Title: *GATA1*-Related Cytopenia *GeneReview* Table 2 – *GATA1* Genotype-Phenotype Observations

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Table 2. *GATA1* Genotype-Phenotype Observations

DNA Nucleotide Change	Predicted Protein Change	Platelet Phenotype [1]	Red Cell Phenotype	Other Features	References
Pathogenic Variants Resulting in GATA-1s					
c.94delG	p.Val32PhefsTer 105	↓ to ↓↓ Dysplastic megakaryocytes	Normocytic to macrocytic, mild-to-severe anemia	TMD w/o DS Hypercellular, fibrotic marrow Reported in heterozygous females only	Camargo et al [2022]
c.220G>C	p.Val74Leu	Normal or ↓ Dysplastic megakaryocytes	Macrocytic anemia of variable severity	Neutropenia	Hollanda et al [2006], Sankaran et al [2012], Klar et al [2014]
c.-19-2A>G (-21A>G)	--	Normal to ↑ Dysplastic megakaryocytes	Dyserythropoiesis Macrocytic anemia ↑ HbF	Occasional neutropenia Non-DS-AMKL, MDS, AML	Zucker et al [2016], Hasle et al [2022]
c.2T>C	p.Met1?	Normal to ↑ Dysplastic megakaryocytes	Dyserythropoiesis Severe macrocytic anemia Clinical features of DBA	Progression to MDS Megaloblastic change DS-AMKL w/o DS	Ludwig et al [2014], Parrella et al [2014], Hasle et al [2022], van Dooijewert et al [2022]
c.3G>A	p.Met1?	↓ (fluctuating)	Moderate-to-severe normocytic anemia Clinical features of DBA	Hypertelorism & flat nasal bridge Hepatomegaly	Chen et al [2022]
c.220+2T>C	--	↑	Dyserythropoiesis		van Dooijewe

		Mild dysplastic megakaryocytes	Moderate macrocytic anemia Clinical features of DBA		ert et al [2022]
c.220+1delG	--	Normal	Anemia Clinical features of DBA		Sankaran et al [2012]
Pathogenic Variants Affecting the N-terminal or C-terminal Zinc Finger Domain, FOG-1 Binding, or DNA Binding					
c.871-24C>T	--	Nl to ↓↓ Large Dysplastic megakaryocytes ↓ aggregation	Dyserythropoiesis Hydrops fetalis Severe infantile anemia improves w/age ↑ anemia w/illness ↑ HbF	Cryptorchidism Hypospadius Occasional dysplastic myeloid cells Progression to aplastic anemia	Abdulhay et al [2019], Kobayashi et al [2022]
c.613G>A	p.Val205Met	↓ Large	↓ Dyserythropoiesis Fetal hydrops	Cryptorchidism [2]	Nichols et al [2000], Bouchghoul et al [2018]
c.622G>A	p.Gly208Arg	↓↓ Large	↓ Dyserythropoiesis	Cryptorchidism in proband & in 2 sibs w/o *GATA1* pathogenic variant [2] No response to splenectomy &/or steroids ↓ bleeding episodes w/age, despite persistence of thrombocytopenia	Del Vecchio et al [2005], Kratz et al [2008]
c.622_623delGGinsTC	c.Gly208Ser	↓ Large ↓ aggregation Hypogranular	Normal	No response to splenectomy &/or steroids ↓ bleeding episodes w/age, despite persistence of thrombocytopenia	Mehaffey et al [2001], Martin et al [2021]

c.647G>A	p.Arg216Gln	↓ Large Normal aggregation Prolonged bleeding time	Mild anemia	Splenomegaly	Thompson et al [1977], Raskind et al [2000], Yu et al [2002], Balduini et al [2004], Hughan et al [2005], Tubman et al [2007], Campbell et al [2013], Åström et al [2015]
c.646C>T	p.Arg216Trp	↓	Mild anemia	CEP, splenomegaly	Hindmarsh [1986], Phillips et al [2007], Campbell et al [2013]
c.653A>G	p.Asp218Gly	↓ Large ↓ aggregation	Dyserythropoiesis w/o anemia		Freson et al [2001], White [2007], White et al [2007]
c.652G>T	p.Asp218Tyr	↓↓ Large	Severe anemia	Platelets in heterozygous female expressed only wild type allele	Freson et al [2002]
c.652G>A	p.Asp218Asn	↓↓ Large ↓ aggregation Prolonged bleeding time	Dyserythropoiesis w/o anemia	Splenomegaly	Hermans et al [2014], Bastida et al [2022]
c.788C>T	p.Thr263Met	↓ Dysplastic megakaryocytes	Mild dyserythropoiesis Mild anemia	↑ neutrophils Hypercellular, fibrotic marrow Reported in heterozygous females only [3]	Svidnicki et al [2021]
c.865C>T	p.His289Tyr [4]	Normal or ↓ Anisocytic thrombocytes ↓ aggregation	Dyserythropoiesis Normal to mild anemia		Bastida et al [2022]

		↓ αIIbβ3 integrin activation & α-granule secretion Prolonged bleeding time			
c.886A>C	p.Thr296Pro	↓ Large α-/δ (AN subtype)-storage pool deficiency	Mild dyserythropoiesis w/mild anemia ↑ HbF	Lu(a-b-) red cells (low expression in heterozygote)	Jurk et al [2022]
c.919C>T	p.Arg307Cys	↓	Mild dyserythropoiesis Hemolytic anemia	ADA overproduction	Ludwig et al [2022]
c.920G>A	p.Arg307His	↓ Large	Variable dyserythropoiesis Postnatal hyperchromic macrocytosis w/o anemia Hemolytic anemia ↑ HbF Hydrops fetalis	ADA overproduction Lu(a-b-) red cells Low birth weight Hypospadias Splenomegaly	Hetzer et al [2022], Ludwig et al [2022]
c.1240T>C	p.Ter414Arg	↓ Large	Normal	Lu(a-b-) red cells	Singleton et al [2013]

ADA = adenosine deaminase; AMKL = acute megakaryoblastic leukemia; AML = acute myeloid leukemia; CEP = congenital erythropoietic porphyria; DBA = Diamond-Blackfan anemia; DS = Down syndrome; FOG-1 = friend of GATA-1; GATA-1s = GATA-1 short; HbF = fetal hemoglobin; MDS = myelodysplastic syndrome; TMD = transient myeloproliferative disorder

1. Decreased platelet alpha granules are observed in all affected males studied.
2. Cryptorchidism has been reported in several males with *GATA1* pathogenic variants [Nichols et al 2000, Del Vecchio et al 2005]. Although *Gata1* is expressed in mouse testis, knockout of *Gata1* in Sertoli cells within the testis had no effect, suggesting that *Gata1* is not essential for Sertoli cell function [Lindeboom et al 2003]. The independent segregation of cryptorchidism and *GATA1* pathogenic variants in one of the two families [Del Vecchio et al 2005], in conjunction with the mouse data, make the mechanistic relationship between *GATA1* pathogenic variants and cryptorchidism unclear at this point.
3. Affected individuals also had a germline *JAK3* p.Val718Leu variant.
4. Variant affects amino acids outside the zinc finger domain (N-zinc finger domain: aa204-228, C-zing finger domain: aa258-282) but is predicted to potentially affect protein conformation and thus zinc finger binding.

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