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Alpha-Thalassemia

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Summary

Disease characteristics. Alpha-thalassemia (α-thalassemia) has two clinically significant forms: hemoglobin Bart hydrops fetalis (Hb Bart) syndrome and hemoglobin H (HbH) disease. **Hb Bart syndrome**, the most severe form, is characterized by fetal onset of generalized edema, pleural and pericardial effusions, and severe hypochromic anemia, in the absence of ABO or Rh blood group incompatibility. Clinical features include: hepatosplenomegaly, extramedullary erythropoiesis, hydrocephaly, and cardiac and urogenital defects. Death usually occurs in the neonatal period. **HbH disease** is characterized by microcytic hypochromic hemolytic anemia, hepatosplenomegaly, mild jaundice, and sometimes thalassemia-like bone changes. Carriers of α^o-thalassemia (α-thalassemia trait) show microcytosis, hypochromia, and normal percentages of HbA2 and HbF. Carriers of α^+-thalassemia (α-thalassemia silent carrier) have either a silent hematologic phenotype or present with a moderate thalassemia-like hematologic picture. Homozygosity for α^+-thalassemia results in an α^o-thalassemia (α-thalassemia trait) hematologic phenotype.

Diagnosis/testing. All four α-globin alleles are deleted or inactivated in Hb Bart syndrome. Deletion or dysfunction of three alleles results in HbH disease. Alpha^o-thalassemia results from deletion or dysfunction of two alleles, and α^+-thalassemia results from deletion or dysfunction of one allele. Testing for α-thalassemia includes: hematologic testing of red blood cell indices, peripheral blood smear, supravital stain to detect RBC inclusion bodies, and qualitative and quantitative hemoglobin analysis. *HBA1*, the gene encoding α_1-globin, and *HBA2*, the gene encoding α_2-globin, are the two genes most commonly associated with α-thalassemia. Molecular genetic testing of *HBA1* and *HBA2* detects deletions in about 90% and point mutations in about 10% of affected individuals.

Management. *Treatment of manifestations:* No treatment is effective for Hb Bart hydrops fetalis. For HbH disease, 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. *Prevention of primary manifestations:* Prenatal diagnosis and early termination of pregnancies at risk for Hb Bart hydrops fetalis are recommended because of the disease severity and risk for maternal complications. *Prevention of secondary complications:* Monitor individuals with HbH disease for hemolytic crisis during febrile

episodes. *Surveillance:* hematologic evaluation every six to 12 months; assessment of growth and development in children every six to 12 months; monitoring of iron load. *Agents/ circumstances to avoid:* in HbH disease, inappropriate iron therapy, oxidant drugs such as sulphonamides, and some antimalarials. *Testing 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.

Genetic counseling. Alpha-thalassemia is usually inherited in an autosomal recessive manner. At conception, each sib of an individual with Hb Bart syndrome has a 25% chance of having Hb Bart syndrome, a 50% chance of having α^o-thalassemia (α-thalassemia trait), and a 25% chance of being unaffected and not a carrier. Once an at-risk sib is known to be unaffected, the risk of his/her having α^o-thalassemia (α-thalassemia trait) is 2/3. At conception, each sib of an individual with HbH disease has a 25% chance of having HbH disease, a 25% chance of having α^o-thalassemia (α-thalassemia trait), a 25% chance of having α^+-thalassemia (α-thalassemia silent carrier), and a 25% chance of being unaffected and not a carrier. Once an at-risk sib is known to be unaffected, the risk of his/her having either α^o-thalassemia (α-thalassemia trait) or α^+-thalassemia (α-thalassemia silent carrier) is 2/3. Each child of an individual with HbH disease inherits the mutation for either α^o-thalassemia or α^+-thalassemia and is thus an obligate heterozygote. Family members, members of ethnic groups at risk, and gamete donors should be considered for carrier testing. Couples who are members of at-risk populations for α^o-thalassemia carrier status can be identified prior to pregnancy to avoid conceiving a fetus with Hb Bart syndrome. Prenatal 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^o-thalassemia carrier and it is unknown whether the other parent has the mutation.

Diagnosis

Clinical Diagnosis

Alpha-thalassemia (α-thalassemia) has two clinically significant forms:

- **Hemoglobin Bart hydrops fetalis (Hb Bart) syndrome**, the most severe form of α-thalassemia, is characterized by fetal onset of generalized edema, ascites, pleural and pericardial effusions, and severe hypochromic anemia, in the absence of ABO or Rh blood group incompatibility. It is usually detected by ultrasonography at 22 to 28 weeks' gestation and can be suspected in an at-risk pregnancy at 13 to 14 weeks' gestation when increased nuchal thickness, possible placental thickness, and increased cardiothoracic ratio are present. Death in the neonatal period is almost inevitable. All four α-globin alleles are deleted or dysfunctional (inactivated).
- **Hemoglobin H (HbH) disease** should be suspected in an infant or child with a mild-to-moderate (rarely severe) microcytic hypochromic hemolytic anemia and hepatosplenomegaly. Mild thalassemia-like bone changes are present in approximately one-third of affected individuals. Unlike Hb Bart syndrome, HbH disease is compatible with survival into adulthood. HbH disease is a result of deletion or dysfunction of three of four α-globin alleles.

Alpha-thalassemia also has two carrier states:

- **Alpha^o-thalassemia** generally results from deletion or dysfunction of two α-globin genes, in cis (--/αα) (See Molecular Genetic Testing)
- **Alpha$^+$-thalassemia** usually results from deletion or dysfunction of one α-globin gene. Homozygosity for α^+ thalassemia results in an α-thalassemia trait hematologic phenotype.

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Testing

Hematologic Testing—Red blood cell indices show microcytic anemia in HbH disease or α-thalassemia trait; indices are usually normal in silent carriers and macrocytic in Hb Bart syndrome as a result of extreme reticulocytosis and megaloblastoid erythropoiesis (Table 1).

Table 1. Red Blood Cell Indices in Adults with Alpha-Thalassemia

Red Blood Cell Indices	Normal		Affected		Carrier [1]	
	Male	Female	Hemoglobin Bart Hydrops Fetalis [2]	Hemoglobin H Disease [3]	Alpha-Thalassemia Trait [4] (--/αα or -α/-α)	Alpha-Thalassemia Silent Carrier
Mean corpuscular volume (MCV, fl)	89.1±5.01	87.6±5.5	136±5.1	56±5 (children); 61 ±4 (adults)	71.6±4.1	81.2±6.9
Mean corpuscular hemoglobin (MCH, pg)	30.9±1.9	30.2±2.1	31.9±9	18.4±1.2	22.9±1.3	26.2±2.3
Hemoglobin (Hb, g/dL)	15.9±1.0	14.0±0.9	3-8	M10.9±1.0 F9.5±0.8	M13.9±1.7 F12.0±1.0	M14.3±1.4 F12.6±1.2

1. Higgs & Bowden [2001]
2. Vaeusorn et al [1985]
3. Galanello et al [1992]
4. Alpha-thalassemia carriers with the two gene in cis (--/αα) genotype have slightly lower RBC indices.

Reticulocytosis

- **Hb Bart syndrome.** Variable, may be more than 60%
- **HbH disease.** Moderate, between 3% and 6%

Peripheral blood smear

- **Hb Bart syndrome.** Large, hypochromic red cells and severe anisopoikilocytosis
- **HbH disease.** Microcytosis, hypochromia, anisocytosis, poikilocytosis (spiculated tear-drop and elongated cells), and very rare nucleated red blood cells (i.e., erythroblasts)
- **Carriers.** Reduced MCV, MCH, and RBC morphologic changes that are less severe than those in affected individuals; erythroblasts are not seen.

Supravital stain to detect RBC inclusion bodies. HbH inclusions (β_4 tetramers) can be demonstrated in 5% to 80% of the erythrocytes of individuals with HbH disease following incubation of fresh blood smears with 1% brilliant cresyl blue (BCB) for four to 24 hours. Small amounts of inclusions can also be detected in subjects with α-thalassemia trait and the silent carrier state as well.

Qualitative and quantitative hemoglobin analysis (by cellulose acetate electrophoresis, weak-cation high-performance liquid chromatography (HPLC), and supplemental techniques such as isoelectric focusing and citrate agar electrophoresis) identifies the amount and type of Hb present. Hb types most relevant to α-thalassemia:

- **Hemoglobin A (HbA).** Two α-globin chains and two β-globin chains ($\alpha_2\beta_2$)
- **Hemoglobin H (HbH).** Four β-globin chains (β_4)
- **Hemoglobin Bart (Hb Bart).** Four γ-globin chains (γ_4)

- **Hemoglobin Portland.** Two ζ-globin chains and two γ-globin chains ($\zeta_2\gamma_2$)

The Hb pattern in α-thalassemia varies by α-thalassemia type (Table 2).

Table 2. Hemoglobin Patterns in Alpha-Thalassemia (Age >12 Months)

Hemoglobin Type	Normal	Affected		Carrier	
		Hb Bart Hydrops Fetalis Syndrome [1]	HbH Disease [2]	Alpha-Thalassemia Trait [3]	Alpha-Thalassemia Silent Carrier [4]
HbA	96%-98%	0	60%-90%	96%-98%	96%-98%
HbF	<1%	0	<1.0%	<1.0%	<1.0%
Hb Bart	0	85%-90%	2%-5%	0	0
HbH	0	0	0.8%-40%	0	0
HbA2	2%-3%	0	<2.0%	1.5%-3.0%	2%-3%

1. Deletion or inactivation of all four α-globin chains makes it impossible to assemble HbF and HbA. Fetal blood contains mainly Hb Bart (γ4) and 10%-15% of the embryonic hemoglobin Portland (ζ2γ2).

2. Deletion or inactivation of three α-globin chains

3. Deletion or inactivation of two α-globin chains either in cis configuration (--/αα) or in trans configuration (-α/-α); also known as α°-thalassemia

4. Deletion or inactivation of one of the α-globin gene (-α/αα); also known as α+-thalassemia

In HbH disease, bone marrow is extremely cellular, mainly as a result of marked erythroid hyperplasia.

Note: Bone marrow examination is usually not necessary for diagnosis of affected individuals.

Newborn screening for sickle cell disease offered by several states/countries may detect Hb Bart in the newborn with α-thalassemia. (See National Newborn Screening Status Report; pdf.)

Note: (1) Newborns with concentrations of Hb Bart greater than 15% need further evaluation (i.e., clinical and hematologic evaluation and molecular genetic testing), as they may develop HbH disease. (2) Low concentrations of Hb Bart (1%-8%) are indicative of the carrier states and usually do not need further evaluation. Reference ranges may very among laboratories performing newborn screening.

Molecular Genetic Testing

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

Molecular Genetic Testing—Genes. *HBA1*, the gene encoding α_1-globin, and *HBA2*, the gene encoding α_2-globin, are the two genes associated with α-thalassemia. They are localized to the telomeric region of chromosome 16p in a cluster containing the embryonically expressed *HBZ* gene encoding ζ-globin and a cis-acting regulatory element, HS-40, located 40 kb upstream of the *HBZ* gene. All regulatory-element and trans-acting mutations causing α-thalassemia also ultimately alter expression of all these genes:

- *HBA1* is the α_1 gene.
- *HBA2* is the α_2 gene; it is 20 kb away from the embryonic ζ gene (Figure 1).

Clinical testing

- **Targeted mutation analysis**

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- **Deletions.** (1) Polymerase chain reaction (PCR)-based methods that use specific primers flanking the deletion breakpoints detect deletion of a single α-globin gene (α^{+}-thalassemia mutations) and deletion of both α-globin genes on one chromosome 16 (α^{o}-thalassemia mutations). Primer panels targeted to the most common mutations found in the area of geographic origin of the proband can be used. [Galanello et al 1998, Chong et al 2000, Old 2001]. (2) Southern blot analysis or multiple ligation-dependent probe amplification (MLPA) [Harteveld et al 2005] may be used to detect less common or novel deletions.

  Deletion of a single α-globin gene (α^{+}-thalassemia mutations). Reciprocal recombination between either the Z boxes (Figure 1), which are 3.7 kb apart, or the X boxes, which are 4.2 kb apart, deletes one α-globin gene. The two resulting deletions are referred to respectively as the 3.7-kb rightward deletion ($-\alpha^{3.7}$) and the 4.2-kb leftward deletion ($-\alpha^{4.2}$).

  In addition to these two common deletions, three rare deletions involving a single α-globin gene have been reported.

  Deletion of both α-globin genes on one chromosome (α^{o}-thalassemia mutations). More than 20 different deletions ranging from approximately 6 kb to more than 300 kb and removing both α-globin genes (and sometimes the embryonic *HBZ* gene) have been reported. The most common are $--^{SEA}$, $--^{FIL}$, $--^{MED}$, which in the homozygous state result in Hb Bart syndrome. When any of these alleles occur in combination with another allele carrying a single α-globin gene deletion (e.g., $-\alpha^{3.7}$), the result is HbH disease.

- **Sequence variants** such as $Hb^{Constant\ Spring}$ (Hb^{CS}), a common missense mutation of the termination codon of *HBA2,* lead to an elongated protein chain and can be detected indirectly by digestion of the amplified gene by *Mse*I restriction endonuclease by ARMS or directly by sequence analysis [Tangvarasittichai et al 2005]. Several of the non-deletion mutations, which downregulate α-globin expression or result in a dysfunctional protein α chain, create or destroy a restriction enzyme site and may be detected by restriction enzyme digestion of the amplified product (i.e., *Nco*I digestion for detection of initiation codon mutation of *HBA2* [*HBA2*:c.2T>C] and *Hph*I digestion for the pentanucleotide *HBA2* IVS-1 deletion [*HBA2*:c.95+2_95+6delTGAGG]).

- **Sequence analysis** can be used to identify point mutations (including rare termination codon mutations and hyperunstable α-globin variants) in the coding regions of *HBA1* and *HBA2* when an α-globin deletion is not identified and suspicion for α-thalassemia is high [Traeger-Synodinos et al 2000].

  Note: A mutation in the HS-40 regulatory region located 40 kb upstream from the α-globin cluster, described in several pedigrees, would not be detected by DNA analysis of the alpha cluster region alone.

- **Deletion/duplication analysis** can be used to detect common, rare, and/or novel deletions and duplications involving *HBA1* and *HBA2*.

Table 3 summarizes molecular genetic testing for this disorder.

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Table 3. Molecular Genetic Testing Used in Alpha-Thalassemia

Gene Name	Test Method	Mutations Detected	Percent of Alleles	Mutation Detection Frequency by Test Method	Test Availability
HBA1 and *HBA2*	Targeted mutation analysis	Deletions [1]	~90% [2]	Variable	Clinical Testing
		HBA2 sequence variants [3]	Variable [4]	Variable [4]	
	Sequence analysis	*HBA1*, *HBA2* sequence variants	~ 9%–10%[3]	Theoretically 100%	
	Deletion/ duplication analysis	Deletions and duplications	Unknown	Variable [4]	

1. May detect both deletions of a single α-globin gene and two α-globin gene deletions (either --/αα or -α/-α) on one chromosome. Deletions detected may vary among laboratories.

2. Varies by population

3. Targeted analysis of known sequence variants by restriction endonuclease digestion or other direct DNA methods

4. Varies by population, testing laboratory, and test method

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

Testing Strategy

The following screening tests can be used if α-thalassemia is suspected:

- Red blood cell indices
- Peripheral blood smear
- Red blood cell supravital stain of peripheral blood
- Qualitative and quantitative hemoglobin analysis

To confirm the diagnosis in a proband. Molecular genetic testing

Carrier testing for at-risk relatives. Molecular genetic testing is requested in the parents of individuals with Hb Bart syndrome and HbH disease.

Prenatal diagnosis is requested in pregnancies at risk for Hb Bart syndrome.

Genetically Related (Allelic) Disorders

Alpha-thalassemia retardation-16 (ATR-16) syndrome, a contiguous gene deletion syndrome, results from a large deletion on the short arm of chromosome 16 from band 16p13.3 to the terminus, which removes the *HBA1* and *HBA2* genes together with other 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 (club foot) 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). While routine cytogenetic studies may be sufficient to identify the deletion, in some instances, cryptic subtelomeric deletions are detected only with subtelomeric FISH studies, MLPA, or array CGH [Harteveld et al 2007, Gibson et al 2008]. 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 mutations 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 cases of ATMDS have been linked to mutations in the *ATRX* gene 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 mental retardation syndrome is NOT an allelic disorder. (See Differential Diagnosis)

Clinical Description

Natural History

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 α-globin chain defect (See Genotype-Phenotype Correlations).

Hb Bart syndrome is the most severe clinical condition related to α-thalassemia. It is usually not compatible with postnatal life. Affected fetuses are either stillborn or die soon after birth. Red cells with Hb Bart have an extremely high oxygen affinity and are incapable of effective tissue oxygen delivery.

The clinical features are severe anemia, marked hepatosplenomegaly, diffuse edema, heart failure, and extramedullary erythropoiesis.

Developmental abnormalities, including hydrocephaly and cardiac and urogenital defects, have been reported.

Maternal complications during pregnancy commonly include: preeclampsia (hypertension, edema, and proteinuria), polyhydramnios (excessive amniotic fluid) or oligohydramnios (reduced amniotic fluid), antepartum hemorrhage, and premature delivery.

HbH disease. The phenotype of HbH disease varies [Chui et al 2003, Origa et al 2007]. Although clinical features usually develop in the first years of life, it may not present until adulthood or may be diagnosed only during routine hematologic analyses in asymptomatic individuals.

The majority of individuals show microcytic hypochromic hemolytic anemia (Table 1), enlargement of the spleen and less commonly the liver, mild jaundice, and sometimes mild-to-moderate thalassemia-like skeletal changes (such as hypertrophy of the maxilla, bossing of the skull, and prominence of the malar eminences) that mainly affect the facial features.

Individuals with HbH disease may develop hypersplenism and gallstones and experience acute episodes of hemolysis in response to oxidant drugs and infections.

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

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Iron overload is uncommon but has been reported in older individuals, usually as a result of repeated blood transfusions or increased iron absorption.

Pregnancy is possible in women with HbH disease; however, worsening of anemia requiring blood transfusion has been reported [Origa et al 2007].

Genotype-Phenotype Correlations

The phenotype of the α-thalassemia syndromes depends on the degree of α-globin chain deficiency relative to β-globin production. The correlation between different α-thalassemia mutations, α-globin mRNA levels, α-globin synthesis, and clinical manifestations of α-thalassemia is well documented. The wide spectrum of hematologic and clinical phenotypes results from the presence and interaction of many α-thalassemia mutations.

The different α-thalassemia mutations vary widely in severity. From most to least severe, they are: non-deletion *HBA2*, -$\alpha^{3.7}$ (because of compensatory increase of the α-globin gene output from the remaining *HBA1* gene), and non-deletion *HBA1*. For the -$\alpha^{4.2}$ deletion, evidence is inconclusive for a compensatory increase in the expression of the remaining α gene. The phenotype may be modified by triplication or quadruplication of the α-globin genes on one chromosome.

Alpha-thalassemia silent carrier results from a deletion or "non-deletion" mutation that inactivates one of the two α-globin genes (i.e., *HBA1* or *HBA2*) on one chromosome (α^{+}-thalassemia).

Non-deletion α^{+}-thalassemia defects include the following:

- Inactivating point mutations, including those important for gene expression (initiation codon mutation [*HBA2*:c.2T>C]); splicing sites (*HBA2*:c.95+2_95+6delTGAGG); termination codon $Hb^{Constant\ Spring}$
- A frameshift caused by a deletion/insertion in the coding regions (i.e., (*HBA2*:c.94_95delAG), *HBA2*:c.[339C>G; 340_351delCTCCCCGCCGAG])
- Rarely, very rapid post-synthetic degradation of a hyper-unstable α-globin variant. Non-deletion forms of α-thalassemia mainly occur in *HBA2*.

Carriers of α^{+} thalassemia may have a completely silent hematologic phenotype or may present with a moderate, thalassemia-like hematologic picture (i.e., reduced MCV and MCH, but normal HbA2 and HbF), similar to carriers of α^{o}-thalassemia (See **Alpha-thalassemia trait**).

Alpha-thalassemia trait results from deletion or inactivation of two α-globin genes (--/αα in cis configuration or -α/-α in trans configuration). Carriers of α^{o}-thalassemia show microcytosis (low MCV), hypochromia (low MCH), normal percentages of HbA2 and HbF, and RBC inclusion bodies.

Note: While the phenotype between cis configuration and trans configuration may not vary significantly, the genetic counseling implications are significant. See Genetic Counseling.

HbH disease results from deletion or inactivation of three α-globin genes, usually as a result of the compound heterozygous state for α^{o}-thalassemia and α^{+}-thalassemia. The phenotype of HbH disease (chronic microcytic, hypochromic hemolytic anemia of variable severity) mainly correlates with the severity of the α^{+}-thalassemia defect:

- Individuals with non-deletion HbH disease have a more severe phenotype with earlier presentation, more severe anemia, jaundice, bone changes, and greater hepatosplenomegaly. As a consequence of the more severe hematologic phenotype,

they may need red cell transfusions more frequently than individuals with deletion HbH.

- Individuals who are homozygous for non-deletion α-thalassemia defect (i.e., 2 of 4 α genes affected, but both with non-deletion mutations) may have HbH disease. For example, homozygotes for $Hb^{Constant\ Spring}$ show a mild hemolytic anemia. Red blood cell indices are characterized by low red blood cell count, normal MCV, and slightly decreased MCV. Hb electrophoresis shows HbA - HbA2, $Hb^{Constant\ Spring}$ (2.6%-11.6%), and Hb Bart.

Deletions of the HS-40 regulatory region found approximately 40 kb telomeric to the *HBZ* gene (Figure 1) cause α°-thalassemia and have been reported in a few families with HbH disease [Higgs 2001]. The phenotype is like that of the deletion type of HbH disease.

Hb Bart syndrome results from deletion of four α-globin chains and rarely may involve non-deletion defects.

Nomenclature

The α-thalassemias are classified on the basis of the total globin production from each of the two α-globin genes present on each chromosome 16:

- When both α-genes on a chromosome are deleted (--/αα) or inactivated, the condition is called α°-thalassemia (no output of α-globin from the chromosome). Previously, α ° thalassemia was called α-thalassemia 1.
- When one α-gene on a chromosome is deleted or inactivated by a mutation (i.e., non-deletion mutation) the condition is called α^+ thalassemia (previously known as α-thalassemia 2). In this case, some α globin is produced. Non-deletion mutants are indicated as ($\alpha^{ND}\alpha$/) or ($\alpha^T\alpha$/).

Prevalence

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

More precise data have been obtained using restriction endonuclease analysis. For detailed references for the frequency of α-thalassemia in each population, see Bernini [2001].

Africa

- The highest gene frequency (0.30-0.40) of the $-\alpha^{3.7}$allele (causing α^+-thalassemia) has been observed in the equatorial belt including Nigeria, Ivory Coast, and Kenya.
- Alpha°-thalassemia has been reported very rarely in North Africa and in the African-American population.

The Mediterranean

- $Alpha^+$-thalassemia (caused by the $-\alpha^{3.7}$allele) is common, with the highest frequency reported in Sardinia (0.18) and the lowest in Spain.
- Alpha°-thalassemia is very rare (0.002); thus, Hb Bart hydrops fetalis is only rarely reported.
- A remarkable aspect of α-thalassemia (mainly α^+) in the Mediterranean population is the heterogeneity of mutations, particularly the non-deletion mutations.

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The Arabian Peninsula

- Gene frequencies of the $-\alpha^{3.7}$ allele (causing α^{+}-thalassemia) vary from 0.01 to 0.67, with the highest values being observed in Oman.
- Alpha^{o}-thalassemia determinants are extremely rare.

India

- Deletion α^{+}-thalassemia reaches very high 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 the deletion α^{+}-thalassemia.
- Alpha^{o}-thalassemia is very rare.

Southeast Asia

- Alpha^{o}-thalassemia ($--^{SEA}$, $--^{THAI}$, $--^{FIL}$) and α^{+}-thalassemia are very common, causing a major public health burden.
- The non-deletion form of α^{+}-thalassemia, caused by the $Hb^{Constant\ Spring}$ allele, is common.
- The incidence of Hb Bart hydrops fetalis is expected to be between 0.5 and five per 1000 births and HbH disease between four and 20 per 1000 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.
- The specific mutations causing α-thalassemia have not been identified in all areas; for example, some affected individuals on the island of Vanuatu have normal α-globin genes without deletions or mutations. Mutations in a regulatory element are suspected.
- Alpha^{o}-thalassemia is very rare.

Differential Diagnosis

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

Hydrops fetalis is associated with many conditions in addition to Hb Bart, including immune-related disorders (alloimmune hemolytic disease or Rh isoimmunization), fetal cardiac anomalies, chromosomal 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 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 vital stain; and (4) absence of morphologic or enzymatic changes characteristic of other forms of inherited hemolytic anemia (e.g., hereditary spherocytosis/elliptocytosis, G6PD deficiency).

- **Alpha-thalassemia X-linked mental retardation (ATRX) syndrome** is a rare form of α-thalassemia characterized by distinctive craniofacial features, genital anomalies, and severe developmental delays with hypotonia and mental retardation [Gibbons 2006]. Affected individuals usually have a normal 46,XY karyotype. Genital anomalies, observed in 80% of children, range from hypospadias, micropenis, and undescended testicles to ambiguous genitalia. Global developmental delays are evident in infancy, and some affected individuals never walk independently or develop significant speech. Affected individuals do not reproduce. Inheritance is X-linked.

  An unknown percent of affected 46,XY individuals have a mild form of HbH disease, evident as hemoglobin H inclusions (β_4 tetramers) in erythrocytes following incubation of fresh blood smears with 1% brilliant cresyl blue (BCB).

  Mutations in the *ATRX* gene are causative. The ATR-X protein is a novel member of the SWI2/ SNF2 family of molecular motors that remodel chromatin using hydrolysis of ATP as a source of energy. The chromatin remodeling alters the access of DNA to trans-acting factors, thereby influencing transcription, replication, repair, and methylation and thus regulating the expression of a restricted class of genes including the α-globin genes [Picketts et al 1998, Higgs 2004].

  Note: In ATRX syndrome, the α-globin gene cluster and the HS-40 regulatory region of chromosome 16 are structurally intact.

- Acquired mutations 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^o-thalassemia and α^+-thalassemia)

- **Beta-thalassemia**. Whereas microcytosis and hypochromia are present in α^o-thalassemia carriers, hematologically manifesting α^+-thalassemia carriers, and β-thalassemia carriers, β-thalassemia carriers are distinguished by a high percent of HbA2.

- Iron deficiency anemia

  - The α^o-thalassemia carrier state and the hematologically evident forms of α^+-thalassemia can be confused with iron-deficiency anemia because MCV and MCH 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^o-thalassemia carriers.

  - Though there is some overlap, individuals with iron deficiency anemia show a marked increase in red blood cell distribution width (RDW), a quantitative measure of RBC anisocytosis. The RDW is usually normal or close to normal in thalassemia.

  - The determination of the RBC zinc protoporphyrin concentration and iron studies (serum iron concentration, transferrin saturation) can be used to diagnose iron deficiency anemia with certainty.

  - Iron deficiency and thalassemia can coexist, complicating diagnosis.

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Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with alpha-thalassemia (α-thalassemia), the following phenotype-based evaluations are recommended:

- **Hemoglobin Bart hydrops fetalis (Hb Bart) syndrome.** See Prenatal 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* is important at presentation because of varying severity.

Treatment of Manifestations

Hb Bart syndrome currently has no effective treatment.

HbH disease

- Most individuals with HbH disease are clinically well and survive without any treatment.
- Occasional red blood cell transfusions may be needed if the hemoglobin level suddenly drops because of hemolytic or aplastic crises.
- Chronic red blood cell transfusions should be considered in selected individuals only. 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.)
- Splenectomy should be performed only in case of massive splenomegaly or hypersplenism; but the risk of severe, life-threatening 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 hydrops fetalis syndrome

- Early treatment with intrauterine transfusions or in utero hematopoietic stem cell transplantation has been unsuccessful and also may be not be justified in view of the unknown future risks for normal development. In fact, these neonates have marked cardiopulmonary problems and a high frequency of congenital malformations (patent ductus arteriosus, limb and genital abnormalities) in addition to the hematopoietic failure. In those infants surviving the immediate post-natal period, subsequent development has been abnormal. All these infants obviously require regular blood transfusions and iron chelation therapy. Given these results, further human experimentation should be discouraged until more effective therapies (e.g., somatic gene therapy) are available.
- Because of the severity of Hb Bart hydrops fetalis syndrome and the risk of maternal complications during the pregnancy with a fetus with this disorder, prenatal diagnosis and early termination of at-risk pregnancies are usually recommended.

Prevention of Secondary Complications

HbH disease

- During febrile episodes, a clinical evaluation is recommended because of the increased risk of hemolytic crisis (similar to G6PD deficiency, hemolysis in HbH disease can be triggered by infection or oxidative stresses).
- When chronic blood 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).
- Some clinicians recommend folic acid supplementation, as for other hemolytic anemias.
- If splenectomy is required, antimicrobial prophylaxis is usually provided, at least until age five years, to decrease the risk of overwhelming sepsis caused by encapsulated organisms. Despite the use of antimicrobial prophylaxis, a careful clinical evaluation of splenectomized individuals with fever is recommended.

Surveillance

HbH disease

- Hematologic evaluation every six to 12 months to determine the steady state levels of hemoglobin
- 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

Agents/Circumstances to Avoid

HbH disease

- Inappropriate iron therapy
- Oxidant drugs including sulphonamides; some antimalarials, because of the risk of hemolytic crisis

Testing of Relatives at Risk

The sibs of a proband should be tested as soon as possible after birth to determine if they have HbH disease so that appropriate monitoring can be instituted.

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

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: Therapy studies for this disorder may not currently be ongoing.

Other

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

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

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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 hydrops fetalis are obligate heterozygotes for two α-globin gene deletions (α^{o}-thalassemia or α-thalassemia trait).
- Individuals with α-thalassemia trait typically have mild hypochromia (low MCH) microcytosis (low MCV) anemia and normal HbA2 and HbF.

Sibs of a proband

- At conception, each sib of a proband with Hb Bart hydrops fetalis has a 25% chance of having Hb Bart hydrops fetalis syndrome, a 50% chance of having α^{o}-thalassemia (α-thalassemia trait), and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her having α^{o}-thalassemia (α-thalassemia trait) is 2/3.

Offspring of a proband. The Hb Bart hydrops fetalis syndrome is usually not compatible with postnatal life.

Other family members of a proband. Each sib of the proband's parents is at 50% risk of being a carrier of two α-globin gene deletions (α^{o}-thalassemia or α-thalassemia trait).

Individuals with α-thalassemia trait typically have mild hypochromia (low MCH), microcytosis (low MCV), anemia, and normal HbA2 and HbF.

Risk to Family Members — Hemoglobin H (HbH) Disease

Parents of a proband

- The parents of a child with HbH disease usually have different types of α^{o}-thalassemia (α-thalassemia trait) and α^{+}-thalassemia (α-thalassemia silent carrier) mutations:
  - Most commonly, one parent has α^{o}-thalassemia and the other parent has α^{+}-thalassemia. Rarely, one parent has α^{o}-thalassemia and the other parent has α^{+}-thalassemia resulting from a non-deletion mutation.
  - Uncommonly, both parents carry a specific *HBA2* non-deletion α-thalassemia mutation (α^{T}Saudi, -$\alpha^{IN:\,2\,bp\,del}$) or an initiation codon mutation (*HBA2*:c.2T>C).

- Individuals with α^o-thalassemia typically have mild microcytosis and normal HbA2 and HbF.
- Individuals with α^+-thalassemia are either hematologically normal or have a mild reduction of MCV and MCH.

Sibs of a proband

- At conception, each sib of an individual with HbH disease has a 25% chance of having HbH disease, a 25% chance of having α^o-thalassemia (α-thalassemia trait), a 25% chance of having α^+-thalassemia (α-thalassemia silent carrier), and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her having either α^o-thalassemia or α^+-thalassemia is 2/3.

Offspring of a proband

- Each child of an individual with HbH disease inherits the mutation for either α^o-thalassemia (α-thalassemia trait) or α^+-thalassemia (α-thalassemia silent carrier) and is thus an obligate heterozygote.
- Given the high carrier rate of α^o-thalassemia in certain populations, it is appropriate to offer carrier testing to the reproductive partner of an individual with α^o-thalassemia.

Other family members of a proband with either Hb Bart hydrops fetalis or HbH disease. Each sib of the proband's parents is at risk of having α^+-thalassemia (α-thalassemia silent carrier) and/or α^o-thalassemia (α-thalassemia trait), depending on the genetic status of the relative.

Carrier Detection

Individuals who should be considered for carrier testing:

- Family members
- Members of ethnic groups at risk (see Prevalence)
- Gamete donors for assisted reproductive technologies (ART)

Alpha^o-thalassemia carriers (α-thalassemia trait carriers) have a moderate, thalassemia-like hematologic picture. Red blood cell indices show microcytosis (low MCV) and a reduced content of Hb per red cell (low MCH); blood film prepared following incubation of red cells with vital stain displays inclusion bodies in 1:1000 to 1:10,000 red blood cells. Quantitative Hb analysis shows normal percentage of HbA2 and HbF. Identification relies on molecular genetic testing of the α-globin genes, *HBA1* and *HBA2* (See Table 1 and Table 2). After brilliant cresyl blue (BCB) incubation, rare red blood cell inclusion bodies can be detected in α^o-thalassemia carriers.

Alpha$^+$-thalassemia carriers (α-thalassemia silent carriers) may have normal hematologic findings or may have a moderate, thalassemia-like hematologic picture similar to that of a carrier of α^o-thalassemia. Identification relies on molecular genetic testing of the α-globin genes, *HBA1* and *HBA2*.

Population Screening

Alpha^o-thalassemia. Because of the high carrier rate for α^o-thalassemia in certain populations and the availability of genetic counseling and prenatal diagnosis, it is ideal to screen couples who are members of at-risk populations for α^o-thalassemia carrier status to identify those at risk of conceiving a fetus with Hb Bart hydrops fetalis syndrome prior to or in early pregnancy:

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- If both members of a couple are carriers of an α°-thalassemia deletion mutation (e.g., genotype αα/--^{SEA}), each of their offspring has a 1/4 risk of having Hb Bart hydrops fetalis syndrome.
- If both members of the couple are carriers of the α°-thalassemia deletion mutation in which both *HBA1* and *HBA2* genes along with the *HBZ* are deleted (i.e., genotype αα/--^{FIL} or genotype of αα/--^{THAI}), they are not at risk of having offspring with Hb Bart hydrops fetalis syndrome, because homozygotes for such mutations are lost shortly after conception.
- If both members of the couple are carriers of a deletion involving both the *HBA1* and *HBA2* genes, but only one of them has a deletion that extends into the *HBZ* gene (e.g., a couple with genotypes αα/--^{SEA} and αα/--^{FIL}), the couple is at risk of having offspring with Hb Bart hydrops fetalis syndrome because the single *HBZ* gene in the fetus produces sufficient ζ-globin for fetal development [Chui & Waye 1998].

Alpha^{+}-thalassemia. Prospective identification of carriers of α^{+}-thalassemia is not strongly indicated, as the offspring of these carriers are not at risk for Hb Bart hydrops fetalis syndrome.

Related Genetic Counseling Issues

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

Prenatal Testing

High-risk pregnancies. Prenatal testing is available for couples confirmed by DNA analysis to be at risk of having a fetus with Hb Bart hydrops fetalis syndrome because both parents are carriers of deletion α°-thalassemia. Molecular genetic testing can be performed either on fetal DNA extracted from cells obtained by chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation or by amniocentesis usually performed at about 15 to 18 weeks' gestation.

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

Ultrasound examination. Ultrasonography can also be useful in the management of pregnancies at risk for Hb Bart hydrops fetalis 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 in which:

- One parent is an α°-thalassemia carrier and the other has an α-thalassemia-like hematologic picture but no α°-thalassemia mutation identified by molecular genetic testing.
- The mother is a known α°-thalassemia carrier 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.

In both cases, the options for prenatal testing should be discussed in the context of formal genetic counseling. In such cases, the strategy is fetal DNA analysis for the known α°-thalassemia mutation; if the known α°-thalassemia mutation is present, globin chain synthesis analysis is performed using a fetal blood sample obtained by percutaneous umbilical blood sampling (PUBS) at about 18 to 21 weeks' gestation.

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

Molecular Genetics

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

Table A. Molecular Genetics of Alpha-Thalassemia

Gene Symbol	Chromosomal Locus	Protein Name
HBA1	16pter-p13.3	Hemoglobin subunit alpha
HBA2	16pter-p13.3	Hemoglobin subunit alpha
HBZ	16pter-p13.3	Hemoglobin subunit zeta

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

Table B. OMIM Entries for Alpha-Thalassemia

141800	HEMOGLOBIN--ALPHA LOCUS 1; HBA1
141850	HEMOGLOBIN--ALPHA LOCUS 2; HBA2
142310	HEMOGLOBIN--ZETA LOCUS; HBZ
604131	THALASSEMIAS

Table C. Genomic Databases for Alpha-Thalassemia

Gene Symbol	Locus Specific	Entrez Gene	HGMD
HBA1	HBA1	3039 (MIM No. 141800)	HBA1
HBA2	HBA2	3040 (MIM No. 141850)	HBA2
HBZ		3050 (MIM No. 142310)	

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

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

HBA1*, *HBA2*, and *HBZ

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Alpha-globin genes are duplicated (*HBA1* and *HBA2*) and lie in the telomeric region of chromosome 16 (16p13.3) within a cluster that also contains an embryonic α-like gene (*HBZ*) and three pseudogenes (*HBZP* (ψ-ζ), *HBAP1* (ψ-α_1), *HBM* (ψ-α_2). A θ gene (*HBQ1*) with an unknown function is located at the 5' end of the cluster (See Figure 1).

HBA1 and *HBA2* are embedded within two markedly homologous regions that extend for approximately 4 kb. Their sequence homology is maintained by gene conversion and unequal crossover events. In this DNA region, three highly homologous segments, named X, Y, and Z, separated by non-homologous segments, have been defined (Figure 1).

As a result of unequal genetic exchange, individuals who are phenotypically normal may have four, five, or six α-globin genes and two to six *HBZ*-like genes. *HBA*-like globin genes are arranged in the cluster in the order in which they are expressed during development. The genes encoding the α_1-globin chain *(HBA1*) and the α_2-globin chain *(HBA2*) display a marked homology resulting from repeated rounds of gene conversion.

The level of transcription of the two genes differs, as *HBA2* produces two to three times more α-globin than *HBA1*. Regarding the translation profile of *HBA1* mRNA and *HBA2* mRNA, contrasting results in which percentages of *HBA2* mRNA are higher or only slightly higher than percentages of *HBA1* mRNA have been reported. The different expression of the two α-globin genes has important clinical implications for the amount of structural α-variant resulting from mutation of *HBA1* or *HBA2*, and for the pathophysiology of the deletion and non-deletion pathologic variants of the *HBA1* and *HBA2* genes.

The expression of *HBA1* and *HBA2* genes is regulated by a region (HS-40) located 40 kb upstream from the α-globin cluster (Figure 1). This region contains multiple binding sites for transcriptional factors (NF-E2, GATA-1). The deletion of HS-40 results in an α-thalassemia phenotype, in spite of the structural integrity of both α-globin genes.

Normal allelic variants. Both *HBA1* and *HBA2* genes have three coding exons. The mRNAs produced by the *HBA1* and *HBA2* genes have identical coding regions and can be distinguished only by their 3' UTR.

Pathologic allelic variants. See Table 4. Deletion of one or both *HBA1* and *HBA2* genes is the most common cause of α-thalassemia:

- **Alpha$^+$-thalassemia.** Reciprocal recombination between the Z boxes, which are 3.7 kb apart, or between the X boxes, 4.2 kb apart, gives rise to chromosomes with a single α-globin gene. The two resulting α-thalassemia mutations are referred to respectively as the 3.7-kb rightward deletion ($-\alpha^{3.7}$) and the 4.2-kb leftward deletion ($-\alpha^{4.2}$) (Figure 1):
  - In relation to the location of the crossover within the Z box, the $-\alpha^{3.7}$ deletion is subdivided into three varieties named I, II, and III.
  - In addition to the $-\alpha^{3.7}$ and the $-\alpha^{4.2}$ common alleles, other rare deletions involving a single α-globin gene have been reported.
  - These recombinational events also result in the production of chromosomes containing three α-globin genes. A triplicated α-globin gene inherited with heterozygous β-thalassemia results in a mild thalassemia intermedia phenotype.
- **Alpha^o-thalassemia.** Extended deletions varying from 100 kb to more than 250 kb and removing both α-globin genes *(HBA1* and *HBA2*) (and sometimes the embryonic *HBZ* gene) result in the complete absence of α-chain production from that allele. Most

such deletions are founder mutations that arose by one of several molecular mechanisms, including illegitimate recombination, reciprocal translocation, and truncation of chromosome 16. More than 20 different α°-thalassemia deletions have been reported to date:

- The most common alleles are the Southeast Asian ($--^{SEA}$) and the Filipino ($--^{FIL}$) types.
- Two deletion alleles, $-\alpha^{5.2}$ and $-\alpha^{20.5}$, which remove *HBA2* and part of *HBA1*, produce α°-thalassemia [Higgs 2001].
- A deletion removing *HBA1* and the theta gene (*HBQ1*) and extending downstream centromeric from the α-globin gene cluster results in α°-thalassemia. The silencing of intact *HBA2* in this chromosome is related to an antisense RNA transcribed from the widely expressed *LUC7L* gene, becoming juxtaposed to the normal *HBA2* by the deletion, and running through the *HBA2* sequences [Tufarelli et al 2003].
- Nine deletions of the HS-40 region also result in the silencing of the intact α-globin genes, thereby producing α°-thalassemia [Higgs 2001].

Non-deletion α-thalassemia. Less frequently, α-thalassemia results from single point mutations or oligonucleotide insertion/deletion in regions critical for α-globin gene expression. In non-deletion α-thalassemia, the affected gene is denoted T (e.g., α^{T}Saudi). Considered as a group, the non-deletion α-thalassemia mutations appear to have a more severe effect on α-globin gene expression and hematologic phenotype than single α-globin gene deletions. This phenomenon may be explained by the majority of the mutations affecting *HBA2*, whose expression may predominate over *HBA1* [Higgs 2001]. No compensatory increase in expression in the remaining functional α gene occurs when the other is inactivated by a point mutation, in contrast to the compensatory increase in expression in the remaining functional α gene when a single α-globin gene is deleted (e.g., the $-\alpha^{3.7}$ deletion).

At present, more than 45 well-defined causes of non-deletion α-thalassemia are known.

The molecular mechanisms leading to the silencing of either *HBA1* or *HBA2* include: mutations involving RNA splicing, the poly (A) additional signal, the initiation of mRNA translation, as well as missense mutation of the termination, in-frame deletions, frame-shift mutations, and nonsense mutations. Mutations of α-globin genes that result in the production of hyper-unstable globin variants such as $Hb^{Quong\ Sze}$ and that are unable to assemble into stable β_4 tetramers and are thus rapidly degraded, may also result in α-thalassemia (Table 1) [Higgs 2001].

The most common non-deletion mutation, which is frequently seen in Southeast Asia, is $Hb^{Constant\ Spring}$ ($Hb^{CS)}$, resulting from a mutation of the stop codon of *HBA2*. This mutation leads to the production of an α-globin chain elongated by 31 amino acids. Hb^{CS} is produced in very small amounts because its mRNA is unstable. Heterozygotes for Hb^{CS} and other rare elongated variants, along with the presence of the Hb variant, produce the α°-thalassemia phenotype.

Some of the mutations causing α-chain structural variants may occur in a chromosome with only one α-globin gene (e.g., $HbQ^{Thailand}$, $HbG^{Philadelphia}$). (For more information, see Genomic Databases table.)

Table 4. *HBA1* and *HBA2* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change [1] (Standard Nomenclature [2])	Protein Amino-Acid Change [1] or Functional Globin Genes Deleted [3] (Standard Nomenclature [2])	Reference Sequence
(*HBA2*:c.2T>C)	Alpha2 initiation codon Met>Thr; $-\alpha^{NcoI}$ of *HBA2* (*HBA2*:p.Met1Thr)	NM_000517.4 NP_000508.1
(*HBA2*:c.377T>C)	Alpha2 Leu125Pro, $Hb^{Quong\ Sze}$ (*HBA2*:p.Leu126Pro)	
(*HBA2*:c.427T>C)	Alpha2 142, Stop>Gln $Hb^{Constant\ Spring}$ (Hb^{CS}) (*HBA2*:p.X143Glnext32)	
Codon 30/31 2-bp deletion (*HBA2*:c.94_95delAG)	The deletion of 2 nucleotides causes a frameshift & premature termination at codon(TAA) (*HBA2*:p.Arg32AspfsX24)	
HBA2:c.[339C>G ; 340_351delCTCCCCGCCGAG]	Alpha2 His112Gln *and* deletion of codons 113-116 - Leu-Pro-Ala-Glu, Hb Lleida (*HBA2*:p.His113Gln; p.Leu114_ Glu117del)	NM_000517.4 NP_000508.1
Splicing sites $-\alpha^{HphI}$ α, *Hph*I digestion for the pentanucleotide *HBA2* IVS-1 deletion (*HBA2*:c.95+2_95+6delTGAGG)	--	
HBA1:c.223G>C	Asp74Gly, $Hb^{Q\text{-}Thailand}$ (*HBA1*:p.Asp75Gly)	NM_000558.3 NP_000549.1
HBA2:c.[207C>G (or *HBA1*) or 207C>A]	Asn68Lys, $Hb^{G\ Philadelphia}$ (*HBA2* or *HBA1* p:Asn69Lys)	NM_000517.4 NP_000508.1
PolyA addition site of the *HBA2* gene (AATAAA >AATAAG) (*HBA2*:c.*+94A>G)	Alpha2 α^{T}Saudi	
-α IN: 2 bp del (c.[-2_-3delAC; $-\alpha^{3.7}$][4])	Deletion of *HBA2* and of nucleotides that additionally impair translation	
$-\alpha^{3.7}$	Deletion of *HBA2*	Z84721.1
$-\alpha^{4.2}$	Deletion of *HBA2*	
$-\alpha^{5.2}$	Deletion of *HBA2* and 5' end of *HBA1* [5]	
$-\alpha^{20.5}$ (g.15164_37864del22701)	Deletion of *HBA2* and 5' end of *HBA1*	
$--^{FIL}$ (g.11684_43534del31851)	Deletion of *HBA2* and *HBA1*	
$--^{MED}$ (g.24664_41064del16401)	Deletion of *HBA2* and *HBA1*	
$--^{SEA}$ (g.26264_45564del19301)	Deletion of *HBA2* and *HBA1*	
$--^{THAI}$ (g.10664_44164del33501)	Deletion of *HBA2* and *HBA1*	

See Quick Reference for an explanation of nomenclature.

1. Globin mutations are given by their conventional nomenclature (http://globin.cse.psu.edu/)

2. Standard naming conventions of the Human Genome Variation Society (http://www.hgvs.org), as listed by the Globin Gene Server (http://globin.cse.psu.edu/)

4. Denotes two variations in one allele: deletion of AC at -2 and -3 before ATG initiation codon in cis configuration on an -α3.7 deletion allele [Viprakasit et al 2003]

5. Pressley et al [1980]

3. Only functional globin genes involved in the deletion are given; deleted pseudogenes are not listed.

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Normal gene product: The α-globin chains produced by *HBA1* and *HBA2* mRNAs have identical amino acid sequences. The heterodimer protein hemoglobin A is made up of two α chains and two β chains.

Abnormal gene product: The consequence of a single α-globin gene deletion is reduced production of α-globin chains by the affected chromosome (α^{+}-thalassemia). Measurement of α-globin mRNA indicates that the -$\alpha^{4.2}$ mutation is not associated with a compensatory increase in expression in the remaining *HBA1* gene, whereas with the -$\alpha^{3.7}$ mutation, the remaining *HBA1* gene expression is roughly halfway between that of the normal *HBA2* and *HBA1* genes (Figure 1)

Resources

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

Cooley's Anemia Foundation
330 Seventh Avenue Suite 900
New York NY 10001
Phone: 800-522-7222
Fax: 212-279-5999
Email: info@cooleysanemia.org
Alpha Thalassemia

NCBI Genes and Disease
Thalassemia

References

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

Published Statements and Policies Regarding Genetic Testing

Clinical Management Guidelines for Obstetrician-Gynecologists Number 78. *Obstet Gynecol* 2007;109:227–37.

Literature Cited

Bernini LF (2001) Geographic distribution of alpha thalassemia. In: Steinberg MH, Forget PG, Higgs DR, Nagel RL (eds) Disorders of Hemoglobin: Genetics, Pathophysiology, and Clinical Management. Cambridge University Press, Cambridge, UK. pp 878-94

Chong SS, Boehm CD, Higgs DR, Cutting GR. Single-tube multiplex-PCR screen for common deletional determinants of alpha-thalassemia. *Blood* 2000;95:360–2. [PubMed: 10607725]

Chui DH, Waye JS. Hydrops fetalis caused by alpha-thalassemia: an emerging health care problem. *Blood* 1998;91:2213–22. [PubMed: 9516118]

Chui DH, Fucharoen S, Chan V. Hemoglobin H disease: not necessarily a benign disorder. *Blood* 2003;101:791–800. [PubMed: 12393486]

Galanello R, Aru B, Dessi C, Addis M, Paglietti E, Melis MA, Cocco S, Massa P, Giagu N, Barella S. HbH disease in Sardinia: molecular, hematological and clinical aspects. *Acta Haematol* 1992;88:1–6. [PubMed: 1414154]

GeneReviews GeneReviews GeneReviews GeneReviews

Galanello R, Sollaino C, Paglietti E, Barella S, Perra C, Doneddu I, Pirroni MG, Maccioni L, Cao A. Alpha-thalassemia carrier identification by DNA analysis in the screening for thalassemia. *Am J Hematol* 1998;59:273–8. [PubMed: 9840907]

Gibbons R (2006) Alpha thalassaemia-mental retardation, X linked. *Orphanet J Rare Dis* 4:1:15

Gibbons RJ, Pellagatti A, Garrick D, Wood WG, Malik N, Ayyub H, Langford C, Boultwood J, Wainscoat JS, Higgs DR. Identification of acquired somatic mutations in the gene encoding chromatin-remodeling factor ATRX in the alpha-thalassemia myelodysplasia syndrome (ATMDS). *Nat Genet* 2003;34:446–9. [PubMed: 12858175]

Gibson WT, Harvard C, Qiao Y, Somerville MJ, Lewis ME, Rajcan-Separovic E. Phenotype-genotype characterization of alpha-thalassemia mental retardation syndrome due to isolated monosomy of 16p13.3. *Am J Med Genet A* 2008;146:225–32.

Harteveld CL, Kriek M, Bijlsma EK, Erjavec Z, Balak D, Phylipsen M, Voskamp A, Capua E, White SJ, Giordano PC. Refinement of the genetic cause of ATR-16. *Hum Genet* 2007;122:283–92. [PubMed: 17598130]

Harteveld CL, Voskamp A, Phylipsen M, Akkermans N, den Dunned JT, White SJ, Giordano PC. Nine unknown rearrangements in 16p13.3 and 11p15.4 causing alpha-and beta-thalassemias characterized by high resolution multiplex ligation-dependent probe amplification. *J Med Genet* 2005;42:922–31. [PubMed: 15894596]

Higgs DR (2001) Molecular mechanisms of alpha thalassemia. In: Steinberg MH, Forget PG, Higgs DR, Nagel RL (eds) Disorders of Hemoglobin: Genetics, Pathophysiology, and Clinical Management. Cambridge University Press, Cambridge, UK. pp 405-30

Higgs DR. Gene regulation in hematopoiesis: new lessons from thalassemia. *Hematology Am Soc Hematol Educ Program* 2004;2004:1–13.

Higgs DR, Bowden DK (2001) Clinical and laboratory features of the alpha-thalassemia syndromes. In: Steinberg MH, Forget PG, Higgs DR, Nagel RL (eds) Disorders of Hemoglobin: Genetics, Pathophysiology, and Clinical Management. Cambridge University Press, Cambridge, UK. pp 431-69

Lindor NM, Valdes MG, Wick M, Thibodeau SN, Jalal S. De novo 16p deletion: ATR-16 syndrome. *Am J Med Genet* 1997;72:451–4. [PubMed: 9375730]

Lorey F, Charoenkwan P, Witkowska HE, Lafferty J, Patterson M, Eng B, Waye JS, Finklestein JZ, Chui DH. Hb H hydrops foetalis syndrome: a case report and review of literature. *Br J Haematol* 2001;115:72–8. [PubMed: 11722414]

Old JM (2001) DNA-based diagnosis of the hemoglobin disorders. In: Steinberg MH, Forget PG, Higgs DR, Nagel RL (eds) Disorders of Hemoglobin: Genetics, Pathophysiology, and Clinical Management. Cambridge University Press, Cambridge, UK. pp 941-57

Origa R, Sollaino MC, Giagu N, Barella S, Campus S. Clinical and molecular analysis of haemoglobin H disease in Sardinia: hematological, obstetric and cardiac aspects in patients with different genotypes. *Br J Haematol* 2007;136:326–32. [PubMed: 17129226]

Picketts DJ, Tastan AO, Higgs DR, Gibbons RJ. Comparison of the human and murine ATRX gene identifies highly conserved, functionally important domains. *Mamm Genome* 1998;9:400–3. [PubMed: 9545503]

Pressley L, Higgs DR, Aldridge B, Metaxatou-Mavromati A, Clegg JB, Weatherall DJ. Characterisation of a new alpha thalassemia 1 defect due to a partial deletion of the alpha globin gene complex. *Nucleic Acids Res* 1980;8:4889–98. [PubMed: 6255436]

Steensma DP, Gibbons RJ, Higgs DR. Acquired alpha-thalassemia in association with myelodysplastic syndrome and other hematologic malignancies. *Blood* 2005;105:443–52. [PubMed: 15358626]

Steensma DP, Higgs DR, Fisher CA, Gibbons RJ. Acquired somatic ATRX mutations in myelodysplastic syndrome associated with alpha thalassemia (ATMDS) convey a more severe hematologic phenotype than germline ATRX mutations. *Blood* 2004a;103:2019–26. [PubMed: 14592816]

Steensma DP, Viprakasit V, Hendrick A, Goff DK, Leach J, Gibbons RJ, Higgs DR. Deletion of the alpha-globin gene cluster as a cause of acquired alpha-thalassemia in myelodysplastic syndrome. *Blood* 2004b;103:1518–20. [PubMed: 14576055]

Tangvarasittichai O, Jeenapongsa R, Sitthiworanan C, Sanguansermsri T. Laboratory investigation of Hb Constant Spring. *Clin Lab Haem* 2005;27:47–9.

GeneReviews GeneReviews GeneReviews GeneReviews

Traeger-Synodinos J, Papassotiriou I, Metaxotou-Mavrommati A, Vrettou C, Stamoulakatou A, Kanavakis E. Distinct phenotypic expression associated with a new hyperunstable alpha globin variant (Hb Heraklion, alpha1cd37 (C2)Pro>0): comparison to other alpha-thalassemic hemoglobinopathies. *Blood Cell Mol Dis* 2000;26:276–84.

Tufarelli C, Stanley JA, Garrick D, Sharpe JA, Ayyub H, Wood WG, Higgs DR. Transcription of antisense RNA leading to gene silencing and methylation as a novel cause of human genetic disease. *Nat Genet* 2003;34:157–65. [PubMed: 12730694]

Vaeusorn O, Fucharoen S, Ruangpiroj T et al (1985) Fetal pathology and maternal morbidity in hemoglobin Bart's hydrops fetalis: An analysis of 65 cases. Abstract presented at the first International Conference on Thalassemia, Bangkok

Viprakasit V, Ayyub H, May A. Dinucleotide deletion in -alpha3.7 allele causes a severe form of alpha + thalassemia. *European Journal of Haematology* 2003;71:133–6. [PubMed: 12890155]

Chapter Notes

Revision History

- 14 July 2008 (me) Comprehensive update posted live
- 1 November 2005 (me) Review posted to live Web site
- 3 January 2005 (rg) Original submission

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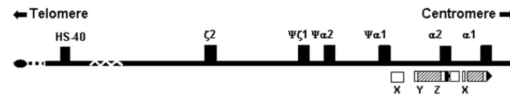

Figure 1. Diagram of the α-globin gene cluster. In order from centromere to telomere, the genes include: α1 (HBA1, encoding α1-globin); α2 (HBA2, encoding α2-globin); the pseudogenes ψα1, ψα2, and ψζ1, which are not expressed; and ζ2 (HBZ, encoding ζ2-globin). HS-40 is a cis-acting regulatory element located 40 kb upstream of the HBZ gene. X, Y, and Z are homologous regions separated by non-homologous DNA regions; they constitute evolutionary duplication units. During meiosis, misalignment of chromosome homologs followed by reciprocal recombination at X, Y, or Z results in deletion-duplication events, i.e., the loss of a single α-globin gene on one chromosome and the triplication of α-globin genes on the other chromosome.

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