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Alpha-Thalassemia

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Summary

Clinical characteristics

Alpha-thalassemia (α-thalassemia) has two clinically significant forms: hemoglobin Bart hydrops fetalis (Hb Bart) syndrome (caused by deletion/inactivation of all four alpha globin [α-globin] genes; --/--), and hemoglobin H (HbH) disease (most frequently caused by deletion/inactivation of three α-globin genes; --/-α).

- **Hb Bart syndrome,** the more severe form, is characterized by prenatal onset of generalized edema and pleural and pericardial effusions as a result of congestive heart failure induced by severe anemia. Extramedullary erythropoiesis, marked hepatosplenomegaly, and a massive placenta are common. Death usually occurs in the neonatal period.
- **HbH disease** has a broad phenotypic spectrum: although clinical features usually develop in the first years of life, HbH disease may not present until adulthood or may be diagnosed only during routine hematologic analysis in an asymptomatic individual. The majority of individuals have enlargement of the spleen (and less commonly of the liver), mild jaundice, and sometimes thalassemia-like bone changes. Individuals with HbH disease may develop gallstones and experience acute episodes of hemolysis in response to infections or exposure to oxidant drugs.

Diagnosis/testing

The diagnosis of Hb Bart syndrome is established in a fetus with characteristic hematologic and hemoglobin (Hb) findings and molecular genetic testing that identifies biallelic pathogenic variants in both *HBA1* and *HBA2* that result in deletion or inactivation of all four α-globin alleles.

The diagnosis of HbH disease is established in a proband with hematologic and Hb findings and molecular genetic testing that identifies biallelic pathogenic variants in *HBA1* and *HBA2* that result in deletion or inactivation of three α-globin alleles.

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Management

Treatment of manifestations: Hb Bart syndrome: intrauterine blood transfusions, improved transfusion strategies, and rarely curative hematopoietic stem cell transplant may allow survival of children. HbH disease: while most individuals are clinically well and survive without any treatment, occasional red blood cell transfusions may be needed during hemolytic or aplastic crises. Red blood cell transfusions are very rarely needed for severe anemia affecting cardiac function and erythroid expansion that results in severe bone changes and extramedullary erythropoiesis. In contrast, persons with non-deletional HbH disease may be more severely affected and transfusion dependent.

Prevention of primary manifestations: Because of the severity of Hb Bart syndrome, the occasional presence of congenital anomalies, and the risk for maternal complications, prenatal testing and early termination of pregnancies at risk have usually been considered. However, recent advances in intrauterine and postnatal therapy have increased treatment options, thus complicating the ethical issues for health care providers and families facing an affected pregnancy.

Prevention of secondary complications: Monitor individuals with HbH disease for hemolytic/aplastic crisis during febrile episodes; in those who require chronic red blood cell transfusions, iron chelation therapy should be instituted; for those who are not red blood cell transfusion dependent, iron chelation with deferasirox can be considered to reduce liver iron concentration.

Surveillance: For HbH disease, hematologic evaluation every six to 12 months; assessment of growth and development in children every six to 12 months; monitoring of iron load with serum ferritin concentration and periodic quantitative measurement of liver iron concentration.

Agents/circumstances to avoid: In persons with HbH disease: inappropriate iron therapy and oxidant drugs (i.e., the same drugs to be avoided by individuals with glucose-6-phosphate dehydrogenase deficiency).

Evaluation of relatives at risk: Test the sibs of a proband as soon as possible after birth for HbH disease so that monitoring can be instituted.

Pregnancy management: Complications reported in pregnant women with HbH disease include worsening anemia, preeclampsia, congestive heart failure, and threatened miscarriage; monitoring for these issues during pregnancy is recommended.

Genetic counseling

Alpha-thalassemia is usually inherited in an autosomal recessive manner.

- **Hb Bart syndrome.** At conception, each sib of a proband with Hb Bart syndrome has a 25% chance of having Hb Bart syndrome (e.g., --/--), a 50% chance of having α-thalassemia trait with deletion or inactivation of two α-globin genes in *cis* (e.g., --/αα), and a 25% chance of being unaffected and not a carrier.
- **HbH disease.** The risk to sibs of a proband depends on genotype of the parents.
- **Carrier testing.** Family members, members of ethnic groups at risk, and gamete donors should be considered for carrier testing. Couples who are members of populations at risk for α-thalassemia trait with a two-gene deletion in *cis* (--/αα) can be identified prior to pregnancy as being at risk of conceiving a fetus with Hb Bart syndrome.

Prenatal and preimplantation genetic testing may be carried out for couples who are at high risk of having a fetus with Hb Bart syndrome or for a pregnancy in which one parent is a known α-thalassemia carrier with a two-gene deletion in *cis* (--/αα) when the other parent is either unknown or unavailable for testing.

GeneReview Scope

Alpha-Thalassemia (α-Thalassemia)	
Phenotype [1]	Possible Genotypes
Hemoglobin Bart hydrops fetalis (Hb Bart) syndrome	Deletion/inactivation of all four α-globin genes (--/--)
Hemoglobin H (HbH) disease	Deletion/inactivation of three α-globin genes (--/-α)
α-thalassemia trait/carrier	Deletion/inactivation of two α-globin genes either in *cis* (--/αα, or -α^0 carrier) or in *trans* (-α/-α)
α-thalassemia silent carrier	Deletion/inactivation of one α-globin gene (-α/αα or α^+ carrier)

For synonyms and outdated names see Nomenclature.
1. In descending order of severity

Diagnosis

Suggestive Findings

Alpha-thalassemia (α-thalassemia) has two clinically significant forms: hemoglobin Bart hydrops fetalis (Hb bart) syndrome (deletion/inactivation of all four alpha globin [α-globin] genes; --/--), and hemoglobin H (HbH) disease (most frequently caused by deletion/inactivation of three α-globin genes; --/-α) (see Figure 1).

Hb Bart syndrome should be suspected in the following:

- An at-risk fetus with increased nuchal thickness, thickened placenta, increased cerebral media artery velocity, and increased cardiothoracic ratio on ultrasonography examination at 13-14 weeks' gestation
- A fetus with generalized edema, ascites, and pleural and pericardial effusions on ultrasonography examination at 22-28 weeks' gestation

HbH disease should be suspected in an infant or child with the following clinical or newborn screening findings:

- **Clinical findings**
  - Mild jaundice
  - Hepatosplenomegaly
  - Mild thalassemia-like bone changes (e.g., hypertrophy of the maxilla, bossing of the skull, and prominence of the malar eminences)
- **Newborn screening findings**. Hb Bart >15% at birth

  Note: (1) Newborn screening for sickle cell disease offered by several states/countries may detect Hb Bart in the newborn with α-thalassemia. (2) Reference ranges may vary among laboratories performing newborn screening. (3) Low concentrations of Hb Bart (1%-8%) are indicative of the carrier states, and while this finding usually does not indicate a need for further evaluation of the newborn, genetic counseling may be recommended for the parents of the newborn [Ferguson 2018, Fogel et al 2018].

Establishing the Diagnosis

The diagnosis of **Hb Bart syndrome is established** in a fetus based on the following:

- **Hematologic findings**
  - Red blood cell indices. Severe macrocytic hypochromic anemia, in the absence of ABO or Rh blood group incompatibility (See Table 1.)

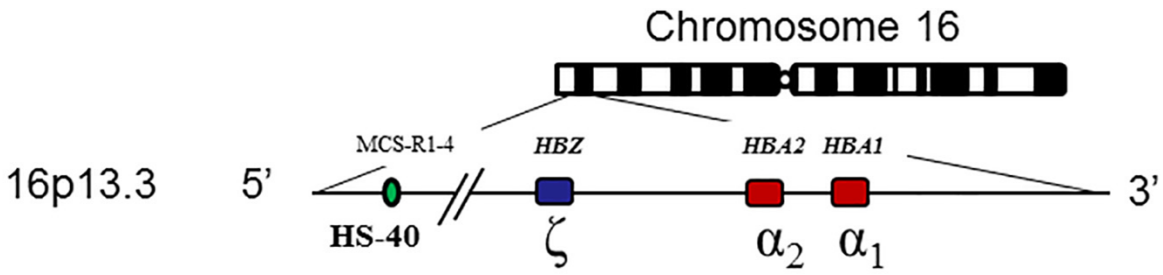

Figure 1. Schematic presentation of the chromosomal location of the alpha globin gene cluster on chromosome 16p. The genes are indicated as boxes; gene symbols are above and the hemoglobin is expressed below. The alpha globin regulatory region (MCS-R1 to -R4; also known as HS-40) is indicated.

Modified from Farashi & Harteveld [2018]

- Reticulocytosis. Variable; may be >60%
- Peripheral blood smear with large, hypochromic red cells, severe anisopoikilocytosis, and numerous nucleated red cells

- **Hemoglobin analysis** that reveals decreased amounts or complete absence of hemoglobin A and increased amounts of Hb Bart (See Table 2.)
- **Molecular genetic testing** that identifies biallelic pathogenic variants in both *HBA1* and *HBA2* that result in deletion or inactivation of all four α-globin alleles (e.g., homozygous deletion of both *HBA1* and *HBA2* on both chromosomes; --/--; see Table 3), which confirms the diagnosis and allows for family studies

The diagnosis of **HbH disease is established** in a proband based on the following:

- **Hematologic findings**
  - Red blood cell indices. Mild-to-moderate (rarely severe) microcytic hypochromic hemolytic anemia (See Table 1.)
  - Moderate reticulocytosis (3%-6%)
  - Peripheral blood smear with anisopoikilocytosis, and very rarely nucleated red blood cells (i.e., erythroblasts)
  - Red blood cell supravital stain showing HbH inclusions (β_4 tetramers) in 5%-80% of erythrocytes following incubation of fresh blood smears with 1% brilliant cresyl blue for one to three hours
- **Hemoglobin analysis** that reveals presence of 0.8%-40% HbH and 60%-90% hemoglobin A (See Table 2.)
- **Molecular genetic testing** that identifies biallelic pathogenic variants in both *HBA1* and *HBA2* that result in deletion or inactivation of three α-globin genes (e.g., a deletion of two globin alleles in *trans* with a deletion of one α-globin allele; --/-$\alpha^{3.7}$) (see Table 3), which confirms the diagnosis and allows for family studies

Hematologic Findings

Table 1. Red Blood Cell Indices in Individuals with Hb Bart Syndrome and HbH Disease

Red Blood Cell Indices [1]	Normal		Affected	
	Male	Female	Hb Bart syndrome [2]	HbH disease [3]
Mean corpuscular volume (MCV, in fL)	89.1 ± 5.01	87.6 ± 5.5	136 ± 5.1	Children: 56 ± 5
				Adults: 61 ± 4
Mean corpuscular hemoglobin (MCH, in pg)	30.9 ± 1.9	30.2 ± 2.1	31.9 ± 9	18.4 ± 1.2

Table 1. continued from previous page.

Red Blood Cell Indices [1]	Normal		Affected	
	Male	Female	Hb Bart syndrome [2]	HbH disease [3]
Hemoglobin (Hb, in g/dL)	15.9 ± 1.0	14.0 ± 0.9	3-8	Male: 10.9 ± 1.0
				Female: 9.5 ± 0.8

1. Reference ranges may vary among laboratories.
2. Vaeusorn et al [1985]
3. Galanello et al [1992]

Hemoglobin Analysis

If available, qualitative and quantitative hemoglobin (Hb) analysis by weak-cation high-performance liquid chromatography identifies the amount and type of Hb present. The Hb pattern in α-thalassemia varies by α-thalassemia type (see Table 2). The Hb types most relevant to α-thalassemia are:

- Hemoglobin A (HbA). Two alpha globin chains and two beta globin chains ($\alpha_2\beta_2$)
- Hemoglobin F (HbF). Two alpha globin chains and two gamma globin chains ($\alpha_2\gamma_2$)
- Hemoglobin Bart (Hb Bart). Four gamma globin chains (γ_4)
- Hemoglobin H (HbH). Four beta globin chains (β_4)
- Hemoglobin A_2 (HbA_2). Two alpha globin chains and two delta globin chains ($\alpha_2\delta_2$)
- Hemoglobin Portland. Two zeta globin chains and two gamma globin chains ($\zeta_2\gamma_2$)

Table 2. Hemoglobin Patterns in Alpha-Thalassemia

Hemoglobin Type [1]	Normal	Affected	
		Hb Bart syndrome [2]	HbH disease [3]
HbA	96%-98%	0	60%-90%
HbF	<1%	0	<1.0%
Hb Bart	0	85%-90%	2%-5%
HbH	0	0	0.8%-40%
HbA_2	2%-3%	0	<2.0%
Hb Portland	0	10%-15%	0

1. Reference ranges may vary among laboratories.
2. Deletion or inactivation of all four α-globin chains makes it impossible to assemble HbF and HbA. Fetal blood contains mainly Hb Bart (γ_4) and 10%-15% of the embryonic hemoglobin Portland ($\zeta_2\gamma_2$).
3. Deletion or inactivation of three α-globin chains

Note: Hematologic testing to identify α-thalassemia trait and α-thalassemia silent carrier status is addressed in Genetic Counseling.

Molecular Genetic Testing

Molecular testing approaches can include **targeted deletion analysis** for **common deletions** of *HBA1* and *HBA2*, **sequence analysis** of *HBA1* and *HBA2*, and **deletion/duplication analysis** of *HBA1*, *HBA2*, and the regulatory region multispecies conserved sequence 2 (MCS-R2; previously called HS-40) for uncommon deletions. See Figure 1.

Note: Multiple ligation-dependent probe amplification (MLPA) assay specifically designed for the α-globin locus has been described.

Targeted deletion analysis for common deletions of *HBA1* and *HBA2* can be performed first.

- Common deletions of two α-globin genes include the following:
  - Southeast Asian deletion (--^{SEA})
  - Filipino deletion (--^{FIL})
  - Mediterranean deletion (--^{MED})

  Note: (1) These common deletions are typically founder variants (see Prevalence). (2) More than 20 different deletions ranging from ~6 kb to >300 kb and removing both α-globin genes (and sometimes the embryonic zeta globin gene *HBZ*) have been reported (see Farashi & Harteveld [2018] Figure 4 and Table A, **Locus-Specific Databases**).

- Common deletions of a single α-globin gene include:
  - 3.7-kb deletion (-α$^{3.7}$) deletion
  - 4.2-kb deletion (-α$^{4.2}$) deletion

  Note: In addition to these two common deletions, other deletions involving a single α-globin gene have been reported.

Sequence analysis of *HBA1* and *HBA2* can be performed if a common deletion was not identified.

Note: "Non-deletion" or "trait" *HBA2* variant alleles are designated as (αNDα/) or (α^{T}α/), respectively; *HBA1* variant alleles are designated as (ααND/) or (αα^{T}/), respectively (see Molecular Genetics).

Gene-targeted deletion analysis MLPA of *HBA1*, *HBA2*, and the MCS-R2 regulatory region located 40 kb upstream from the α-globin cluster can be performed to detect uncommon deletions associated with α-thalassemia if pathogenic variants have not been identified by targeted deletion analysis or sequence analysis [Kipp et al 2011].

Further testing for genes associated with genetic disorders similar to α-thalassemia, such as *ATRX* and *HBB* (see Differential Diagnosis), may also be considered if clinically indicated.

Table 3. Molecular Genetic Testing Used in Alpha-Thalassemia

Gene [1]	Proportion of α-Thalassemia Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method		
		Sequence analysis [3]	Gene-targeted deletion/duplication analysis [4]	
			Common deletions	Other deletions
HBA1 & *HBA2*	>98%	~15%	~85%	<5%
MCS-R2 locus [5]	<1%			<1%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in these genes.
3. 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.
4. Methods used to detect common, rare, or previously undescribed deletions/duplications within the α-globin gene cluster and regulatory elements may include Gap PCR, MLPA (also known as break-point PCR), chromosomal microarray analysis (CMA) using oligonucleotide or SNP arrays, and next-generation sequencing (NGS) for analysis of deletion breakpoints [Kipp et al 2011, Clark et al 2017]. Note that methods such as Southern blotting, quantitative PCR, and long-range PCR have been used in the past.
5. See Sollaino et al [2010] and Nomenclature.

Clinical Characteristics

Clinical Description

The clinically significant phenotypes of alpha-thalassemia (α-thalassemia) are hemoglobin Bart hydrops fetalis (Hb Bart) syndrome and hemoglobin H (HbH) disease. The severity of the α-thalassemia syndromes depends on the extent of alpha globin (α-globin) chain defect (see Genotype-Phenotype Correlations).

Hb Bart syndrome is the most severe clinical condition related to α-thalassemia. Affected fetuses are either delivered stillborn at 30-40 weeks' gestation or die soon after birth.

The main clinical features are generalized edema and pleural and pericardial effusions as a result of congestive heart failure induced by severe anemia. Notably, red cells with Hb Bart have an extremely high oxygen affinity and are incapable of effective oxygen delivery. Extramedullary erythropoiesis, marked hepatosplenomegaly, and a massive placenta are common.

Retardation in brain growth, hydrocephalus, cardiovascular deformities, and urogenital defects have been reported.

A very small number of newborns survive following intrauterine transfusions and repeated frequent transfusions after birth.

Maternal complications during pregnancy commonly include preeclampsia, polyhydramnios or oligohydramnios, antepartum hemorrhage, and premature delivery.

HbH disease. The phenotype of HbH disease varies; however, clinical features are usually only diagnosed during routine hematologic analysis in an asymptomatic individual.

The majority of individuals have enlargement of the spleen and less commonly of the liver, mild jaundice, and sometimes mild-to-moderate thalassemia-like skeletal changes (e.g., hypertrophy of the maxilla, bossing of the skull, and prominence of the malar eminences) that affect the facial features. Leg ulcers are rare.

Individuals with HbH disease may develop gallstones and experience acute episodes of hemolysis in response to oxidant drugs and infections. Rarely, infection with parvovirus B19 can cause an aplastic crisis.

While the majority of individuals with HbH disease have minor disability, some are severely affected, requiring regular blood transfusions; in very rare cases hydrops fetalis is present [Lorey et al 2001, Chui et al 2003].

Significant iron overload is uncommon but has been reported in older individuals, usually resulting from repeated blood transfusions or increased iron absorption [Taher et al 2012].

Genotype-Phenotype Correlations

The phenotype of the α-thalassemia syndromes depends on the degree of α-globin chain deficiency relative to beta globin chain production. The correlation between α-thalassemia pathogenic variants, α-globin mRNA levels, α-globin synthesis, and clinical manifestations of α-thalassemia is well documented.

Hb Bart syndrome

- Most often caused by large deletions on both alleles (--/--)
- Rarely, an individual with Hb Bart syndrome will have a non-deletion variant (--/α^{ND}-).

HbH disease

- Most often caused by a large deletion on one allele in *trans* with a single α-globin gene deletion (--/-α) or other non-deletion inactivating variant (--/α^{ND}α or --/ααND)
- Individuals homozygous for *HBA2* pathogenic variants ($\alpha^{ND}\alpha/\alpha^{ND}\alpha$) may have HbH disease.
- Individuals who are homozygous or compound heterozygous for highly unstable α-globin gene variants may have HbH disease.
- Rarely, HbH disease is caused by compound heterozygosity for an MCS-R2 (see Nomenclature and Figure 1) deletion and an additional alpha gene deletion [$(\alpha\alpha)^{MCS\text{-}R2}$/-α] [Coelho et al 2010, Sollaino et al 2010].

Nomenclature

The α-thalassemia carrier states have been classified on the basis of the total globin protein produced from each of the two α-globin genes and by the number of globin genes that are missing or abnormal (see Table 4).

Table 4. Carrier State Nomenclature

Number of Deleted/ Inactivated α-Globin Genes	Nomenclature Based on # of Deleted/ Inactivated α-Globin Genes	Haplotype (i.e., *cis* or *trans*) [1]	Genotype Example	Nomenclature Based on Protein [2]		Carrier State Terminology
				Symbol	Definition	
1	α-thalassemia silent carrier [3]	NA	-α/αα [4]	α^+	Some α-globin protein is produced from one chromosome 16.	α-thalassemia silent carrier
2	α-thalassemia trait/ carrier [3]	*Cis*	--/αα	α^0	Zero α-globin protein is produced from one chromosome 16.	α^0 trait (α^0-thalassemia)
		Trans	-α/-α	α^+	Some α-globin protein is produced from each of two chromosomes 16.	α^+-thalassemia trait

1. Cis: both α-globin genes on one chromosome 16 are deleted or inactivated; *trans*: one α-globin gene on one chromosome 16 is deleted or inactivated by a non-deletion variant.
2. HBA2 encodes two to three times more globin than *HBA1*.
3. Lehmann & Carrell [1984]
4. The most common genotypes are the $-\alpha^{3.7}$ and $-\alpha^{4.2}$ deletion alleles (see Table 6 and Table 10).

Genotype nomenclature. In the expression αα/αα, the first alpha in each pair (**α**α/**α**α) typically refers to *HBA2* and the second alpha in each pair (α**α**/α**α**) to *HBA1*.

The terms "**α-thalassemia 1**" and "**α-thalassemia 2**" (referring to α-thalassemia silent carrier and α-thalassemia trait, respectively) are no longer in use [Weatherall et al 1988].

MCS-R2, a *m*ultispecies *c*onserved *s*equence previously known as HS-40, is a *cis*-acting regulatory element about 40 kb upstream of *HBZ* that is required for α-globin expression [reviewed by Farashi & Harteveld 2018] (see Figure 1).

Prevalence

Since the early 1960s, prevalence of α-thalassemia has been determined in several populations using the percent of Hb Bart in cord blood. However, because not all newborns with α-thalassemia (mainly α-thalassemia silent carriers) have increased Hb Bart, the prevalence of α-thalassemia derived from this measure may be underestimated.

Data that are more precise have been obtained using molecular testing. For detailed references for the frequency of α-thalassemia in each population, see Piel & Weatherall [2014].

Africa

The highest allele frequency (0.30-0.40) of the $-\alpha^{3.7}$ allele has been observed in the equatorial belt including Nigeria, Ivory Coast, and Kenya.

Deletion of the two α-globin genes in *cis* (--/αα) has been reported very rarely in North Africa and in the African American population.

The Mediterranean

Alpha-thalassemia trait caused by $-\alpha^{3.7}/-\alpha^{3.7}$ is common, with the highest allele frequency reported in Sardinia (0.18) and the lowest in Spain.

Deletion of the two α-globin genes in *cis* (--/αα) is very rare (0.002); thus, Hb Bart hydrops fetalis is only rarely reported.

A remarkable aspect of α-thalassemia variants identified in the Mediterranean population is the heterogeneity of variants, particularly the non-deletion variants.

The Arabian Peninsula

Frequency of the $-\alpha^{3.7}$ allele (causing α-thalassemia trait) varies from 0.01 to 0.67, with the highest values being observed in Oman.

Deletion of the two α-globin genes in *cis* (--/αα) is extremely rare.

India

Alpha-thalassemia trait reaches very high allele frequency (0.35-0.92) in the Indian tribal population of Andra Pradesh; in other tribes, the frequency is much lower (0.03-0.12). Both the $-\alpha^{3.7}$ allele and the $-\alpha^{4.2}$ allele variably contribute to incidence of α-thalassemia trait.

Deletion of the two α-globin genes in *cis* (--/αα) is very rare.

Southeast Asia

Alpha^0-thalassemia alleles ($--^{SEA}$, $--^{THAI}$, $--^{FIL}$) and α^+-thalassemia alleles (-α) are very common, causing a major public health burden.

Alpha-thalassemia caused by Hb Constant Spring alleles is also common.

The incidence of Hb Bart hydrops fetalis is expected to be in the range of 0.5-5:1,000 births and HbH disease the range of 4-20:1,000 births.

Oceania

The distribution of α-thalassemia, extensively studied by DNA-based methods, follows a pattern consistent with the degree of malaria endemicity. The prevalence of α-thalassemia is low in the highlands and high in the coastal areas and the lowlands where malaria is hyperendemic.

Some α-thalassemias have unusual mutation mechanisms; for example, some affected individuals on the island of Vanuatu who have normal α-globin genes without deletions or variants have a variant in a regulatory element that creates a GATA-1 site and activates a cryptic promoter [De Gobbi et al 2006].

Deletion of the two α-globin genes in *cis* (--/αα) is very rare.

Genetically Related (Allelic) Disorders

Alpha-thalassemia / intellectual disability syndrome, chromosome 16-related (ATR-16 syndrome) (OMIM 141750), a contiguous gene deletion syndrome, results from a large terminal deletion of the distal short arm of chromosome 16 from 16p13.3, which includes *HBA1* and *HBA2* and additional flanking genes. Among the few reported individuals with deletion of 16p (without deletion or duplication of other genomic material), microcephaly and short stature were variable; IQ ranged from 53 to 76 [Lindor et al 1997, Gibson et al 2008]. Facial features are distinctive; talipes equinovarus (clubfoot) is common, as are hypospadias and cryptorchidism in males [Lindor et al 1997]. Typically, hematologic features are those of the α-thalassemia trait reflecting deletion of *HBA1* and *HBA2* in *cis* configuration (i.e., --/αα). The subtelomeric deletions can be identified by MLPA [Harteveld et al 2007, Gibson et al 2008] or chromosomal microarray [Gibbons 2012]. The deletion may be *de novo* or inherited from a parent who carries a balanced chromosome rearrangement.

Acquired α-thalassemia (α-thalassemia-myelodysplastic syndrome; ATMDS). In the context of a clonal myeloid disorder such as myelodysplastic syndrome, somatic variants causing an acquired form of α-thalassemia HbH disease in individuals who were previously hematologically normal may arise [Steensma et al 2005]. Red cell indices are usually hypochromic and microcytic, in contrast to the normocytic or macrocytic indices typical of myelodysplastic syndrome. Although most instances of ATMDS have been linked to pathogenic variants in *ATRX* on the X chromosome [Gibbons et al 2003, Steensma et al 2004a], acquired deletions of chromosome 16p may be causative [Steensma et al 2004b]. For unknown reasons, some individuals with myeloid disorders have small amounts (<1%) of HbH.

Alpha-thalassemia X-linked intellectual disability syndrome is NOT an allelic disorder (see Differential Diagnosis).

Differential Diagnosis

Hydrops Fetalis

Hydrops fetalis is associated with many conditions in addition to Hb Bart, including immune-related disorders (e.g., alloimmune hemolytic disease, Rh isoimmunization), fetal cardiac anomalies, chromosome abnormalities, fetal infections, genetic disorders, and maternal and placental disorders. The combination of a hydropic fetus with a very high proportion of Hb Bart, however, is found in no other condition.

Hemoglobin H (HbH) Disease

Hemolytic anemias. HbH disease can be distinguished from other hemolytic anemias by: (1) microcytosis, which is uncommon in other forms of hemolytic anemia; (2) the fast-moving band (HbH) on hemoglobin electrophoresis; (3) the presence of inclusion bodies (precipitated HbH) in red blood cells after supravital stain; and (4) absence of morphologic or enzymatic changes characteristic of other forms of inherited hemolytic anemia (e.g., hereditary spherocytosis/elliptocytosis, G6PD deficiency). See *EPB42*-Related Hereditary Spherocytosis.

Alpha-thalassemia X-linked intellectual disability (ATRX) syndrome is characterized by distinctive craniofacial features, genital anomalies, severe developmental delays, hypotonia, intellectual disability, and mild-to-moderate anemia secondary to α-thalassemia. Craniofacial abnormalities include small head circumference, telecanthus or widely spaced eyes, short nose, tented vermilion of the upper lip, and thick or everted vermilion of the lower lip with coarsening of the facial features over time. Although all individuals with ATRX syndrome have a normal 46,XY karyotype, genital anomalies range from hypospadias and undescended testes, to severe hypospadias and ambiguous genitalia, to normal-appearing female genitalia. Global developmental delays are evident in infancy and some affected individuals never walk independently or develop significant speech.

Affected individuals do not reproduce. ATRX syndrome is caused by a hemizygous *ATRX* variant in affected males and inherited in an X-linked manner.

An unknown percent of 46,XY individuals with ATRX syndrome have a mild form of HbH disease, evident as HbH inclusions (β_4 tetramers) in erythrocytes following incubation of fresh blood smears with 1% brilliant cresyl blue. In ATRX syndrome, the alpha globin gene cluster and the MCS-R1-4 regulatory regions of chromosome 16 are structurally intact (see Figure 1).

Acquired variants in *ATRX* can arise in myelodysplastic syndrome and cause an acquired form of HbH disease (see Genetically Related Disorders, **Acquired α-thalassemia**).

Carrier States (α^0-Thalassemia and α^+-Thalassemia)

Beta-thalassemia. Microcytosis and hypochromia are present in α^0-thalassemia carriers, hematologically manifesting α^+-thalassemia carriers, and β-thalassemia carriers. Of note, β-thalassemia carriers are distinguished by a high percentage of HbA_2.

Iron deficiency anemia. Alpha-thalassemia trait can be confused with iron deficiency anemia because mean corpuscular volume and mean corpuscular hemoglobin are lower than normal in both conditions. However, in iron deficiency anemia, the red blood cell count is decreased, while it is usually increased in α^0-thalassemia carriers. Although some overlap with α-thalassemia carrier states exists, iron deficiency anemia is characterized by a marked increase in red blood cell distribution width, a quantitative measure of red blood cell anisocytosis. Iron studies (serum iron concentration, transferrin saturation, and serum ferritin) can be used to diagnose iron deficiency anemia with certainty. Iron deficiency and α-thalassemia can coexist, complicating diagnosis.

Management

In 2017, the Thalassemia International Federation updated its Guidelines for the Management of Non-Transfusion-Dependent Thalassemia, including beta-thalassemia (β-thalassemia) intermedia, HbH disease, and hemoglobin E/β-thalassemia [Taher et al 2017].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with alpha-thalassemia (α-thalassemia), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Hemoglobin Bart hydrops fetalis (Hb Bart) syndrome. See Prenatal Testing and Preimplantation Genetic Testing.

Hemoglobin H (HbH) disease

- Differentiation of deletion (mild) from non-deletion (moderate to severe) forms of HbH disease by appropriate molecular genetic testing of *HBA1* and *HBA2* at presentation because of varying severity
- Referral to a hematologist
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of α-thalassemia in order to facilitate medical and personal decision making

Treatment of Manifestations

Hb Bart syndrome was previously considered a universally fatal condition; however, its prognosis is shifting because of prenatal testing, intrauterine blood transfusions, improved transfusion strategies, and (rarely)

curative hematopoietic stem cell transplantation [Pecker et al 2017]. In an international registry, 39 of 69 infants were alive; however, 40%-50% of survivors had growth restriction and 20% had neurodevelopmental delay; congenital anomalies were common. Most affected individuals required lifelong transfusion [Songdej et al 2017]. Individuals with the most severe forms of non-deletional HbH disease may become transfusion dependent (HbH hydrops) and should be managed similarly to those with β-thalassemia major [Taher et al 2017].

The advances in intrauterine and postnatal therapy have resulted in ethical dilemmas for the family and health care provider; consultation with a clinical ethics service may be helpful in assessing health care decisions in the context of the best interest of the child and the values and preferences of the family.

HbH disease. Most individuals with HbH disease are clinically well and survive without any treatment. Individuals with non-deletional HbH disease who have biallelic *HBA2* pathogenic variants (e.g., $\alpha^{\text{Constant Spring}}\alpha/\alpha^{\text{Constant Spring}}\alpha$) may be more severely affected and, thus, be transfusion dependent.

- Individuals with deletional HbH disease may need occasional red blood cell transfusions if the hemoglobin (Hb) level suddenly drops because of hemolytic or aplastic crises.
- Clear indications for red blood cell transfusions are severe anemia affecting cardiac function and massive erythroid expansion, resulting in severe bone changes and extramedullary erythropoiesis. Note: These events are quite rare in HbH disease.
- Iron chelation therapy may be needed in individuals with iron loading caused by regular blood transfusion, inappropriate iron therapy, or abnormal iron absorption.
- Splenectomy should be performed only in individuals with massive splenomegaly or hypersplenism; the associated risks for severe, life-threatening sepsis and venous thrombosis should be considered.
- Other complications, such as gallstones and leg ulcers, require appropriate medical or surgical treatment.

Prevention of Primary Manifestations

Hb Bart syndrome. Because of the severity of Hb Bart syndrome and the risk for maternal complications during pregnancy with a fetus with this disorder, prenatal diagnosis and early termination of affected pregnancies is usually considered. Future studies on the functional outcomes of children with Hb Bart syndrome who have received chronic transfusion, intrauterine transfusions, and hematopoietic stem cell transplantation will allow physicians to improve the informed decision-making process for families weighing the risk-benefit profile of present treatment options.

Prevention of Secondary Complications

HbH disease. During febrile episodes, a clinical evaluation is recommended because of the increased risk for hemolytic/aplastic crisis (similar to G6PD deficiency, hemolysis in HbH disease can be triggered by oxidative stresses or infection).

When chronic red blood cell transfusions are instituted for individuals with HbH disease, the management should be the same as for all individuals who have been polytransfused, including use of iron chelation therapy (see Beta-Thalassemia).

In individuals with HbH disease who are not red blood cell transfusion dependent, the only iron chelator specifically approved is deferasirox, shown to be superior to placebo in reducing liver iron concentration in those older than age ten years with β-thalassemia intermedia, hemoglobin E/β-thalassemia, or HbH disease [Taher et al 2012].

Regular folic acid supplementation should be recommended, as for other hemolytic anemias.

If splenectomy is required, antimicrobial prophylaxis is usually provided, at least until age five years, to decrease the risk for overwhelming sepsis caused by encapsulated organisms. Use of antimicrobial prophylaxis

notwithstanding, a careful clinical evaluation of individuals who have undergone splenectomy and have a fever is recommended.

Surveillance

HbH disease

- Hematologic evaluation every six to 12 months to determine the steady state levels of Hb
- In children, assessment of growth and development every six to 12 months
- Monitoring of iron load with annual determination of serum ferritin concentration in individuals who have been transfused, in older individuals, and in those given inappropriate iron supplementation. Since serum ferritin may underestimate the degree of iron overload, a periodic noninvasive quantitative measurement of liver iron concentration by MRI is also recommended [Musallam et al 2012].

Agents/Circumstances to Avoid

HbH disease. Avoid the following:

- Inappropriate iron therapy
- Oxidant drugs according to recommendations for G6PD deficiency [Bubp et al 2015] (full text; note especially Table 1. Drugs To Be Avoided by G6PD-Deficient Patients, and Table 2. Drugs To Be Used With Caution in Therapeutic Doses for Patients With G6PD Deficiency).

Evaluation of Relatives at Risk

The sibs of a proband should be evaluated as soon as possible after birth to determine if they have HbH disease so that appropriate management (including agents/circumstances to avoid) can be implemented. Evaluations can include:

- Evaluation of red blood cell indices, red blood cell supravital stain for HbH inclusions, and hemoglobin analysis by high-performance liquid chromatography
- Targeted molecular analysis if the pathogenic variants in the family are known
- Molecular genetic analysis (according to the frequency of alpha globin gene pathogenic variants by geographic area) if the pathogenic variants in the family are not known

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

Pregnancy Management

During pregnancy, complications reported in women with HbH disease include worsening of anemia (with occasional need for red cell transfusions), preeclampsia, congestive heart failure, and threatened miscarriage [Origa et al 2007]. Monitoring for these possible complications is recommended.

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

Alpha-thalassemia (α-thalassemia) is usually inherited in an autosomal recessive manner.

Risk to Family Members

Hemoglobin Bart Hydrops Fetalis (Hb Bart) Syndrome

Parents of a proband. The parents of a fetus with Hb Bart syndrome have α-thalassemia trait caused by deletion or inactivation of two alpha globin (α-globin) genes in *cis* (e.g., --/αα).

Sibs of a proband. At conception, each sib of a proband with Hb Bart syndrome has a 25% chance of having Hb Bart syndrome (e.g., --/--), a 50% chance of having α-thalassemia trait with deletion or inactivation of two α-globin genes in *cis* (e.g., --/αα), and a 25% chance of being unaffected and not a carrier.

Offspring of a proband. Hb Bart syndrome is often not compatible with postnatal life.

Other family members. Each sib of the proband's parents is at a 50% risk of having α-thalassemia trait with deletion or inactivation of two α-globin genes in *cis* (e.g., --/αα).

Hemoglobin H (HbH) Disease

Parents and sibs of a proband. The parents of a child with HbH disease usually have different genotypes; the risk to sibs of a proband depends on the genotype of the parents (see Table 5).

Table 5. Possible Parental Genotypes and Corresponding Outcomes in Sibs of a Proband with HbH Disease

Genotype of One Parent of Proband [1]	Genotype of Other Parent of Proband	Likelihood of Possible Outcomes in Sibs of Proband
Silent carrier [-α/αα]	α^+-thalassemia trait/carrier [--/αα]	• 25% HbH disease • 25% silent carrier • 25% α^+-thalassemia trait/carrier • 25% normal Hb
Silent carrier [-α/αα]	α^+-thalassemia trait/carrier [-α/-α]	• 50% silent carrier • 50% α^+-thalassemia trait/carrier
α^+-thalassemia trait/carrier with single-nucleotide variant in α2 [α^{ND}α/αα]	α^+-thalassemia trait/carrier with single-nucleotide variant in α2 [α^{ND}α/αα]	• 25% HbH disease [α^{ND}α/α^{ND}α] • 50% α-thalassemia trait [α^{ND}α/αα] • 25% normal Hb
Silent carrier [-α/αα]	α^+-thalassemia trait/carrier with single-nucleotide variant in α2 [α^{ND}α/αα]	• 25% HbH disease • 25% silent carrier • 25% α^+-thalassemia trait/carrier • 25% normal Hb

Hb = hemoglobin

1. Genotype frequency depends on geographic region (e.g., in the Mediterranean region, single-nucleotide variants are relatively frequent, while they are rare in the Far East).

Offspring of a proband

- Each child of an individual with HbH disease inherits:

- Deletion or inactivation of two α-globin genes in *cis* (e.g. ,--/αα, α-thalassemia trait/carrier);

  OR

- Non-deletion inactivation of α2-globin gene (α-thalassemia trait/carrier).

- Given the high carrier rate of α-thalassemia in certain populations, it is appropriate to offer carrier testing to the reproductive partner of an individual with:
  - HbH disease

    OR

  - Alpha-thalassemia trait/carrier associated with either deletion of the two α-globin genes in *cis* (--/αα) or a non-deletional variant (α^{ND}α/αα) in *HBA2*.

Other family members of a proband with either Hb Bart syndrome or HbH disease. Each sib of the proband's parents is at risk of having a deletion (-α/αα, silent carrier) or non-deletion inactivation (α^{ND}α/αα, α^{+} trait/carrier) and/or α^{0}-thalassemia trait/carrier with deletion or inactivation of two α-globin genes in *cis* (e.g., --/αα).

Carrier Detection for Individuals with a Positive Family History of Hb Bart Syndrome or HbH Disease

Molecular genetic testing of the α-globin genes *HBA1* and *HBA2* can be used to detect α-thalassemia trait or α-thalassemia silent carrier status in at-risk relatives if biallelic pathogenic variants in *HBA1* and *HBA2* resulting in deletion or inactivation of three (or four) α-globin genes have been detected in a family member with HbH disease (or Hb Bart syndrome).

Table 6. Alpha-Thalassemia Carrier States

Term (Comment)	Genotype		Genotype-Phenotype Correlations
α-thalassemia trait/carrier (person is asymptomatic with microcytosis & mild anemia) [1]	Deletion/ inactivation of 2 α-globin genes	• **In *cis*** (e.g., --/αα) [2] • **In *trans*** (e.g., -α/-α, $-\alpha^{3.7}/-\alpha^{3.7}$, $-\alpha^{4.2}/-\alpha^{4.2}$)	Deletion or inactivation of 2 α-globin genes in *cis* is assoc with slightly lower RBC indices than persons with 2-gene deletion in *trans* (-α/-α) due to compensatory increase of α-globin production from remaining *HBA1*.
	Non-deletional inactivation of *HBA2* globin gene	E.g., α^{ND}α/αα	• Single-nucleotide variants are usually more severe than a 1-gene deletion due to lack of compensatory increase of α-globin production assoc with a 1-gene deletion. • Moreover, pathogenic variants in *HBA2* are more severe than those in *HBA1* because *HBA2* produces 2-3x more α-globin.
α-thalassemia silent carrier (completely silent hematologic phenotype or very mild microcytosis) [1]	Deletion of 1 α-globin gene	E.g., -α/αα, α-/αα	Completely silent hematologic phenotype or very mild microcytosis
	Non-deletional inactivation of *HBA1*	E.g., ααND/αα	Because *HBA1* produces 2x less α-globin than *HBA2*, pathogenic variants in *HBA1* are assoc with a milder phenotype.

RBC = red blood cell

1. Moderate thalassemia-like hematologic picture refers to mild hypochromic (low mean corpuscular hemoglobin), microcytic (low mean corpuscular volume) anemia and normal hemoglobin A_2 and hemoglobin F (see Table 7).

2. Individuals with this genotype may be referred to as α^{0} carriers.

Population Screening for α-Thalassemia Trait

Because of the high carrier rate for the two-gene deletion in *cis* (--/αα) in certain populations and the availability of genetic counseling and prenatal testing, it is ideal to screen (prior to or early in pregnancy) couples who are members of at-risk populations to identify those at risk of conceiving a fetus with Hb Bart syndrome.

Note: Since $--^{SEA}/--^{SEA}$ deletions spare *HBZ* (zeta globin gene), a fetus has 10%-20% Portland Hb (which is capable of O_2 delivery to tissues) and will survive until the third trimester. However, a fetus with deletion of all four α-globin genes that includes *HBZ*, such as $--^{FIL}/--^{FIL}$, will nevertheless succumb to hypoxia and heart failure in utero or shortly after birth.

Note: Prospective identification of α-thalassemia silent carriers (i.e., -α/αα or $αα^{ND}$/αα) is not strongly indicated, as the offspring of these carriers are not at risk for Hb Bart syndrome.

Evaluations to Detect Carrier States

Table 7. Hematologic Findings in Alpha-Thalassemia Trait and Alpha-Thalassemia Silent Carriers

Red Blood Cell Indices [1]	Normal		Carrier [2]	
	Male	Female	α-Thalassemia Trait [3] (--/αα or -α/-α)	α-Thalassemia Silent Carrier (-α/αα)
Mean corpuscular volume (MCV, in fL)	89.1 ± 5.01	87.6 ± 5.5	71.6 ± 4.1	81.2 ± 6.9
Mean corpuscular hemoglobin (MCH, in pg)	30.9 ± 1.9	30.2 ± 2.1	22.9 ± 1.3	26.2 ± 2.3
Hemoglobin (Hb, in g/dL)	15.9 ± 1.0	14.0 ± 0.9	Male: 13.9 ± 1.7	Male: 14.3 ± 1.4
			Female: 12.0 ± 1.0	Female: 12.6 ± 1.2

1. Reference ranges may vary by laboratory.
2. Higgs & Bowden [2001]
3. Alpha-thalassemia carriers with the two-gene deletion in *cis* (--/αα) have slightly lower red blood cell indices.

Qualitative and quantitative hemoglobin (Hb) analysis (by cellulose acetate electrophoresis, weak-cation high-performance liquid chromatography, and supplemental techniques such as isoelectric focusing and citrate agar electrophoresis) identifies the amount and type of Hb present (see Table 8).

- Hemoglobin A (HbA). Two alpha globin chains and two beta globin chains ($α_2β_2$)
- Hemoglobin F (HbF). Two alpha globin chains and two gamma globin chains ($α_2γ_2$)
- Hemoglobin H (HbH). Four beta globin chains ($β_4$)
- Hemoglobin A2 (HbA_2). Two alpha globin chains and two delta globin chains ($α_2δ_2$)
- Hemoglobin Bart (Hb Bart). Four gamma globin chains ($γ_4$)
- Hemoglobin Portland. Two zeta globin chains and two gamma globin chains ($ζ_2γ_2$)

Table 8. Hemoglobin Analysis in Alpha-Thalassemia Trait and Alpha-Thalassemia Silent Carriers

Hemoglobin Type	Normal	α-Thalassemia Trait [1] (--/αα or -α/-α)	α-Thalassemia Silent Carrier [2] (-α/αα)
HbA	96%-98%	96%-98%	96%-98%
HbF	<1%	<1.0%	<1.0%
HbH	0	0	0
HbA_2	2%-3%	1.5%-3.0%	2%-3%
Hb Bart	0	0	0

Table 8. continued from previous page.

Hemoglobin Type	Normal	α-Thalassemia Trait [1] (--/αα or -α/-α)	α-Thalassemia Silent Carrier [2] (-α/αα)
Hb Portland	0	0	0

1. Deletion or inactivation of two α-globin genes either in *cis* configuration (--/αα) or in *trans* configuration (-α/-α)
2. Deletion or inactivation of one α-globin gene (-α/αα)

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, clarification of carrier status, 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 have HbH disease, are carriers, or are at risk of being carriers.

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

High-risk pregnancies. Prenatal testing and preimplantation genetic testing are possible for couples confirmed by DNA analysis to be at risk of having a fetus with Hb Bart syndrome because both parents are carriers of a two-gene deletion in *cis* (--/αα, --/α^{ND}-).

Ultrasound examination. Ultrasonography can be useful in the management of pregnancies at risk for Hb Bart syndrome. In the first trimester, increased nuchal thickness, particularly in an at-risk pregnancy, should prompt appropriate evaluation.

Indeterminate-risk pregnancies. An indeterminate-risk pregnancy is a pregnancy for which ONE of the following is true:

- One parent has an α-thalassemia trait with a two-gene deletion in *cis* (--/αα) and the other has an α-thalassemia-like hematologic picture but no α-thalassemia variant identified by molecular genetic testing.
- The mother has a known α-thalassemia trait with a two-gene deletion in *cis* (--/αα) and the father is unknown or unavailable for testing. This is of concern if the father belongs to a population with a high carrier rate for α-thalassemia pathogenic variants.

In both instances, the options for prenatal testing should be discussed in the context of formal genetic counseling. Analysis of fetal DNA for the known α-thalassemia variant is recommended as the first step in prenatal testing for indeterminate-risk pregnancies; if the known α-thalassemia variant is present, globin chain synthesis analysis is performed using a fetal blood sample obtained by percutaneous umbilical blood sampling.

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.

- **Cooley's Anemia Foundation**
  330 Seventh Avenue
  #200
  New York NY 10001
  Phone: 212-279-8090
  Fax: 212-279-5999
  Alpha Thalassemia (PDF file)
- **MedlinePlus**
  Alpha thalassemia
- **Thalassaemia International Federation (TIF)**
  Cyprus
  Phone: +357 22 319129
  Fax: +357 22 314552
  Email: thalassaemia@cytanet.com.cy
  www.thalassaemia.org.cy

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. Alpha-Thalassemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HBA1	16p13.3	Hemoglobin subunit alpha	HBA1 @ LOVD HbVar: A Database of Human Hemoglobin Variants and Thalassemias (HBA1)	HBA1	HBA1
HBA2	16p13.3	Hemoglobin subunit alpha	HBA2 @ LOVD HbVar: A Database of Human Hemoglobin Variants and Thalassemias (HBA2)	HBA2	HBA2
HBZ	16p13.3	Hemoglobin subunit zeta	HbVar: A Database of Human Hemoglobin Variants and Thalassemias (HBZ)	HBZ	HBZ

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 Alpha-Thalassemia (View All in OMIM)

141800	HEMOGLOBIN--ALPHA LOCUS 1; HBA1
141850	HEMOGLOBIN--ALPHA LOCUS 2; HBA2
142310	HEMOGLOBIN--ZETA LOCUS; HBZ

Table B. continued from previous page.

604131	ALPHA-THALASSEMIA

Molecular Pathogenesis

Mechanism of disease causation. Normally each individual has four alpha globin (α-globin) genes, i.e., *HBA1* and *HBA2* on both number 16 chromosomes. Inactivation of *HBA1* or *HBA2* reduces production of α-globin chains; thus, the more α-globin genes inactivated, the fewer α-globin chains are synthesized, leading to an increasing imbalance between α-globin chains and beta globin chains.

The level of transcription of *HBA1* and *HBA2* differs: *HBA2* produces two to three times more α-globin chains than *HBA1*. This difference has important clinical implications; for example, inactivation of *HBA2* results in fewer α-globin chains than inactivation of *HBA1*.

MCS-R1 to -R4 region. The expression of *HBA1* and *HBA2* is regulated by the *m*ultispecies *c*onserved *s*equences (MCS-R1 to -R4) region located about 40 kb upstream from the α-globin cluster (see Figure 1). The MCS-R2 region comprises multiple binding sites for transcriptional factors (NF-E2, GATA-1). The deletion of MCS-R2 results in an alpha-thalassemia (α-thalassemia) phenotype in spite of the structural integrity of both α-globin genes [Coelho et al 2010, Sollaino et al 2010, Higgs 2013, Wu et al 2017].

Gene-specific laboratory technical considerations. See Table 9.

Table 9. Gene-Specific Laboratory Technical Considerations: Genes Causing Alpha-Thalassemia

Gene/ Locus	Special Consideration
HBA1	• Judicious primer/probe design is required due to marked nucleotide homology between *HBA1* & *HBA2* and of the 2 flanking regions. • Note that locus-specific databases (see Table A) and the literature employ variable numbering systems for pathogenic variants (detailed at globin.bx.psu.edu/hbvar); current nomenclature recommendations (varnomen.hgvs.org) may not be followed.
HBA2	
MCS-R2	Deletion of this regulatory locus upstream of the α-globin gene cluster is a disease-causing variant.

Notable variants by genes causing α-thalassemia. The molecular mechanisms leading to the silencing of either *HBA1* or *HBA2* include variants affecting RNA splicing, polyadenylation signal, and initiation of mRNA translation, as well as missense variants of the stop codon, in-frame deletions, frameshift variants, and nonsense variants. Non-deletion variants of α-globin genes resulting in the production of hyper-unstable globin variants such as Hb Quong Sze are unable to assemble into stable β_4 tetramers and thus are rapidly degraded, and may also result in α-thalassemia [Higgs 2013].

Table 10. Notable Pathogenic Variants in Genes Causing Alpha-Thalassemia

Gene [1]	Reference Sequences	DNA Nucleotide Change [2]	Predicted Protein Change			Description
			HGVS standard nomenclature [3]	Globin Gene Server nomenclature [4]	Hemoglobin variant [5]	
Non-deletional						
HBA1	NM_000558.5 NP_000549.1	c.223G>C	p.Asp75His	p.Asp74His	$HbQ_{Thailand}$	Variant electrophoretic & functional properties
HBA2	NM_000517.6 NP_000508.1	c.377T>C	p.Leu126Pro	p.Leu125Pro	Hb Quong Sze	Unstable α-globin protein

Table 10. continued from previous page.

Gene [1]	Reference Sequences	DNA Nucleotide Change [2]	Predicted Protein Change			Description
			HGVS standard nomenclature [3]	Globin Gene Server nomenclature [4]	Hemoglobin variant [5]	
		c.427T>C	p.Ter143Glnext32		Hb Constant Spring	Stop codon is changed to a Gln residue, thereby extending the protein by 32 additional residues.
		c.*94A>G	--	--	NA	Pathogenic variant in 3'UTR polyadenlylation signal (AATAAA>AATAAG) that is 94 nucleotides past the stop codon; also known as allele **$\alpha^{T\text{-}Saudi}$**
		c.95+2_95+6delTGAGG	--	--	NA	Abolishes intron 1 donor splice site & activates alternative site within exon 1 leading to truncated mRNA; also an **HphI restriction site**
Deletion of 1 α-globin gene						
HBA2	Z84721.1	$-\alpha^{3.7}$	See footnote 6.	See footnote 7.	See footnote 7.	NA	3.7-kb deletion of *HBA2*
		$-\alpha^{4.2}$				4.2-kb deletion of *HBA2*
HBA2, partial *HBA1*		$-\alpha^{20.5}$				20.5-kb deletion of *HBA2* & 5' end of *HBA1*
Deletion of 2 α-globin genes in *cis*						

Table 10. continued from previous page.

Gene [1]	Reference Sequences	DNA Nucleotide Change [2]		Predicted Protein Change			Description
				HGVS standard nomenclature [3]	Globin Gene Server nomenclature [4]	Hemoglobin variant [5]	
HBA1 *HBA2*	Z84721.1	--SEA	See footnote 6.	See footnote 7.	See footnote 7.	NA	~20-kb deletion incl both *HBA2* & *HBA1*
HBA1 *HBA2* *HBZ*		--FIL					~30-kb deletion incl *HBZ*, *HBA2*, & *HBA1*
		--THAI					~34-kb deletion involving *HBZ*, *HBA2*, & *HBA1*
		--MED					~26-kb deletion involving *HBZ*, *HBA2*, & *HBA1*

Variants listed in the table have been provided by the authors.*GeneReviews* staff have not independently verified the classification of variants (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
General references for data in this table are the Globin Gene Server and Mettananda & Higgs [2018] and references therein.
1. For deletions, only functional globin genes are included; deleted pseudogenes are omitted.
2. For nucleotide variants, *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (HGVS) (varnomen.hgvs.org).
3. For predicted protein variants, *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org) where the initiator methionine is residue number 1.
4. The Globin Gene Server considers the amino acid **after** the initiator methionine is number 1 [i.e., Val]. Therefore, the amino acid numbering is typically one less that of the HGVS. (Nomenclature differences detailed here.) Of historical note, the amino acid sequence of the α-globin genes was determined by protein sequencing prior to identification and sequencing of the genes. Post-translational modification excises the initiator methionine from the mature α-globin genes; therefore, the initiating methionine was not part of the protein sequence as initially determined. The second amino acid valine was thus designated as residue number 1.
5. Variant forms of hemoglobin typically detected in the laboratory by altered electrophoretic properties. Name, protein characteristics, and hematologic findings are detailed in Globin Gene Server.
6. The nucleotide coordinates for globin gene deletions vary and typically are not designated; however, a few breakpoints have been reported (see Globin Gene Server).
7. Because deletions involve partial or whole-gene deletions, predicted protein changes are not applicable.

Chapter Notes

Author Notes

Hannah Tamary, MD, was the head of Hematology Unit in Schneider Children's Medical Center of Israel for more than 20 years. Currently she is the director of the Pediatric Molecular Hematology Laboratory there, the only laboratory in Israel using next-generation sequencing technology and providing diagnosis for all types of anemias, as well as inherited predisposition to myelodysplastic syndrome/leukemias and bone marrow failure syndromes. She also investigates erythropoiesis through the study of congenital dyserythropoietic anemia.

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