antigens in individuals receiving frequent transfusions can reduce the risk of alloimmunization.

Neutropenia. Patients with neutropenia who present with fever should be evaluated promptly with a physical examination, complete blood count, and blood culture and should receive appropriate parenteral antibiotics.

Bone marrow transplantation (BMT). For severe cases, BMT can be curative [Phillips et al 2005, Hollanda et al 2006]. BMT should be considered in individuals with severe phenotypes of *GATA1*-related cytopenia, particularly if an HLA-matched donor is available. While BMT may offer a cure, clinical experience with BMT in this disease is limited and families must be counseled on the significant risks and morbidities of BMT.

Prevention of Primary Manifestations

The only definitive cure for *GATA1*-related disease is bone marrow transplantation (BMT).

Prevention of Secondary Complications

Individuals with thrombocytopenia and/or platelet aggregation defects should receive a platelet transfusion prior to surgical or invasive dental procedures.

Individuals with neutropenia should be counseled regarding their increased risk of infection. They should avoid crowds and contact with individuals who have communicable diseases. When febrile, patients who are severely neutropenic (absolute neutrophil count <500) should seek medical attention; typically blood cultures are obtained and parenteral antibiotics are administered to avoid the possibility of life-threatening sepsis.

Surveillance

Depending on the phenotype of the disease, complete blood counts should be monitored so that supportive care can be provided as needed.

Individuals undergoing repeated erythrocyte transfusions should be monitored for iron overload and managed appropriately with iron chelation therapy.

Agents/Circumstances to Avoid

Individuals with thrombocytopenia should avoid antiplatelet agents including aspirin and nonsteroidal anti-inflammatory agents (NSAIDs) (e.g., ibuprofen).

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

Individuals with significant splenomegaly should avoid contact sports, which involved increased risk for traumatic splenic rupture.

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

Testing of Relatives at Risk

If a *GATA1* mutation 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 screening complete blood count to evaluate for thrombocytopenia, anemia, or neutropenia as these conditions have implications for their medical care. However, normal results do not rule out *GATA1*-related disease as platelet, erythrocyte, and neutrophil counts can vary significantly in individuals with *GATA1* mutations.

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

Therapies Under Investigation

In the future, this disorder may be treatable by adoptive gene therapy approaches to restore GATA-1 activity in hematopoietic cells.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Unlike immune-mediated platelet disorders such as ITP, *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.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- The father of an affected male will not have the disease nor will he be a carrier of the mutation.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier.
- If pedigree analysis reveals that the proband is the only affected family member, the mother may be a carrier or the affected male may have a *de novo* gene mutation, in which case the mother is not a carrier.
  - Because very few families with *GATA1* mutations have been described to date, the frequency of *de novo* mutations is not known.
  - Evidence of germline mosaicism has not been observed.
  - These characteristics of *GATA1*-related cytopenia will be more precisely defined as more families are studied.
- If a woman has more than one affected son and the disease-causing mutation cannot be detected in her DNA, she has germline mosaicism.
- When an affected male is the only affected individual in the family; several possibilities regarding his mother's carrier status need to be considered:
  - He has a *de novo* disease-causing mutation in the *GATA1* gene and his mother is not a carrier.
  - His mother has a *de novo* disease-causing mutation in the *GATA1* gene, either a) as a "germline mutation" (i.e., present at the time of her conception and therefore in every cell of her body); or b) as "germline mosaicism" (i.e., present in some of her germ cells only).
  - His mother has a disease-causing mutation that she inherited from a maternal female ancestor.

Sibs of a proband

- The risk to sibs depends upon the carrier status of the mother.
- If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%.
  - Male sibs who inherit the mutation will be affected.
  - Female sibs who inherit the mutation will be carriers and will usually not be affected, but may have reduced hematocrits and platelet counts to a variable degree. Large platelets may also be present and carriers of the XLTT subtype may have splenomegaly and slightly decreased β-globin synthesis.
- If the disease-causing mutation cannot be detected in the DNA of the mother of the only affected male in the family, the risk to sibs is low but greater than that of the general population because, although not yet observed, the possibility of germline mosaicism exists.

Offspring of a proband. Males will pass the disease-causing mutation to all of their daughters and none of their sons.

Other family members of a proband. The proband's maternal aunts may be at risk of being carriers and the aunt's offspring, depending upon their gender, may be at risk of being carriers or of being affected.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutation has been identified in the family.

Related Genetic Counseling Issues

It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

If the *GATA1* mutation has been identified in a family member, prenatal testing is possible for pregnancies at increased risk. The usual procedure is to determine fetal sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at about ten to 12 weeks' gestation or by amniocentesis usually performed at about 15-18 weeks' gestation. If the karyotype is 46,XY, DNA from fetal cells can be analyzed for the known disease-causing mutation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of GATA1-Related Cytopenia

Gene Symbol	Chromosomal Locus	Protein Name
GATA1	Xp11.2	Erythroid transcription factor

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for GATA1-Related Cytopenia

300367	DYSERYTHROPOIETIC ANEMIA WITH THROMBOCYTOPENIA
305371	GATA-BINDING PROTEIN 1; GATA1
314050	THROMBOCYTOPENIA, PLATELET DYSFUNCTION, HEMOLYSIS, AND IMBALANCED GLOBIN SYNTHESIS

Table C. Genomic Databases for GATA1-Related Cytopenia

Gene Symbol	Entrez Gene	HGMD
GATA1	2623 (MIM No. 305371)	GATA1

For a description of the genomic databases listed, click here.

Normal allelic variants: *GATA1* has five coding exons and two alternative untranslated regions.

Pathologic allelic variants: Most germline *GATA1* alterations associated with cytopenias are missense mutations. These mutations cluster in exon 4 amino acid residues 205, 208, 216, and 218 within the amino-terminal zinc finger domain. The mutations either affect erythroid transcription factor (GATA-1) binding to DNA or interaction of GATA-1 with its essential cofactor, Friend of GATA (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].

A mutation in exon 2 of *GATA1* that alters splicing was found in one family with anemia and neutropenia [Hollanda et al 2006]. This mutation results in the exclusive production of an amino-truncated isoform of GATA-1, termed GATA-1s (for GATA-1 short; also discussed in Allelic Disorders). In the context of Down syndrome (DS, trisomy 21), somatic mutations resulting in the production of only GATA-1s are associated with leukemia and transient myeloproliferative disorder (TMD) [Wechsler et al 2002]; however, the same *GATA1* mutations present in the germline of persons who do not have DS cause cytopenia but not leukemia [Hollanda et al 2006]. In mice, analogous mutations increase the proliferative capacity of embryonic megakaryocyte precursors but produce a minimal hematopoietic phenotype in adults [Li et al 2005].

Normal gene product: *GATA1* encodes a nuclear protein that contains two zinc fingers and an acidic amino terminal domain that can function as a transcriptional activator [Ferreira et al 2005, Lowry & Mackay 2006]. The C-terminal zinc finger is responsible for DNA binding activity to most or all target genes and the N-terminal zinc finger plays a role in stabilization of GATA-1 binding to DNA at a subset of target sites containing duplicated or palindromic GATA-1 motifs [Ohneda & Yamamoto 2002]. The N-f is also critical for binding of GATA-1 to numerous partner proteins, including FOG1, an essential factor required for many GATA-1 functions [Tsang et al 1997, Fox et al 1999]. GATA-1 is expressed in hematopoitic lineages and in Sertoli cells of testis. Gene targeting studies in mice indicate that GATA-1 is essential for the development of erythrocyte, megakaryocyte, mast cell, and eosinophil lineages. It is not known whether individuals with inherited *GATA1* mutations have defects in the latter two cell lineages.

Abnormal gene product: All disease-causing mutations are missense or splice site substitutions resulting in the production of an abnormal protein. Missense mutations in N-f affect its ability to bind either *GATA1* sites in DNA, the cofactor FOG1, or both. A splice site mutation results in a short form of the protein, GATA-1s. The functions of these abnormal proteins and their relationship to disease phenotypes are discussed in genotype-phenotype correlations and in Table 2.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Platelet Disorder Support Association
P.O. Box 61533
Potomac MD 20859
Phone: 877-528-3538; 301-294-5967
Fax: 301-294-3125
Email: pdsa@pdsa.org
www.pdsa.org

Medline Plus
Thrombocytopenia

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Balduini CL, Savoia A. Inherited thrombocytopenias: molecular mechanisms. Semin Thromb Hemost. 2004;30:513–23. [PubMed: 15497094]

Balduini CL, Pecci A, Loffredo G, Izzo P, Noris P, Grosso M, Bergamaschi G, Rosti V, Magrini U, Ceresa IF, Conti V, Poggi V, Savoia A. Effects of the R216Q mutation of GATA-1 on erythropoiesis and megakaryocytopoiesis. Thromb Haemost. 2004;91:129–40. [PubMed: 14691578]

Del Vecchio GC, Giordani L, De Santis A, De Mattia D. Dyserythropoietic anemia and thrombocytopenia due to a novel mutation in GATA-1. Acta Haematol. 2005;114:113–6. [PubMed: 16103636]

Drachman JG. Inherited thrombocytopenia: when a low platelet count does not mean ITP. Blood. 2004;103:390–8. [PubMed: 14504084]

Ferreira R, Ohneda K, Yamamoto M, Philipsen S. GATA1 function, a paradigm for transcription factors in hematopoiesis. Mol Cell Biol. 2005;25:1215–27. [PubMed: 15684376]

Fox AH, Liew C, Holmes M, Kowalski K, Mackay J, Crossley M. Transcriptional cofactors of the FOG family interact with GATA proteins by means of multiple zinc fingers. EMBO J. 1999;18:2812–22. [PubMed: 10329627]

Freson K, Devriendt K, Matthijs G, Van Hoof A, De Vos R, Thys C, Minner K, Hoylaerts MF, Vermylen J, Van Geet C. Platelet characteristics in patients with X-linked macrothrombocytopenia because of a novel GATA1 mutation. Blood. 2001;98:85–92. [PubMed: 11418466]

Freson K, Matthijs G, Thys C, Marien P, Hoylaerts MF, Vermylen J, Van Geet C. Different substitutions at residue D218 of the X-linked transcription factor GATA1 lead to altered clinical severity of macrothrombocytopenia and anemia and are associated with variable skewed X inactivation. Hum Mol Genet. 2002;11:147–52. [PubMed: 11809723]

Grossfeld PD, Mattina T, Lai Z, Favier R, Jones KL, Cotter F, Jones C. The 11q terminal deletion disorder: a prospective study of 110 cases. Am J Med Genet A. 2004;129:51–61. [PubMed: 15266616]

Hitzler JK, Zipursky A. Origins of leukaemia in children with Down syndrome. Nat Rev Cancer. 2005;5:11–20. [PubMed: 15630411]

Hollanda LM, Lima CS, Cunha AF, Albuquerque DM, Vassallo J, Ozelo MC, Joazeiro PP, Saad ST, Costa FF. An inherited mutation leading to production of only the short isoform of GATA-1 is associated with impaired erythropoiesis. Nat Genet. 2006;38:807–12. [PubMed: 16783379]

Li Z, Godinho FJ, Klusmann JH, Garriga-Canut M, Yu C, Orkin SH. Developmental stage-selective effect of somatically mutated leukemogenic transcription factor GATA1. Nat Genet. 2005;37:613–9. [PubMed: 15895080]

Lopez JA, Andrews RK, Afshar-Kharghan V, Berndt MC. Bernard-Soulier syndrome. Blood. 1998;91:4397–418. [PubMed: 9616133]

Lowry JA, Mackay JP. GATA-1: one protein, many partners. Int J Biochem Cell Biol. 2006;38:6–11. [PubMed: 16095949]

Mehaffey MG, Newton AL, Gandhi MJ, Crossley M, Drachman JG. X-linked thrombocytopenia caused by a novel mutation of GATA-1. Blood. 2001;98:2681–8. [PubMed: 11675338]

Muntean AG, Ge Y, Taub JW, Crispino JD. Transcription factor GATA-1 and Down syndrome leukemogenesis. Leuk Lymphoma. 2006;47:986–97. [PubMed: 16840187]

Nichols KE, Crispino JD, Poncz M, White JG, Orkin SH, Maris JM, Weiss MJ. Familial dyserythropoietic anaemia and thrombocytopenia due to an inherited mutation in GATA1. Nat Genet. 2000;24:266–70. [PubMed: 10700180]

Noris P, Pecci A, Di Bari F, Di Stazio MT, Di Pumpo M, Ceresa IF, Arezzi N, Ambaglio C, Savoia A, Balduini CL. Application of a diagnostic algorithm for inherited thrombocytopenias to 46 consecutive patients. Haematologica. 2004;89:1219–25. [PubMed: 15477207]

Ohneda K, Yamamoto M. Roles of hematopoietic transcription factors GATA-1 and GATA-2 in the development of red blood cell lineage. Acta Haematol. 2002;108:237–45. [PubMed: 12432220]

Phillips JD, Steensma DP, Spangrude GJ, Kushner JP. Congenital erythropoietic porphyria, beta-thalassemiaintermedia and thrombocytopenia due to a GATA1 mutation. Blood (ASH Annual Meeting Abstracts). 2005;106:515.

Raskind WH, Niakan KK, Wolff J, Matsushita M, Vaughan T, Stamatoyannopoulos G, Watanabe C, Rios J, Ochs HD. Mapping of a syndrome of X-linked thrombocytopenia with Thalassemia to band Xp11-12: further evidence of genetic heterogeneity of X-linked thrombocytopenia. Blood. 2000;95:2262–8. [PubMed: 10733494]

Seri M, Pecci A, Di Bari F, Cusano R, Savino M, Panza E, Nigro A, Noris P, Gangarossa S, Rocca B, Gresele P, Bizzaro N, Malatesta P, Koivisto PA, Longo I, Musso R, Pecoraro C, Iolascon A, Magrini U, Rodriguez Soriano J, Renieri A, Ghiggeri GM, Ravazzolo R, Balduini CL, Savoia A. MYH9-related disease: May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome are not distinct entities but represent a variable expression of a single illness. Medicine (Baltimore). 2003;82:203–15. [PubMed: 12792306]

Solis C, Aizencang GI, Astrin KH, Bishop DF, Desnick RJ. Uroporphyrinogen III synthase erythroid promoter mutations in adjacent GATA1 and CP2 elements cause congenital erythropoietic porphyria. J Clin Invest. 2001;107:753–62. [PubMed: 11254675]

Sullivan KE. The clinical, immunological, and molecular spectrum of chromosome 22q11.2 deletion syndrome and DiGeorge syndrome. Curr Opin Allergy Clin Immunol. 2004;4:505–12. [PubMed: 15640691]

Thompson AR, Wood WG, Stamatoyannopoulos G. X-linked syndrome of platelet dysfunction, thrombocytopenia, and imbalanced globin chain synthesis with hemolysis. Blood. 1977;50:303–16. [PubMed: 871527]

Tsang AP, Visvader JE, Turner CA, Fujiwara Y, Yu C, Weiss MJ, Crossley M, Orkin SH. FOG, a multitype zinc finger protein, acts as a cofactor for transcription factor GATA-1 in erythroid and megakaryocytic differentiation. Cell. 1997;90:109–19. [PubMed: 9230307]

Tubman VN, Levine JE, Campagna DR, Fleming MD, Neufeld EJ. X-linked gray platelet syndrome due to a GATA1 Arg261Gln mutation. Blood (ASH Annual Meeting Abstracts). 2005;106:515A.

Wechsler J, Greene M, McDevitt MA, Anastasi J, Karp JE, Le Beau MM, Crispino JD. Acquired mutations in GATA1 in the megakaryoblastic leukemia of Down syndrome. Nat Genet. 2002;32:148–52. [PubMed: 12172547]

Yu C, Niakan KK, Matsushita M, Stamatoyannopoulos G, Orkin SH, Raskind WH. X-linked thrombocytopenia with thalassemia from a mutation in the amino finger of GATA-1 affecting DNA binding rather than FOG-1 interaction. Blood. 2002;100:2040–5. [PubMed: 12200364]

Suggested Readings

Cantor AB. GATA transcription factors in hematologic disease. Int J Hematol. 2005;81:378–84. [PubMed: 16158817]

Crispino JD. GATA1 in normal and malignant hematopoiesis. Semin Cell Dev Biol. 2005;16:137–47. [PubMed: 15659348]

French DL, Newman PJ, Poncz M. Inherited disorders of platelets. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B (eds) The Metabolic and Molecular Bases of Inherited Disease (OMMBID), McGraw-Hill, New York, Chap 177. www.ommbid.com. modified 2002

Lowry JA, Mackay JP. GATA-1: one protein, many partners. Int J Biochem Cell Biol. 2006;38:6–11. [PubMed: 16095949]

Morceau F, Schnekenburger M, Dicato M, Diederich M. GATA-1: friends, brothers, and coworkers. Ann N Y Acad Sci. 2004;1030:537–54. [PubMed: 15659837]

Shimizu R, Yamamoto M. Gene expression regulation and domain function of hematopoietic GATA factors. Semin Cell Dev Biol. 2005;16:129–36. [PubMed: 15659347]

Chapter Notes

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Revision History

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- 10 August 2006 (whr) Original submission