U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Sieff C. Diamond-Blackfan Anemia. 2009 Jun 25 [Updated 2023 Mar 23]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Diamond-Blackfan Anemia

Colin Sieff, MBBCh, FRCPath[1]

Created: June 25, 2009; Revised: March 23, 2023.

Summary

Clinical characteristics

Diamond-Blackfan anemia (DBA) is characterized by a profound normochromic and usually macrocytic anemia with normal leukocytes and platelets, congenital malformations in up to 50%, and growth deficiency in 30% of affected individuals. The hematologic complications occur in 90% of affected individuals during the first year of life. The phenotypic spectrum ranges from a mild form (e.g., mild anemia or no anemia with only subtle erythroid abnormalities, physical malformations without anemia) to a severe form of fetal anemia resulting in nonimmune hydrops fetalis. DBA is associated with an increased risk for acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), and solid tumors including osteogenic sarcoma.

Diagnosis/testing

The clinical diagnosis can be established in a proband with macrocytic anemia with onset prior to age one year, no other significant cytopenias, reticulocytopenia, normal marrow cellularity with a paucity of erythroid precursors, and no evidence of another acquired or inherited disorder of bone marrow function.

The molecular diagnosis can be established in a female proband by identification of a heterozygous pathogenic variant in one of the 22 genes associated with DBA.

The molecular diagnosis can be established in a male proband by identification of a heterozygous pathogenic variant in a gene associated with autosomal dominant DBA or identification of a hemizygous pathogenic variant in *GATA1* or *TSR2* (associated with X-linked inheritance).

Management

Treatment of manifestations: Corticosteroid treatment, recommended in children older than age 12 months, improves the red blood cell count in approximately 80% of affected individuals. Chronic transfusion with packed red blood cells is necessary during the first year of life to avoid steroid-induced toxicity in those not responsive to a trial of corticosteroids at age 12 months and in individuals who relapse. Hematopoietic stem cell

Author Affiliation: 1 Boston Children's Hospital and Dana Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; Email: colin.sieff@childrens.harvard.edu.

transplantation, the only curative therapy for the hematologic manifestations of DBA, is often recommended for those who are transfusion dependent or develop other cytopenias. Ocular, skeletal, genitourinary, cardiac, and endocrine complications are best managed in collaboration with appropriate subspecialists. Treatment of malignancies should be coordinated by an oncologist. Chemotherapy must be given cautiously as it may lead to prolonged cytopenia and subsequent toxicities.

Prevention of secondary complications: Transfusion-related iron overload is the most common complication in transfusion-dependent individuals. Iron chelation therapy with deferasirox orally or desferrioxamine subcutaneously is recommended after ten to 12 transfusions. Corticosteroid-related side effects must also be closely monitored, especially as related to risk for infection, growth deficiency, and loss of bone density in growing children. Often individuals will be placed on transfusion therapy if these side effects are intolerable.

Surveillance: Complete blood counts several times a year; bone marrow aspirate/biopsy to evaluate morphology and cellularity only in the event of another cytopenia or a change in response to treatment. In steroid-dependent individuals: monitor blood pressure and (in children) growth. Evaluation by an endocrinologist for those who are steroid dependent and those at risk for transfusion iron overload. Cancer surveillance includes history, physical examination, and blood counts every four to six months. If red blood cell, white blood cell, or platelet counts fall rapidly, bone marrow aspirate with biopsy and cytogenetic studies (including karyotype and FISH analysis) to look for acquired abnormalities in chromosomes 5, 7, and 8 that are associated with myelodysplastic syndrome or leukemia.

Agents/circumstances to avoid: Deferiprone for the treatment of iron overload (which can cause neutropenia); infection (especially in individuals on corticosteroids).

Evaluation of relatives at risk: Molecular genetic testing of at-risk relatives of a proband with a known pathogenic variant allows for early diagnosis and appropriate monitoring for bone marrow failure, physical abnormalities, and related cancers.

Pregnancy management: Management by an obstetrician with expertise in high-risk pregnancies and hematologists with experience in bone marrow failure syndromes. During pregnancy the maternal hemoglobin level must be monitored. Use of low-dose aspirin up to 37 weeks' gestation may help prevent vasculo-placental complications in women with a history of a problematic pregnancy.

Genetic counseling

DBA is most often inherited in an autosomal dominant manner; *GATA1*-related and *TSR2*-related DBA are inherited in an X-linked manner.

- *Autosomal dominant.* Approximately 40%-45% of individuals with autosomal dominant DBA have inherited the pathogenic variant from a parent; approximately 55%-60% have a *de novo* pathogenic variant. Each child of an individual with autosomal dominant DBA has a 50% chance of inheriting the pathogenic variant.
- *X-linked.* Males with *GATA1*- or *TSR2*-related DBA pass the pathogenic variant to all of their daughters and none of their sons. Women heterozygous for a *GATA1* or *TSR2* pathogenic variant have a 50% chance of transmitting the pathogenic variant in each pregnancy: males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers and will usually not be affected. Carrier testing of at-risk female relatives is possible if the *GATA1* or *TSR2* pathogenic variant has been identified in the family.

Once the DBA-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Diamond-Blackfan anemia (DBA) **should be suspected** in individuals with the following clinical, laboratory, and histopathologic features, and no evidence of another inherited disorder of bone marrow function.

Clinical features

- Pallor, weakness, failure to thrive
- Growth deficiency (observed in 30%)
- Congenital malformations (observed in ~30%-50%); in particular craniofacial, upper-limb, heart, and genitourinary malformations

Laboratory features

- Macrocytic anemia with no other significant cytopenias
- Increased erythrocyte mean corpuscular volume
- Reticulocytopenia
- Elevated erythrocyte adenosine deaminase activity (eADA) (observed in 80%-85%)
- Elevated hemoglobin F concentration

Histopathology features (bone marrow aspirate)

- Normal marrow cellularity
- Erythroid hypoplasia
- Marked reduction in normoblasts
- Persistence of pronormoblasts on occasion
- Normal myeloid precursors and megakaryocytes

Other. Individuals show no evidence of another inherited disorder of bone marrow function. See Differential Diagnosis.

Establishing the Diagnosis

The clinical diagnosis of DBA **can be established** in a proband with all of the following clinical, laboratory, and histopathology features:

- Macrocytic anemia with onset prior to age one year
- No other significant cytopenias
- Reticulocytopenia
- Normal marrow cellularity with a paucity of erythroid precursors
- No evidence of another acquired or inherited disorder of bone marrow function (See Differential Diagnosis.)

The molecular diagnosis **can be established in a female** proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in one of the genes listed in Table 1.

The molecular diagnosis **can be established in a male** proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in one of the genes listed in Table 1 associated with autosomal dominant inheritance, or a hemizygous pathogenic (or likely pathogenic) variant in *GATA1* or *TSR2* associated with X-linked inheritance.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular testing approaches usually begin with **a multigene panel** with analysis of DBA-related genes (rare DBA-related genes may not be included in a panel). Failure to identify a gene can be followed by more **comprehensive genomic testing** [Ulirsch et al 2018].

- **A multigene panel** that includes the genes in Table 1 and other genes of interest (see Differential Diagnosis). 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*; thus, clinicians need to determine which multigene panel is most likely 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. (3) In some laboratories, panel options may include a custom laboratory-designed panel, custom phenotype-focused exome analysis, and re-analysis of 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.

- **More comprehensive genomic testing** (when available) including exome sequencing or genome sequencing may be considered if a multigene panel fails to confirm a diagnosis in an individual with features of DBA.

  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 Diamond-Blackfan Anemia (DBA)

Gene [1,2]	Proportion of DBA Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detected by Method	
		Sequence analysis [4,5]	Gene-targeted deletion/ duplication analysis [5,6]
GATA1 [7]	<1% (5 families)	~100%	None reported
RPL5	7%-12%	~95%	<5%
RPL9	<1%	~100%	None reported
RPL11	5%-7%	~90%	~10%
RPL15	~1%	~80%	~20%
RPL18	Rare	1 family	None reported
RPL26	Rare	1 person	None reported
RPL27	Rare	2 persons	None reported
RPL31	Rare	1 person	1 person
RPL35	Rare	1 family	2 persons
RPL35A	2%-3%	~50%	~50%
RPS7	~1%	~100%	None reported

Table 1. continued from previous page.

Gene [1,2]	Proportion of DBA Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detected by Method	
		Sequence analysis [4,5]	Gene-targeted deletion/ duplication analysis [5,6]
RPS10	1%-3%	~100%	None reported
RPS15A	Rare	1 family	None reported
RPS17	1%-3%	<35%	>65%
RPS19	25%-30%	~95%	~5%
RPS24	2%-3%	~90%	1 person
RPS26	6.6%-9%	>80%	<20%
RPS27	Rare	1 person	None reported
RPS28	Rare (2 families)	2 families	None reported
RPS29	~1%	~80%	1 person
TSR2	Rare	1 family	None reported
Unknown	~20%	NA	

Pathogenic variants of any one of the genes included in this table account for ≥1% of DBA.
1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in these genes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. 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.
7. There is not consensus as to whether individuals with a *GATA1* pathogenic variant associated with overlapping clinical features of DBA should be diagnosed with *GATA1*-related cytopenia or DBA.

Clinical Characteristics

Clinical Description

Diamond-Blackfan anemia (DBA) is characterized by early-onset hypoplastic anemia. Congenital anomalies are observed in approximately 50% of affected individuals and more than one anomaly is observed in up to 25% of individuals. Additional features include growth deficiency and predisposition to malignancy.

Table 2. Diamond-Blackfan Anemia: Frequency of Select Features

Feature	% of Persons with Feature [1]	Comment
Anemia	100%	90% in 1st year of life
Craniofacial features	27%	
Upper limb anomalies	16%	
Genitourinary malformations	13%	
Heart defects	11%	
Growth deficiency	30%	

Table 2. continued from previous page.

Feature	% of Persons with Feature [1]	Comment
Malignancy	2%-5%	Acute myelogenous leukemia, myelodysplastic syndrome, & solid tumors incl osteogenic sarcoma & lung, colon, & cervical carcinomas

1. Ball et al [1996], Ramenghi et al [2000], Lipton et al [2006]

Anemia. The primary hematologic feature of DBA is a profound normochromic, macrocytic anemia with normal leukocytes and platelets. The hematologic complications of DBA occur in 90% of affected individuals during the first year of life: the median age at presentation is two months and the median age at diagnosis is three months [Bagby et al 2004, Ohga et al 2004]. Treatment with corticosteroids is recommended in children older than age 12 months (see Management). Approximately 70% of individuals respond but eventually 40% remain steroid dependent and 40% become transfusion dependent; 20% go into remission [Chen et al 2005, Vlachos et al 2008].

Craniofacial features include microcephaly; hypertelorism, epicanthus, ptosis; microtia, low-set ears; broad, depressed nasal bridge; cleft lip/palate, high arched palate; micrognathia; low anterior hairline.

Eye findings include congenital glaucoma, congenital cataract, strabismus.

Neck. Features include webbing, short neck, Klippel-Feil anomaly, Sprengel deformity.

Upper limb and hand including thumb. Findings include absent radial artery; flat thenar eminence; triphalangeal, duplex, bifid, hypoplastic, or absent thumb.

Genitourinary findings include absent kidney, horseshoe kidney; hypospadias.

Heart findings include ventricular septal defect, atrial septal defect, coarctation of the aorta, other cardiac anomalies.

Growth deficiency. Low birth weight was reported in 25% of affected infants. Thirty percent of affected individuals have growth deficiency. Growth deficiency can be influenced by other factors including steroid treatment [Chen et al 2005, Vlachos et al 2008].

Malignancy. DBA is associated with an increased risk for acute myelogenous leukemia, myelodysplastic syndrome, and solid tumors including osteogenic sarcoma [Janov et al 1996, Vlachos et al 2001, Vlachos et al 2012, Alter et al 2018].

Development. Rarely, developmental delay can occur [Kuramitsu et al 2012].

The phenotypic spectrum is broad. Within the same family, affected individuals can have typical DBA or atypical phenotypes including (1) mild anemia; (2) no anemia with only subtle erythroid abnormalities such as macrocytosis, elevated erythrocyte adenosine deaminase activity, and/or increased hemoglobin F concentration; or (3) physical malformations without anemia. Others may have a severe form presenting with fetal anemia that results in nonimmune hydrops fetalis [Dunbar et al 2003, Saladi et al 2004]. Onset of atypical DBA can be later than age one year.

Phenotype Correlations by Gene

RPL5. Craniofacial, congenital heart, and thumb defects were more severe than those seen with pathogenic variants in *RPL11* and *RPS19* [Gazda et al 2008, Quarello et al 2010]. Cleft lip and/or cleft palate (CL/P) was reported in 45% of affected persons with *RPL5* pathogenic variants [Gazda et al 2008] and in 50% of an affected group of Italians with *RPL5* pathogenic variants [Quarello et al 2010]. Small gestational age was reported in

seven (~88%) of eight individuals with an *RPL5* pathogenic variant versus 43% of individuals with an *RPS19* pathogenic variant [Cmejla et al 2009].

RPL11. Pathogenic variants in *RPL11* are predominantly associated with thumb abnormalities [Gazda et al 2008, Cmejla et al 2009].

Genotype-Phenotype Correlations

Many pathogenic variants are unique to a family and no genotype-phenotype correlations have been confirmed.

Penetrance

Penetrance is almost complete with loss-of-function variants in *RPL5*, *RPS19*, and *RPS26.* Penetrance is high with loss-of-function variants in other genes that encode ribosomal subunits. Missense variants (e.g., of *RPS19*) appear to be less penetrant [Ulirsch et al 2018].

Nomenclature

Diamond-Blackfan anemia has previously been known as congenital hypoplastic anemia of Blackfan and Diamond, congenital hypoplastic anemia, Blackfan-Diamond syndrome, Aase syndrome, and Aase-Smith syndrome II.

Prevalence

The incidence of DBA is estimated at between 1:100,000 and 1:200,000 live births; incidence remains consistent across ethnicities [Vlachos et al 2008].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *RPL5*, *RPL9*, *RPL11*, *RPL15*, *RPL18*, *RPL26*, *RPL27*, *RPL31*, *RPL35*, *RPL35A*, *RPS7*, *RPS10*, *RPS15A*, *RPS17*, *RPS19*, *RPS24*, *RPS26*, *RPS27*, *RPS28*, *RPS29*, or *TSR2.*

GATA1. Other germline pathogenic variants in *GATA1* may lead to *GATA1*-related cytopenia in males, which 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, congenital erythropoietic porphyria. 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 decrease spontaneously with age. Females may have mild-to-moderate findings, such as menorrhagia.

Acquired (somatic) *GATA1* pathogenic variants are also found in neonates with Down syndrome with transient abnormal myelopoiesis;10%-20% of these neonates will develop acute megakaryoblastic leukemia [Bhatnagar et al 2016].

Differential Diagnosis

Because of the difficulty of establishing the diagnosis of Diamond-Blackfan anemia (DBA), in some instances the diagnosis may only be established after other disorders in the differential diagnoses have been ruled out.

Transient Erythroblastopenia of Childhood

Transient erythroblastopenia of childhood (TEC) (OMIM 227050) is characterized by acquired anemia caused by decreased production of red blood cell precursors in a previously healthy child. The etiology of TEC is unknown, although an association with viral infections has been proposed. TEC is almost always self-resolving within one to several months and only requires clinical intervention (red blood cell transfusion) in severe cases. Features that distinguish TEC from DBA include older age at diagnosis: more than 80% of children with TEC are age one year or older at diagnosis. Only 10% of children with TEC have elevated erythrocyte adenosine deaminase activity. In children with TEC, anemia is normocytic.

Other Genetic Conditions with Bone Marrow Failure

Table 3. Differential Diagnosis of Diamond-Blackfan Anemia: Genetic Conditions with Bone Marrow Failure

Gene	Disorder	MOI	Clinical Characteristics
ACD *CTC1* *DKC1* *NHP2* *NOP10* *PARN* *RTEL1* *TERC* *TERT* *TINF2* *WRAP53*	Dyskeratosis congenita (DC)	XL AD AR	Telomere biology disorder characterized by a classic triad of dysplastic nails, lacy reticular pigmentation of the upper chest &/or neck, & oral leukoplakia (triad may not be present in all persons). ↑ risk for progressive BMF, MDS or acute AML, solid tumors, & pulmonary fibrosis.
ADA2 (*CECR1*)	Adenosine deaminase 2 (ADA2) deficiency	AR	Vasculitis &/or a DBA phenotype in persons w/ADA2 deficiency
BRCA2 *BRIP1* *FANCA* *FANCB* *FANCC* *FANCD2* *FANCE* *FANCF* *FANCG* *FANCI* (21 genes [1])	Fanconi anemia (FA)	AR AD XL	Physical abnormalities (~75% of affected persons): short stature, abnormal skin pigmentation, skeletal malformations, microcephaly, ophthalmic & genitourinary tract anomalies. Progressive BMF w/ pancytopenia. ↑ risk hematologic malignancies (AML) & solid tumors (head & neck, skin, GI tract, & genital tract).
DNAJC21 *EFL1* *SBDS* *SRP54*	Shwachman-Diamond syndrome (SDS)	AR AD	Exocrine pancreatic dysfunction w/malabsorption, malnutrition, growth failure, bone abnormalities, persistent or intermittent neutropenia, & recurrent infections; cytopenias & susceptibility to MDS & AML.
EPO	DBA-like (OMIM 617911)	AR	Rare pathogenic variants can present w/PRCA but will respond to treatment w/recombinant EPO, unlike DBA.
Mitochondrial DNA [2]	Pearson syndrome (See Mitochondrial DNA Deletion Syndromes.)	Mat	Sideroblastic anemia of childhood, pancytopenia, exocrine pancreatic failure, & renal tubular defects. Progressive liver failure & intractable metabolic acidosis typically result in death in infancy. Those who survive develop neurologic symptoms.
MYSM1	Bone marrow failure syndrome 4 (OMIM 618116)	AR	Transfusion-dependent anemia in early childhood w/other cytopenias

Table 3. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics
NHEJ1	SCID w/microcephaly, growth retardation, & sensitivity to ionizing radiation (OMIM 611291)	AR	Immunodeficiency & dysmorphic facies; 50% have anemia & thrombocytopenia.
RMRP	Cartilage-hair hypoplasia – anauxetic dysplasia (CHH-AD)	AR	Severe short-limb short stature usually present in newborns; joint hypermobility, fine silky hair, immunodeficiency, anemia, ↑ risk for malignancy, gastrointestinal dysfunction, & impaired spermatogenesis. Clinical manifestations are variable even w/in a family.

AD = autosomal dominant; AML = acute myeloid leukemia; AR = autosomal recessive; BMF = bone marrow failure; DBA = Diamond-Blackfan anemia; DD = developmental delay; EPO = erythropoietin; Mat = maternal; MDS = myelodysplastic syndrome; MOI = mode of inheritance; PRCA = acquired pure red cell aplasia; SCID = severe combined immunodeficiency; XL = X-linked

1. Listed genes represent the most commonly associated genes. See Fanconi Anemia for other genes associated with this phenotype.

2. Pearson syndrome is most often caused by *de novo* deletions in mitochondrial DNA; rearrangements (large-scale partial deletions and duplications) have also been found [Morel et al 2009].

Acquired Conditions with Bone Marrow Failure

Infections

- Parvovirus B19 infection; usually asymptomatic, but occasionally can cause red cell aplasia, which is most often mild and self-limited by production of virus-neutralizing antibodies in the host [Parekh et al 2005]. However, in persons with hereditary or acquired anemia, parvovirus infection can be severe and life-threatening, requiring red blood cell transfusions. Seropositivity for parvovirus reaches 50% by age 15 years and 90% in the elderly.
- HIV; associated with pure red cell aplasia (PRCA)
- Viral hepatitis
- Mononucleosis and human T-cell lymphotropic virus type 1

Drugs and toxins

- Anti-seizure medications: diphenylhydantoin, sodium valproate, carbamazepine, sodium dipropylacetate
- Others: azathioprine; chloramphenicol and thiamphenicol; sulfonamides; isoniazid; procainamide

Immune-mediated diseases

- Thymoma, most commonly associated with PRCA. Approximately 5%-10% of persons with thymoma develop PRCA.
- Myasthenia gravis, systemic lupus erythematosus, and multiple endocrinopathies

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Diamond-Blackfan anemia (DBA), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Diamond-Blackfan Anemia

System/Concern	Evaluation	Comment
Anemia	Eval by hematologist for macrocytosis & reticulocytopenia	Macrocytosis is not always present.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Congenital anomalies	Eval by clinical geneticist for congenital malformations	
Eyes	Ophthalmology eval for glaucoma & cataract for persons on steroid therapy	
Skeletal anomalies	Orthopedic eval for persons w/: • Clinical findings suggestive of Klippel-Feil anomaly or Sprengel deformity • Upper-limb &/or thumb anomalies	
Genitourinary anomalies	• Eval by nephrologist & urologist as appropriate • Ultrasound exam of kidneys & urinary tract	
Cardiology	Eval by cardiologist incl echocardiography	
Endocrine	Growth assessment	
Development	Developmental assessment	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of DBA in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

DBA = Diamond-Blackfan anemia; MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Anemia. Corticosteroids can initially improve the red blood count in approximately 80% of affected individuals.

- The recommended corticosteroid is prednisone with a starting dose of 2 mg/kg/day given orally once a day in the morning, beginning after age 12 months and ten days to two weeks after a transfusion. An increase in hemoglobin and reticulocyte count is usually seen in two to four weeks. If there is no response by three weeks, steroids can be tapered over two weeks.
- Corticosteroids may be slowly tapered to the minimal effective dose. Monitoring of blood counts is needed to ensure that the red cell hemoglobin concentration remains at 80-100 g/L, the minimum required for transfusion independence.
- The corticosteroid maintenance dose varies and can be extremely low in some individuals. Concerns about the long-term effects of steroids have led to the recommendation of 0.25 mg/kg/day as a preferable maximum daily dose.
- If after approximately one month the recommended steroid dose does not sustain the red cell hemoglobin concentration in an acceptable range, the corticosteroids should be tapered and discontinued.

Side effects of corticosteroids include osteoporosis, weight gain, cushingoid appearance, hypertension, diabetes mellitus, growth restriction, pathologic bone fractures, gastric ulcers, cataracts, glaucoma, and increased susceptibility to infection.

Red blood cell transfusion. If the individual is resistant to corticosteroid therapy, chronic transfusion with packed red blood cells is necessary. The goal of transfusion therapy is a red cell hemoglobin concentration of 80-100 g/L, which is usually adequate for maintaining growth and development.

Hematopoietic stem cell transplantation (HSCT) is the only curative therapy for DBA. Persons with DBA who are transfusion dependent or develop other cytopenias are often treated with HSCT.

In one study of 61 persons with DBA who underwent bone marrow transplantation (BMT), the majority (67%) received their bone marrow grafts from an HLA-matched related donor. The three-year probability of overall survival was 64% (range 50%-74%). Transplantation from an HLA-identical sib donor was associated with better survival [Roy et al 2005].

The Diamond-Blackfan Anemia Registry of North America describes 36 individuals who underwent HSCT: 21 HLA-matched sib HSCTs and 15 alternative donor HSCTs. Survival greater than five years from HSCT for allogeneic sib transplants was 72.7% ±10.7% versus survival greater than five years from alternative donor transplants of 17.1% ±11.9% [Lipton et al 2006, Vlachos et al 2008]. Survival was the best (92.3%) for children younger than age ten years transplanted using an HLA-matched sib.

In a French/German HSCT study of 70 children with DBA, a matched sib donor was available for 45 individuals, a 10/10 HLA matched unrelated donor in 12 individuals, a 9/10 HLA matched unrelated donor in seven individuals, and a less compatible or incomplete HLA matched donor in six individuals. Overall survival was 91% with no difference by donor type. All individuals engrafted; one individual had secondary graft failure. The difference in chronic GVHD between children transplanted before age ten years compared with older individuals did not reach statistical significance.

Note: (1) It is recommended that the affected individual, sibs, and parents undergo HLA typing at the time of diagnosis of DBA to identify the most suitable bone marrow donor in the event that HSCT would be required. (2) Because penetrance of DBA is incomplete, it is possible that a relative considered as a bone marrow donor could have a pathogenic variant but not manifest findings of DBA. (3) Relatives with a pathogenic variant, regardless of their clinical status, are not suitable bone marrow donors, because their donated bone marrow may fail or not engraft in the recipient.

Treatment of other manifestations

- **Glaucoma and cataract.** As recommended by ophthalmologist
- **Skeletal anomalies.** Surgical management of thumb anomalies as recommended by orthopedist; occupational and physical therapy as needed
- **Genitourinary malformations.** Managed as recommended by nephrologist and/or urologist
- **Congenital heart defects.** As recommended by cardiologist
- **Cancer.** Treatment of malignancies coordinated by oncologist

Prevention of Secondary Complications

Transfusion iron overload is the most common complication in transfusion-dependent individuals. The following methods are used both to assess for evidence of transfusion iron overload and to evaluate the effectiveness of iron chelation therapy:

- Measurement of iron concentration in a liver biopsy specimen, which accurately determines total body iron accumulation
- T_2^*-weighted MRI for assessing iron loading in the liver and heart
- Magnetic biosusceptometry (SQUID), which gives a measurement of hepatic iron concentration

Note: (1) Although the latter two methods of total iron measurement are noninvasive, SQUID is not widely available. MRI is now more widely available and referral to a center with experience in this technique is advisable to obtain a baseline measurement and to more conveniently follow progress after starting chelation therapy. Although liver biopsy is the "gold standard" [Cappellini & Piga 2008, Vlachos et al 2008] it is not a practical choice for long-term follow up. (2) Routine measurement of serum ferritin concentration is not reliable in detecting iron overload because the serum ferritin concentration does not always correlate with total body iron accumulation.

Iron chelation therapy is usually started after ten to 12 transfusions (170-200 mL/kg of packed red blood cells), when serum ferritin concentration reaches 1,000-1,500 µg/L, or when hepatic iron concentration reaches 6-7 mg/g of dry weight liver tissue.

- **Deferasirox** is recommended in individuals age two years or older. It is administered once daily in an oral dose of 20-30 mg/kg/day. Side effects are usually mild and include rash, nausea, creatinine elevation, and rarely proteinuria and transaminase elevation. In affected individuals, satisfaction with deferasirox is greater than with desferrioxamine, mostly because of ease of administration [Cappellini & Piga 2008, Porter et al 2008, Vlachos et al 2008].
- **Desferrioxamine** is administered four to seven nights a week in an eight- to 12-hour subcutaneous infusion via a portable pump. The recommended initial dose is 40 mg/kg/day; the maximum dose is 50-60 mg/kg/day. The dose and frequency of infusion may be modified using the serum ferritin concentration or the hepatic iron concentration as a guide [Cappellini & Piga 2008, Vlachos et al 2008]. Side effects include ocular and auditory toxicity and growth deficiency. Compliance rate is hampered by the demanding administration route and schedule.

Note: Deferiprone is not recommended in the treatment of iron overload in individuals with DBA [Vlachos et al 2008] because its side effects include neutropenia [Henter & Karlen 2007].

Side effects of corticosteroids include osteoporosis, weight gain, cushingoid appearance, hypertension, diabetes mellitus, growth deficiency, pathologic bone fractures, gastric ulcers, cataracts, glaucoma, and increased susceptibility to infection [Alter & Young 1998, Willig et al 1999, Lipton et al 2006].

One of the critical side effects of corticosteroids is growth deficiency. If growth is severely impaired, corticosteroids should be stopped and replaced by a short-term red blood cell transfusion regimen [Vlachos et al 2008].

Surveillance

The following are indicated:

- Complete blood counts several times a year
- Bone marrow aspirate/biopsy to evaluate morphology and cellularity, if evidence of another cytopenia or failure of current treatment is noted
- Monitoring of blood pressure in individuals who are steroid dependent
- Monitoring of growth in individuals who are steroid dependent and in those at risk for transfusion iron overload
- Evaluation by an endocrinologist; recommended for individuals who are steroid dependent and those at risk for transfusion iron overload

Cancer surveillance includes the following:

- In individuals with DBA who are otherwise healthy, every four to six months: an interim history, physical examination, and measurement of blood count

- If red blood cell, white blood cell, or platelet counts fall rapidly, bone marrow aspirate with biopsy and cytogenetic studies (including karyotype and FISH analysis) to look for acquired abnormalities in chromosomes 5, 7, and 8 that are associated with certain cancers [Vlachos et al 2008]

Agents/Circumstances to Avoid

Deferiprone is not recommended in the treatment of iron overload in persons with DBA because its side effects include neutropenia [Vlachos et al 2008].

Individuals with DBA, especially those on corticosteroid treatment, should take reasonable precautions to avoid infections, as steroid-dependent individuals are more prone to complications resulting from immune system dysfunction.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual to allow early diagnosis and appropriate monitoring for bone marrow failure, physical abnormalities, and related cancers. Evaluations include:

- Molecular genetic testing if the pathogenic variant in the family is known;
- Consideration of other testing (e.g., mean corpuscular volume, erythrocyte adenosine deaminase activity, and/or fetal hemoglobin concentration) if the pathogenic variant in the family is not known – especially of relatives being considered as bone marrow donors [Vlachos et al 2008].

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

Pregnancy Management

Management of pregnancy in women with DBA requires obstetricians with expertise in high-risk pregnancies and hematologists with experience with bone marrow failure syndromes [Alter et al 1999, Taher et al 2020].

During pregnancy the maternal hemoglobin level must be monitored.

Use of low-dose aspirin up to 37 weeks' gestation may help prevent vasculo-placental complications in women with a history of a previous problematic pregnancy [Faivre et al 2006].

A study that surveyed 64 pregnancies in women with DBA found a high incidence of complications in both mothers and children. Risks include the following [Faivre et al 2006]:

- Intrauterine growth restriction
- Preeclampsia
- Retroplacental hematoma
- In utero fetal death
- Preterm delivery

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register 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.

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

Most often, Diamond-Blackfan anemia (DBA) is inherited in an autosomal dominant manner. *GATA1*-related DBA and *TSR2*-related DBA are inherited in an X-linked manner.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Approximately 40%-45% of individuals diagnosed with autosomal dominant DBA inherited a DBA-causing pathogenic variant from a parent who may or may not have manifestations of DBA [Orfali et al 2004].
- Approximately 55%-60% of individuals diagnosed with autosomal dominant DBA have the disorder as the result of a *de novo* pathogenic variant.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.

  Note: If a pathogenic variant has not been identified in the proband, other testing options for the parents can be considered (e.g., mean corpuscular volume, erythrocyte adenosine deaminase activity, and/or fetal hemoglobin concentration).
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a mosaic parent. Parental germline mosaicism is suggested in a family described by Cmejla et al [2000] in which neither parent of two affected sibs had the DBA-causing pathogenic variant identified in the affected sibs. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
  - The proband inherited a DBA-causing pathogenic variant from a parent who subsequently developed somatically acquired loss of heterozygosity with preferential loss of the chromosome with the DBA-causing pathogenic variant. This scenario may cause a false negative molecular result when testing leukocyte DNA (see Molecular Pathogenesis) [Venugopal et al 2017, Garelli et al 2019].
- The family history of some individuals diagnosed with DBA may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative

family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected with autosomal dominant DBA and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- The penetrance of DBA in heterozygous sibs is high but may vary somewhat depending on the familial pathogenic variant (see Penetrance). In affected heterozygous sibs, the clinical manifestations of DBA are unpredictable and can range, in the same family, from typical and atypical DBA phenotypes to a severe form presenting with fetal anemia resulting in nonimmune hydrops fetalis (see Clinical Description).
- If the DBA-causing pathogenic variant found in the proband is not detected in the leukocyte DNA of either parent, the recurrence risk to sibs is presumed to be slightly greater than that of the general population for one of two possible reasons:
  - Parental germline mosaicism for the DBA-causing pathogenic variant [Cmejla et al 2000]; or
  - A false negative result in a parent due to preferential loss of the chromosome with the DBA-causing pathogenic variant (see Molecular Pathogenesis).
- If the parents have not been tested for the DBA-causing pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for DBA for one of two possible reasons:
  - A parent has germline mosaicism; or
  - A parent is heterozygous but does not have apparent manifestations of DBA because of reduced penetrance or variable expressivity.

Offspring of a proband. Each child of an individual with autosomal dominant DBA has a 50% chance of inheriting the DBA-causing pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has a DBA-causing pathogenic variant, the parent's family members may be at risk.

X-Linked Inheritance – Risk to Family Members

Parents of a male proband

- The father of a male with *GATA1*- or *TSR2*-related DBA will not have the disorder nor will he be hemizygous for the 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* or *TSR2* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. (No data on the possibility or frequency of germline mosaicism in the mother are available.)
- 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* or *TSR2* pathogenic variant (in which case the mother is not a carrier), or the mother may have somatic/germline mosaicism. (The frequency of *de novo* pathogenic variants is not currently 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 of a male proband depends on the genetic status of the mother:

- If the mother of an affected male has a *GATA1* or *TSR2* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected;
  - Females who inherit the pathogenic variant will be heterozygotes and will usually not be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *GATA1* or *TSR2* 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* or *TSR2* pathogenic variant to all of their daughters 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* or *TSR2* pathogenic variant.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine the genetic risk status of the extended family.

Heterozygote detection. Identification of female heterozygotes is possible once a *GATA1* or *TSR2* pathogenic variant has been identified in an affected family member.

Note: Females who are heterozygous for X-linked DBA will usually not be affected.

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 or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the DBA-causing pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for DBA 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.

- **Diamond Blackfan Anemia Foundation, Inc. (DBAF)**
  PO Box 1092
  West Seneca NY 14224
  Phone: 716-674-2818
  Email: dbafoundation@juno.com
  www.dbafoundation.org
- **National Cancer Institute (NCI)**
  Phone: 800-422-6237
  Email: NCIinfo@nih.gov
  cancer.gov
- **National Organization for Rare Disorders (NORD)**
  Phone: 800-999-6673
  RareCare® Patient Assistance Programs
- **Diamond Blackfan Anemia Registry (DBAR)**
  269-01 76th Avenue
  New Hyde Park NY 11040
  Phone: 888-884-DBAR
  Fax: 718-343-2961
  Email: eatsidaf@nshs.edu
  www.dbafoundation.org/families/dba-registry
- **National Cancer Institute Inherited Bone Marrow Failure Syndromes (IBMFS) Cohort Registry**
  Phone: 800-518-8474
  Email: NCI.IBMFS@westat.com
  marrowfailure.cancer.gov

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. Diamond-Blackfan Anemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GATA1	Xp11.23	Erythroid transcription factor	GATA1 @ LOVD	GATA1	GATA1
RPL5	1p22.1	Large ribosomal subunit protein uL18	RPL5 database	RPL5	RPL5
RPL11	1p36.11	Large ribosomal subunit protein uL5	RPL11 database	RPL11	RPL11
RPL15	3p24.2	Large ribosomal subunit protein eL15		RPL15	RPL15
RPL18	19q13.33	Large ribosomal subunit protein eL18		RPL18	RPL18
RPL26	17p13.1	Large ribosomal subunit protein uL24	RPL26 @ LOVD	RPL26	RPL26
RPL27	17q21.1-q21.2	Large ribosomal subunit protein eL27			RPL27

Table A. continued from previous page.

RPL31	2q11.2	Large ribosomal subunit protein eL31		RPL31	RPL31
RPL35	9q33.3	Large ribosomal subunit protein uL29		RPL35	RPL35
RPL35A	3q29	Large ribosomal subunit protein eL33	RPL35A database	RPL35A	RPL35A
RPS7	2p25.3	Small ribosomal subunit protein eS7	RPS7 database	RPS7	RPS7
RPS10	6p21.31	Small ribosomal subunit protein eS10	RPS10 database	RPS10	RPS10
RPS15A	16p12.3	Small ribosomal subunit protein uS8		RPS15A	RPS15A
RPS17	15q25.2	Small ribosomal subunit protein eS17	RPS17 database	RPS17	RPS17
RPS19	19q13.2	Small ribosomal subunit protein eS19	RPS19 database	RPS19	RPS19
RPS24	10q22.3	Small ribosomal subunit protein eS24	RPS24 database	RPS24	RPS24
RPS26	12q13.2	Small ribosomal subunit protein eS26	RPS26 database	RPS26	RPS26
RPS27	1q21.3	Small ribosomal subunit protein eS27		RPS27	RPS27
RPS28	19p13.2	Small ribosomal subunit protein eS28		RPS28	RPS28
RPS29	14q21.3	Small ribosomal subunit protein uS14		RPS29	RPS29
TSR2	Xp11.22	Pre-rRNA-processing protein TSR2 homolog		TSR2	TSR2

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 Diamond-Blackfan Anemia (View All in OMIM)

105650	DIAMOND-BLACKFAN ANEMIA 1; DBA1
180468	RIBOSOMAL PROTEIN L35A; RPL35A
180472	RIBOSOMAL PROTEIN S17; RPS17
300945	TSR2 RIBOSOME MATURATION FACTOR; TSR2
300946	DIAMOND-BLACKFAN ANEMIA 14 WITH MANDIBULOFACIAL DYSOSTOSIS; DBA14
305371	GATA-BINDING PROTEIN 1; GATA1
602412	RIBOSOMAL PROTEIN S24; RPS24
603474	RIBOSOMAL PROTEIN S19; RPS19
603632	RIBOSOMAL PROTEIN S10; RPS10
603633	RIBOSOMAL PROTEIN S29; RPS29
603634	RIBOSOMAL PROTEIN L5; RPL5
603658	RIBOSOMAL PROTEIN S7; RPS7

Table B. continued from previous page.

603674	RIBOSOMAL PROTEIN S15a; RPS15A
603685	RIBOSOMAL PROTEIN S28; RPS28
603701	RIBOSOMAL PROTEIN S26; RPS26
603702	RIBOSOMAL PROTEIN S27; RPS27
603704	RIBOSOMAL PROTEIN L26; RPL26
604174	RIBOSOMAL PROTEIN L15; RPL15
604175	RIBOSOMAL PROTEIN L11; RPL11
604179	RIBOSOMAL PROTEIN L18; RPL18
606129	DIAMOND-BLACKFAN ANEMIA 2; DBA2
606164	DIAMOND-BLACKFAN ANEMIA 15 WITH MANDIBULOFACIAL DYSOSTOSIS; DBA15
607526	RIBOSOMAL PROTEIN L27; RPL27
610629	DIAMOND-BLACKFAN ANEMIA 3; DBA3
612527	DIAMOND-BLACKFAN ANEMIA 4; DBA4
612528	DIAMOND-BLACKFAN ANEMIA 5; DBA5
612561	DIAMOND-BLACKFAN ANEMIA 6; DBA6
612562	DIAMOND-BLACKFAN ANEMIA 7; DBA7
612563	DIAMOND-BLACKFAN ANEMIA 8; DBA8
613308	DIAMOND-BLACKFAN ANEMIA 9; DBA9
613309	DIAMOND-BLACKFAN ANEMIA 10; DBA10
614900	DIAMOND-BLACKFAN ANEMIA 11; DBA11
615550	DIAMOND-BLACKFAN ANEMIA 12; DBA12
615909	DIAMOND-BLACKFAN ANEMIA 13; DBA13
618310	DIAMOND-BLACKFAN ANEMIA 18; DBA18
618312	DIAMOND-BLACKFAN ANEMIA 19; DBA19
618313	DIAMOND-BLACKFAN ANEMIA 20; DBA20
618315	RIBOSOMAL PROTEIN L35; RPL35

Molecular Pathogenesis

Ribosomes, consisting of a small 40S subunit and a large 60S subunit, catalyze protein synthesis. Small and large subunits are composed of four RNA species and approximately 80 structurally distinct ribosomal proteins (RPs). The proteins encoded by *RPS19*, *RPS24*, *RPS17*, *RPS15*, *RPS7*, *RPS27A*, *RPS10*, and *RPS26* belong to the small ribosomal subunit, whereas those encoded by *RPL5*, *RPL11*, *RPL26*, *RPL35A*, and *RPL36* are components of the large ribosomal subunit.

RPS19 protein has been demonstrated to play an important role in 18S rRNA maturation in yeast and in human cells [Léger-Silvestre et al 2005, Choesmel et al 2007, Flygare et al 2007, Idol et al 2007]. Similarly, alterations of pre-RNA processing of small or large RP subunit synthesis were demonstrated in human cells with RPS24 and RPS7 deficiency and with RPL35A, RPL5, RPL11, and RPL26 deficiency, respectively, further indicating that DBA is a disorder of ribosomes [Choesmel et al 2008, Farrar et al 2008, Gazda et al 2008, Gazda et al 2012]. Deficiency of RPS19 and RPL35A was shown to cause increased apoptosis in hematopoietic cell lines and in bone marrow cells [Farrar et al 2008, Miyake et al 2008], and imbalance of the p53 family proteins has been

suggested as a mechanism of abnormal embryogenesis and anemia in zebrafish on perturbation of *RPS19* expression [Danilova et al 2008].

Mechanism of disease causation. Rarely, missense variants may act in a dominant-negative manner, but haploinsufficiency of a ribosomal protein is the most common mechanism. Evidence suggests that ribosomal stress due to ribosome deficiency leads to stabilization of p53 and consequent p53-mediated cell cycle arrest or apoptosis. Furthermore *GATA1*, a critical erythroid transcription factor, has a complex 5' UTR and is poorly translated when ribosomal proteins are deficient. This can explain why *GATA1* pathogenic variants result in a DBA phenotype [Ludwig et al 2014].

Gene-specific laboratory technical considerations. Revertant mosaicism (e.g., acquired uniparental disomy ablating a *de novo RPS19* pathogenic variant) has rarely been observed to account for spontaneous remission in individuals with DBA [Venugopal et al 2017, Garelli et al 2019].

Table 5. Diamond-Blackfan Anemia: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
RPL5	Large deletions in ~20% [Quarello et al 2012]; long indels can be missed by exome sequencing [Ulirsch et al 2018].
RPL11	Large deletions in ~20% [Quarello et al 2012]
RPL35A	Large deletions in ~20% [Quarello et al 2012]
RPS10	Long indels can be missed by exome sequencing [Ulirsch et al 2018].
RPS17	Large deletions in ~20% [Quarello et al 2012]
RPS19	Large deletions in ~20% [Quarello et al 2012]
RPS24	Long indels can be missed by exome sequencing [Ulirsch et al 2018].
RPS26	Large deletions in ~20% [Quarello et al 2012]; 6 extended or cryptic splicing variants & a 3' UTR variant have been reported [Ulirsch et al 2018].

1. Genes from Table 1 in alphabetic order

Chapter Notes

Acknowledgments

The author acknowledges the generous support of the Diamond Blackfan Anemia Foundation.

Author History

Catherine Clinton, MS, CGC; Dana-Farber/Boston Children's Cancer and Blood Disorders Center (2009-2021)
Hanna T Gazda, MD, PhD; Boston Children's Hospital (2009-2021)
Colin Sieff, MBBCh, FRCPath (2021-present)

Revision History

- 23 March 2023 (sw) Revision: information regarding *GATA1*-related cytopenia added to Table 1
- 17 June 2021 (sw) Comprehensive update posted live
- 7 March 2019 (aa) Revision: *RPL18*, *RPL35*, and *RPS15A* added
- 7 April 2016 (sw) Comprehensive update posted live
- 16 January 2014 (cd) Revision: mutation of *RPL15* causative of DBA12
- 25 July 2013 (me) Comprehensive update posted live
- 27 January 2011 (me) Comprehensive update posted live
- 24 November 2009 (cd) Revision: deletion/duplication analysis for *RPS19* available clinically

- 13 October 2009 (cd) Revision: sequence analysis and prenatal testing available for *RPL5*, *RPL11*, *RPL35A*, *RPS7*, *RPS17* mutations; prenatal testing available for *RPS24* mutations
- 25 June 2009 (et) Review posted live
- 17 February 2009 (hg) Original submission

References

Literature Cited

Alter BP, Giri N, Savage SA, Rosenberg PS. Cancer in the National Cancer Institute inherited bone marrow failure syndrome cohort after fifteen years of follow-up. Haematologica. 2018;103:30–9. PubMed PMID: 29051281.

Alter BP, Kumar M, Lockhart LL, Sprinz PG, Rowe TF. Pregnancy in bone marrow failure syndromes: Diamond-Blackfan anaemia and Shwachman-Diamond syndrome. Br J Haematol. 1999;107:49–54. PubMed PMID: 10520024.

Alter BP, Young NS. The bone marrow failure syndromes. In: Nathan DG, Orkin HS, eds. *Hematology of Infancy and Childhood*. Vol 1. Philadelphia, PA: Saunders; 1998:237-335.

Bagby GC, Lipton JM, Sloand EM, Schiffer CA. Marrow failure. Hematology Am Soc Hematol Educ Program. 2004;1:318–36.

Ball SE, McGuckin CP, Jenkins G, Gordon-Smith EC. Diamond-Blackfan anaemia in the U.K.: analysis of 80 cases from a 20-year birth cohort. Br J Haematol. 1996;94:645–53. PubMed PMID: 8826887.

Bhatnagar N, Nizery L, Tunstall O, Vyas P, Roberts I. Transient abnormal myelopoiesis and AML in Down syndrome: an update. Curr Hematol Malig Rep. 2016;11:333–41. PubMed PMID: 27510823.

Cappellini MD, Piga A. Current status in iron chelation in hemoglobinopathies. Curr Mol Med. 2008;8:663–74. PubMed PMID: 18991652.

Chen S, Warszawski J, Bader-Meunier B, Tchernia G, Da Costa L, Marie I, Dommergues JP. Diamond-blackfan anemia and growth status: the French registry. J Pediatr. 2005;147:669–73. PubMed PMID: 16291361.

Choesmel V, Bacqueville D, Rouquette J, Noaillac-Depeyre J, Fribourg S, Cretien A, Leblanc T, Tchernia G, Da Costa L, Gleizes PE. Impaired ribosome biogenesis in Diamond-Blackfan anemia. Blood. 2007;109:1275–83. PubMed PMID: 17053056.

Choesmel V, Fribourg S, Aguissa-Toure AH, Pinaud N, Legrand P, Gazda HT, Gleizes PE. Mutation of ribosomal protein RPS24 in Diamond-Blackfan anemia results in a ribosome biogenesis disorder. Hum Mol Genet. 2008;17:1253–63. PubMed PMID: 18230666.

Cmejla R, Blafkova J, Stopka T, Zavadil J, Pospisilova D, Mihal V, Petrtylova K, Jelinek J. Ribosomal protein S19 gene mutations in patients with diamond-blackfan anemia and identification of ribosomal protein S19 pseudogenes. Blood Cells Mol Dis. 2000;26:124–32. PubMed PMID: 10753603.

Cmejla R, Cmejlova J, Handrkova H, Petrak J, Petrtylova K, Mihal V, Stary J, Cerna Z, Jabali Y, Pospisilova D. Identification of mutations in the ribosomal protein L5 (RPL5) and ribosomal protein L11 (RPL11) genes in Czech patients with Diamond-Blackfan anemia. Hum Mutat. 2009;30:321–7. PubMed PMID: 19191325.

Danilova N, Sakamoto KM, Lin S. Ribosomal protein S19 deficiency in zebrafish leads to developmental abnormalities and defective erythropoiesis through activation of p53 protein family. Blood. 2008;112:5228–37. PubMed PMID: 18515656.

Dunbar AE 3rd, Moore SL, Hinson RM. Fetal Diamond-Blackfan anemia associated with hydrops fetalis. Am J Perinatol. 2003;20:391–4. PubMed PMID: 14655096.

Faivre L, Meerpohl J, Da Costa L, Marie I, Nouvel C, Gnekow A, Bender-Götze C, Bauters F, Coiffier B, Peaud PY, Rispal P, Berrebi A, Berger C, Flesch M, Sagot P, Varet B, Niemeyer C, Tchernia G, Leblanc T. High-risk pregnancies in Diamond-Blackfan anemia: a survey of 64 pregnancies from the French and German registries. Haematologica. 2006;91:530–3. PubMed PMID: 16537118.

Farrar JE, Nater M, Caywood E, McDevitt MA, Kowalski J, Takemoto CM, Talbot CC Jr, Meltzer P, Esposito D, Beggs AH, Schneider HE, Grabowska A, Ball SE, Niewiadomska E, Sieff CA, Vlachos A, Atsidaftos E, Ellis SR, Lipton JM, Gazda HT, Arceci RJ. Abnormalities of the large ribosomal subunit protein, Rpl35a, in Diamond-Blackfan anemia. Blood. 2008;112:1582–92. PubMed PMID: 18535205.

Flygare J, Aspesi A, Bailey JC, Miyake K, Caffrey JM, Karlsson S, Ellis SR. Human RPS19, the gene mutated in Diamond-Blackfan anemia, encodes a ribosomal protein required for the maturation of 40S ribosomal subunits. Blood. 2007;109:980–6. PubMed PMID: 16990592.

Garelli E, Quarello P, Giorgio E, Carando A, Menegatti E, Mancini C, Di Gregorio E, Crescenzio N, Palumbo O, Carella M, Dimartino P, Pippucci T, Dianzani I, Ramenghi U, Brusco A. Spontaneous remission in a Diamond-Blackfan anaemia patient due to a revertant uniparental disomy ablating a de novo RPS19 mutation. Br J Haematol. 2019;185:994–8. PubMed PMID: 30460677.

Gazda HT, Preti M, Sheen MR, O'Donohue MF, Vlachos A, Davies SM, Kattamis A, Doherty L, Landowski M, Buros C, Ghazvinian R, Sieff CA, Newburger PE, Niewiadomska E, Matysiak M, Glader B, Atsidaftos E, Lipton JM, Gleizes PE, Beggs AH. Frameshift mutation in p53 regulator RPL26 is associated with multiple physical abnormalities and a specific pre-ribosomal RNA processing defect in diamond-blackfan anemia. Hum Mutat. 2012;33:1037–44. PubMed PMID: 22431104.

Gazda HT, Sheen MR, Vlachos A, Choesmel V, O'Donohue MF, Schneider H, Darras N, Hasman C, Sieff CA, Newburger PE, Ball SE, Niewiadomska E, Matysiak M, Zaucha JM, Glader B, Niemeyer C, Meerpohl JJ, Atsidaftos E, Lipton JM, Gleizes PE, Beggs AH. Ribosomal protein L5 and L11 mutations are associated with cleft palate and abnormal thumbs in Diamond-Blackfan anemia patients. Am J Hum Genet. 2008;83:769–80. PubMed PMID: 19061985.

Henter JI, Karlen J. Fatal agranulocytosis after deferiprone therapy in a child with Diamond-Blackfan anemia. Blood. 2007;109:5157–9. PubMed PMID: 17344464.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Idol RA, Robledo S, Du HY, Crimmins DL, Wilson DB, Ladenson JH, Bessler M, Mason PJ. Cells depleted for RPS19, a protein associated with Diamond Blackfan anemia, show defects in 18S ribosomal RNA synthesis and small ribosomal subunit production. Blood Cells Mol Dis. 2007;39:35–43. PubMed PMID: 17376718.

Janov AJ, Leong T, Nathan DG, Guinan EC. Diamond-Blackfan anemia. Natural history and sequelae of treatment. Medicine (Baltimore). 1996;75:77–8. PubMed PMID: 8606629.

Kuramitsu M, Sato-Otsubo A, Morio T, Takagi M, Toki T, Terui K, Wang R, Kanno H, Ohga S, Ohara A, Kojima S, Kitoh T, Goi K, Kudo K, Matsubayashi T, Mizue N, Ozeki M, Masumi A, Momose H, Takizawa K, Mizukami T, Yamaguchi K, Ogawa S, Ito E, Hamaguchi I. Extensive gene deletions in Japanese patients with Diamond Blackfan anemia. Blood. 2012;119:2376–84. PubMed PMID: 22262766.

Léger-Silvestre I, Caffrey JM, Dawaliby R, Alvarez-Arias DA, Gas N, Bertolone SJ, Gleizes PE, Ellis SR. Specific role for yeast homologs of the Diamond Blackfan anemia-associated Rps19 protein in ribosome synthesis. J Biol Chem. 2005;280:38177–85. PubMed PMID: 16159874.

Lipton JM, Atsidaftos E, Zyskind I, Vlachos A. Improving clinical care and elucidating the pathophysiology of Diamond Blackfan anemia: an update from the Diamond Blackfan Anemia Registry. Pediatr Blood Cancer. 2006;46:558–64. PubMed PMID: 16317735.

Ludwig LS, Gazda HT, Eng JC, Eichhorn SW, Thiru P, Ghazvinian R, George TI, Gotlib JR, Beggs AH, Sieff CA, Lodish HF, Lander ES, Sankaran VG. Altered translation of GATA1 in Diamond-Blackfan anemia. Nat Med. 2014;20:748–53. PubMed PMID: 24952648.

Miyake K, Utsugisawa T, Flygare J, Kiefer T, Hamaguchi I, Richter J, Karlsson S. Ribosomal protein S19 deficiency leads to reduced proliferation and increased apoptosis but does not affect terminal erythroid differentiation in a cell line model of Diamond-Blackfan anemia. Stem Cells. 2008;26:323–9. PubMed PMID: 17962699.

Morel AS, Joris N, Meuli R, Jacquemont S, Ballhausen D, Bonafe L, Fattet S, Tolsa JF. Early neurological impairment and severe anemia in a newborn with Pearson syndrome. Eur J Pediatr. 2009;168:311–5. PubMed PMID: 18553104.

Ohga S, Mugishima H, Ohara A, Kojima S, Fujisawa K, Yagi K, Higashigawa M, Tsukimoto I; Aplastic Anemia Committee Japanese Society of Pediatric Hematology. Diamond-Blackfan anemia in Japan: clinical outcomes of prednisolone therapy and hematopoietic stem cell transplantation. Int J Hematol. 2004;79:22–30. PubMed PMID: 14979474.

Orfali KA, Ohene-Abuakwa Y, Ball SE. Diamond Blackfan anaemia in the UK: clinical and genetic heterogeneity. Br J Haematol. 2004;125:243–52. PubMed PMID: 15059149.

Parekh S, Perez A, Yang XY, Billett H. Chronic parvovirus infection and G6PD deficiency masquerading as Diamond-Blackfan anemia. Am J Hematol. 2005;79:54–7. PubMed PMID: 15849759.

Porter J, Galanello R, Saglio G, Neufeld EJ, Vichinsky E, Cappellini MD, Olivieri N, Piga A, Cunningham MJ, Soulières D, Gattermann N, Tchernia G, Maertens J, Giardina P, Kwiatkowski J, Quarta G, Jeng M, Forni GL, Stadler M, Cario H, Debusscher L, Della Porta M, Cazzola M, Greenberg P, Alimena G, Rabault B, Gathmann I, Ford JM, Alberti D, Rose C. Relative response of patients with myelodysplastic syndromes and other transfusion-dependent anaemias to deferasirox (ICL670): a 1-yr prospective study. Eur J Haematol. 2008;80:168–76. PubMed PMID: 18028431.

Quarello P, Garelli E, Brusco A, Carando A, Mancini C, Pappi P, Vinti L, Svahn J, Dianzani I, Ramenghi U. High frequency of ribosomal protein gene deletions in Italian Diamond Blackfan anemia patients detected by Multiplex Ligation-dependent Probe Amplification (MLPA) assay. Haematologica. 2012;97:1813–7. PubMed PMID: 22689679.

Quarello P, Garelli E, Carando A, Brusco A, Calabrese R, Dufour C, Longoni D, Misuraca A, Vinti L, Aspesi A, Biondini L, Loreni F, Dianzani I, Ramenghi U. Diamond-Blackfan anemia: genotype-phenotype correlations in Italian patients with RPL5 and RPL11 mutations. Haematologica. 2010;95:206–13. PubMed PMID: 19773262.

Ramenghi U, Campagnoli MF, Garelli E, Carando A, Brusco A, Bagnara GP, Strippoli P, Izzi GC, Brandalise S, Riccardi R, Dianzani I. Diamond-Blackfan anemia: report of seven further mutations in the RPS19 gene and evidence of mutation heterogeneity in the Italian population. Blood Cells Mol Dis. 2000;26:417–22. PubMed PMID: 11112378.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Roy V, Perez WS, Eapen M, Marsh JC, Pasquini M, Pasquini R, Mustafa MM, Bredeson CN. Bone marrow transplantation for diamond-blackfan anemia. Biol Blood Marrow Transplant. 2005;11:600–8. PubMed PMID: 16041310.

Saladi SM, Chattopadhyay T, Adiotomre PN. Nomimmune hydrops fetalis due to Diamond-Blackfan anemia. Indian Pediatr. 2004;41:187–8. PubMed PMID: 15004307.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Taher AT, Iolascon A, Matar CF, Bou-Fakhredin R, de Franceschi L, Cappellini MD, Barcellini W, Russo R, Andolfo I, Tyan P, Gulbis B, Aydinok Y, Anagnou NP, Bencaiova GA, Tamary H, Martinez PA, Forni G, Vindigni R. Recommendations for pregnancy in rare inherited anemias. Hemasphere. 2020;4:e446. PubMed PMID: 32885142.

Ulirsch JC, Verboon JM, Kazerounian S, Guo MH, Yuan D, Ludwig LS, Handsaker RE, Abdulhay NJ, Fiorini C, Genovese G, Lim ET, Cheng A, Cummings BB, Chao KR, Beggs AH, Genetti CA, Sieff CA, Newburger PE, Niewiadomska E, Matysiak M, Vlachos A, Lipton JM, Atsidaftos E, Glader B, Narla A, Gleizes PE, O'Donohue MF, Montel-Lehry N, Amor DJ, McCarroll SA, O'Donnell-Luria AH, Gupta N, Gabriel SB, MacArthur DG, Lander ES, Lek M, Da Costa L, Nathan DG, Korostelev AA, Do R, Sankaran VG, Gazda HT. The genetic landscape of Diamond-Blackfan anemia. Am J Hum Genet. 2018;103:930–47. PubMed PMID: 30503522.

Venugopal P, Moore S, Lawrence DM, George AJ, Hannan RD, Bray SC, To LB, D'Andrea RJ, Feng J, Tirimacco A, Yeoman AL, Young CC, Fine M, Schreiber AW, Hahn CN, Barnett C, Saxon B, Scott HS. Self-reverting mutations partially correct the blood phenotype in a Diamond Blackfan anemia patient. Haematologica. 2017;102:e506–e509. PubMed PMID: 28971907.

Vlachos A, Ball S, Dahl N, Alter BP, Sheth S, Ramenghi U, Meerpohl J, Karlsson S, Liu JM, Leblanc T, Paley C, Kang EM, Leder EJ, Atsidaftos E, Shimamura A, Bessler M, Glader B, Lipton JM. Diagnosing and treating Diamond Blackfan anaemia: results of an international clinical consensus conference. Br J Haematol. 2008;142:859–76. PubMed PMID: 18671700.

Vlachos A, Klein GW, Lipton JM. The Diamond Blackfan Anemia Registry: tool for investigating the epidemiology and biology of Diamond-Blackfan anemia. J Pediatr Hematol Oncol. 2001;23:377–82. PubMed PMID: 11563775.

Vlachos A, Rosenberg PS, Atsidaftos E, Alter BP, Lipton JM. Incidence of neoplasia in Diamond Blackfan anemia: a report from the Diamond Blackfan Anemia Registry. Blood. 2012; 2012;119:3815–9. PubMed PMID: 22362038.

Willig TN, Draptchinskaia N, Dianzani I, Ball S, Niemeyer C, Ramenghi U, Orfali K, Gustavsson P, Garelli E, Brusco A, Tiemann C, Perignon JL, Bouchier C, Cicchiello L, Dahl N, Mohandas N, Tchernia G. Mutations in ribosomal protein S19 gene and diamond blackfan anemia: wide variations in phenotypic expression. Blood. 1999;94:4294–306. PubMed PMID: 10590074.

License