Hemoglobin--Alpha Locus 2

Alternative Names
HBA2
5-Prime Alpha-Globin Gene
Alpha-Globin Locus, Second
Major Alpha-Globin Locus

Record Category
Gene locus

WHO-ICD
N.B.: Classification not applicable to gene loci.

Incidence per 100,000 Live Births
N/A to gene loci

OMIM Number
141850

Mode of Inheritance
Autosomal dominant

Gene Map Locus
16pter-p13.3

Description
Thalassemia is an inherited disease of faulty synthesis of hemoglobin. The name is derived from the Greek word "thalassa" meaning "the sea" because the condition was first described in populations living near the Mediterranean Sea.

Alpha-thalassemias are characterized by decreased hemoglobin alpha chain synthesis; alpha-zero-thalassemia being the condition where no normal alpha globin is produced, and alpha-plus-thalassemia being the condition where there is reduced globin production. There are two alpha globin genes per haploid genome, and alpha-thalassemia abnormalities can result from one to four gene deletions. A single alpha gene mutation leads to the silent carrier state (alpha-plus). The two gene mutation is a minor clinical condition, with mild hypochromic, microcytic anemia.

Mutation of three of the alpha genes leads to Hemoglobin H disease, characterized by microcytic hypochromic hemolytic anemia, hepatosplenomegaly, mild jaundice, and sometimes thalassemia-like bone changes. Mutation of all four alpha genes results in Hb Bart hydrops fetalis (Hb Bart) syndrome, typified by fetal onset of generalized edema, pleural and pericardial effusions, and severe hypochromic anemia. Death usually occurs in the neonatal period. No effective treatment is available for Hb Bart syndrome. Occasional RBCs transfusion may be required for patients with HbH disease.

Molecular Genetics
The alpha globin gene cluster located on chromosome 16 spans about 30 kb and includes 4 functional genes and 3 pseudogenes. Hemoglobin alpha is produced throughout fetal and adult life. Two alpha chains combine with two beta chains to constitute Hb A, which in normal adult life comprises about 97% of the total hemoglobin.

HBA2 is the gene encoding alpha 2-globin. The alpha 2 and alpha 1 coding sequences are identical. However, the 2 genes differ slightly over the 5-prime untranslated regions and the introns, but significantly over the 3-prime untranslated regions. The HBA2 gene has a dominant expression role; producing 2.6 fold more protein than HBA1. Therefore, mutations in HBA2 usually have more impact than those in HBA1. About 90% of the mutations in these genes are deletions. The 10% point mutations however, are more severe, since they usually affect the HBA2 gene.

Epidemiology in the Arab World
Algeria
Trabuchet et al. (1977) found Hemoglobin J (Mexico) in five generations of a large Algerian family. Nine
Subjects had 55% Hb J although their parents, siblings and offspring had 31%, the usual quantity found in heterozygotes. Those with 55% Hb J were considered to be homozygous for a chromosome carrying both a normal alpha chain locus and a locus for alpha J. The proportion of the abnormal hemoglobin in all the subjects was in favor of an unequal expression of both loci, the amount of protein synthesis directed by the alpha J gene being greater than that directed by the alpha A. In two heterozygotes a slightly higher proportion of the Hb J (38%) suggested the presence of a single normal alpha chain locus in trans.

Morle et al. (1984) described two homozygotes for Hb-G Philadelphia in an Algerian family with a high degree of consanguinity. All homozygotes or heterozygotes displayed microcytosis (with various degrees of poikilocytosis) and a moderately depressed alpha-globin chain synthesis. Hb H and Heinz bodies were absent. DNA mapping revealed the presence of a 3.7 kb deletion resulting from the rightward type of recombination event between alpha 2 and alpha 1 genes on both the alpha A/ and the alpha G/ chromosomes. Morle et al. (1984) indicated that the -alpha A/ and -alpha G/ haplotypes are involved and suggested that the -alpha G/ haplotype, which is very rare in Algeria, had an African Black origin. The data collected from this family suggested that the -alpha A/ haplotypes are heterogeneous in Algerians.

Dahmane-Arbane et al. (1987) report a case of Hb Boumerdes, an alpha chain variant alpha 2(37) (C2) Pro----Arg beta 2, in an Algerian family. The propositus was also homozygous for the sickle cell gene. The abnormal hybrid hemoglobin had an electrophoretic mobility on cellulose acetate pH 8.7 electrophoresis between those of Hb S and Hb A2. Its expression was about 16%. The propositus' sickle cell phenotype was benign.

Bahrain

Jassim et al. (1999) described a simple and robust technique to rapidly detect the hemoglobin alpha (T-Saudi) allele. A total of 32 individuals with proven Hb H disease were studied using a novel mismatched-primer PCR-RFLP approach. This technique involves performing PCR with one of the primers having a deliberately introduced mismatch. The mismatch introduces a Stul restriction enzyme site into the product, which can be cleaved using the restriction enzyme. Hb H levels in the analyzed patients ranged between 5-25% due to homozygosity for the alpha (T-Saudi) allele and compound and simple heterozygosity for various alpha thalassemia alleles. Jassim et al. (1999) indicated that compound heterozygotes for –alpha (3.7) and alpha (T-Saudi) mutations will provide a false homozygous pattern for alpha (T-Saudi) mutations. Two years later, Jassim et al. (2001) utilized PCR amplification, PCR-RFLP, and differential PCR amplification to study the alpha-globin gene in 56 unrelated alpha-thalassemia individuals (age ranging from 14 days to 78 years). With the exception of two, all the other patients were found to have low MCV, MCH, and HbA2. The two exceptional cases were found to have concurrent beta-thalassemia or sickle cell trait. A total of five different alleles were found in the patient population. Of these, the alpha T-Saudi alpha allele was found to be the most common (53%), followed by the deletional –alpha (3.7 kb) allele (32%). The authors conceded that the high frequency of the Saudi allele could be due to a recruitment bias. Other alleles detected were alpha Hph alpha (12%), alpha T-Turkish alpha (1%) and –alpha (4.2 kb) allele (2%). Ten different genotype combinations were found in the study. Of these, homozygosity for the Saudi allele was responsible for all but three cases of HBH. Of the exceptions, one was heterozygous for the Saudi and the Turkish allele. Since both these alleles are poly A signal mutations, the severe phenotype is understandable. The second case was compound heterozygous for –alpha 3.7 and the Saudi allele, whereas the third exceptional case was homozygous for the –alpha 3.7 allele. Jassim et al. (2001) postulated that in both these cases, the –alpha 3.7 allele may be harboring an additional thalassemia mutation.

Iraq

Giordano et al. (1994) reported a new alpha chain variant (Hb Kurdistan) in a 15-year-old Kurdish refugee girl and her family from Amdea, Iraq. Amplification and DNA analysis of both alpha genes indicated an asp-to-tyr substitution (GAC-to-TAC) at position 47 of the HBA2 gene. Replacement with the larger aromatic side chain of tyrosine at this position does not induce any significant instability in the hemoglobin molecule.

Kuwait

Adekile et al. (1994) characterized the alpha thalassemia determinants among Kuwaiti Arabs. PCR, hybridization and DNA sequencing techniques were used to analyze 64 alpha-thalassemia chromosomes. Three mutations were identified in 30 chromosomes from patients with HbH disease. These were: Poly A signal mutation in alpha 2-globin gene.
(86.7%), -alpha (3.7 Kb deletion; 10%), and alpha-5nt alpha (3.3%).

**Saudi Arabia**

Al-Awamy et al. (1985a) described Hb Setif [alpha 2 94(G1)Asp----Tyr beta 2] in a family from Saudi Arabia. In the same year, Al-Awamy et al. (1985b) found Hemoglobin Handsworth [alpha2 18(A16)Gly---Arg beta2] in a Saudi newborn.

El-Hazmi (1986) used restriction endonucleases Bam HI and BglII to investigate the molecular basis of the deletion type of alpha-thalassaemia in the Saudi population. Four homozygous cases and six heterozygous cases of the leftward deletion type of alpha-thalassaemia (-alpha) were identified. This study was the first to report for the first time the presence of leftward deletion in the Saudi population.

**Tunisia**


Siala et al. (2004) described a 3-year-old Tunisian girl who had Hb Bart's (gamma-4) at birth, later on presenting with moderate anemia, microcytosis, and hypochromia; she had a normal HBA2 level and no abnormal hemoglobin fraction. After excluding most of the common Mediterranean mutations, sequencing of the HBA2 gene identified a heterozygous change of codon 23 from GAG (glu) to TAG (ter) (glu23 to ter). The E23X mutation was also found in the mother in heterozygous state.

**United Arab Emirates**

El-Kalla and Baysal (1998) studied alpha-thalassemia in the United Arab Emirates and examined the alpha globin genes of 418 cord blood samples from newborn UAE nationals. Four different non-deletional alpha globin mutations (alpha-T) were identified; which were responsible for about 6% of the total mutations. These were; alpha-PA-1, alpha-PA-2, HbCS, and alpha-5nt del. Most of the patients, with compound heterozygous mutations for the alpha-thalassemia-2, were asymptomatic for HbH disease.

**Yemen**

Oron-Karni et al. (1997) described two unrelated individuals of Yemenite-Jewish origin with a deletion/duplication mutation in the HBA2 gene, which consisted of a deletion of 9 bp (codons 39 to 41), which was replaced by a nucleotide insertion, duplicating the adjacent downstream sequence. Oron-Karni et al. (1997) proposed that the mutation arose by slipped strand mispairing (SSM), creating a single-stranded loop, followed by DNA elongation, strand breathing, and the formation of a mismatch bubble. The patients were referred for evaluation of unexplained mild microcytic anemia. The hematologic data were compatible with alpha-thalassemia trait. Because of the rarity of the mutation and the fact that it had been found only in the two individuals of Yemenite-Jewish origin, The subjects may have had a common ancestor.

**References**


Al-Awamy B, Niazi GA, Wilson JB, Huisman TH. Hb Setif or alpha 2 94(G1)Asp----Tyr beta 2 observed in a Saudi Arabian family. Hemoglobin. 1985a; 9(1):87-90. PMID: 3997545


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http://www.emedicine.com/MED/topic2259.htm
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Contributors
Abeer Fareed: 10.4.2007
Pratibha Nair: 28.1.2007
Ghazi O. Tadmouri: 17.5.2006
Abeer Fareed: 17.5.2006
Pratibha Nair: 17.5.2006
Sarah Al-Haj Ali: 17.5.2006