Hemoglobin - Alpha Locus 1

Alternative Names
HBA1
3-Prime @Alpha-Globin Gene
Minor Alpha-Globin Locus
Alpha-Thalassemia
Alpha-Thalassemias
Methemoglobinemia, Alpha-Globin Type
Erythremia, Alpha-Globin Type

Record Category
Disease phenotype

WHO-ICD
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism > Haemolytic anaemias

Incidence per 100,000 Live Births
101- ~

OMIM Number
141800

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.

Alpha-thalassemia is prevalent in Africa, the Mediterranean countries, India, Southeast Asia, Oceania and the Arabian Peninsula. In the Arabian Peninsula, gene frequencies for the alpha 3.7 Kb deletion vary from 0.01 to 0.67, with Oman having the highest values.

Molecular Genetics
The alpha globin gene cluster located on chromosome 16 spans about 30 kb and includes four functional genes and three pseudogenes. HBA1 is the gene encoding alpha 1-globin and is localized to the telomeric region of chromosome 16p. The gene is 84 Kb in size and consists of three exons. About 90% of the mutations in HBA1 are deletions and only 10% are point mutations. Hemoglobin alpha is produced throughout fetal and adult life. Two alpha chains combine with two beta chains to constitute HbA, which in normal adult life comprises about 97% of the total hemoglobin. The expression of HBA1 is regulated by a region (HS40) located 40 Kb upstream of the alpha globin cluster.

Epidemiology in the Arab World
Algeria
Wajcman et al. (1972) described Hb Setif in an Algerian family.
Baklouti et al. (1988a) described hemoglobin Loire [alpha 88(F9)Ala----Ser] in a 10-year-old Algerian boy born in Loire. The child had erythrocytosis and microcytosis, the latter being due to iron deficiency. The oxygen binding curves, at equilibrium, and the kinetic measurements demonstrated that the substitution of alpha 88(F9) Ala for a Ser results in increased oxygen affinity and decreased n50 value.

Wajcman et al. (1993) found Hb Melusine in an Algerian patient during a systematic neonatal hemoglobinopathy screening program in Luxembourg. Using isoelectric focusing and reverse phase high performance liquid chromatography (RP-HPLC), Wajcman et al. (1993) determined that the molecular mutation at amino acid position 114 of the HBA1 gene changed the residue from proline to serine.

**Bahrain**

Mohammad (1991) analyzed 76 Bahraini nationals with the Hb H disease. Variability in the clinical spectrum was observed, with three different forms of clinical presentations. In neonates, the presentation was severe, with anemia, massive hepatosplenomegaly and heart failure. Adults, however, were asymptomatic, behaved like beta-thalassemia trait, and were only identified in the course of family screening. The third group was intermediate, and comprised mostly of children in the age group of 1-10 years. They presented with chronic hemolytic anemia with an intermediary severity, which required regular blood transfusions. Though 40.9% of them had detectable splenomegaly, none had massive hepatosplenomegaly. Since the Bahraini population is an extension of the Eastern province of Saudi Arabia, Mohammad (1991) proposed that the Hb H disease in the Bahraini population may be due to homozygous forms of the non-deletional alpha-globin gene defect, as reported earlier for the Saudi Arabian population.

Mohammed et al. (1992) conducted a cord blood screening program to determine the frequency of Alpha Thalassemia in Bahrain. A total of 10,327 cord blood samples, representing over 80% of all Bahraini neonates born in 1985 were analyzed in the study. The incidence of alpha-thalassemia gene based on elevated Bart’s hemoglobin was found to be 24%.

Al-Mukharraq (1999) demonstrated the clinical presentation of 26 Bahraini children (11 males and 15 females) with Hb H disease aged 1-17 years. Diagnosis was established by hemoglobin electrophoresis and the cases were retrospectively studied. Four patients received frequent transfusion (their mean Hb H level was 20.2%) and nine cases required less than five transfusions (their mean Hb H level was 14.4%). The other 13 patients had not received transfusion with a mean Hb H level of 16.2%. Two patients had splenomegaly. Growth percentile findings showed that 17 children had above average growth and nine had below average growth. Although the genotype was not studied for those patients, Al-Mukharraq (1999) proposed that the patients were suffering from a mild to moderate disease.

Shome et al. (2002) studied the clinical and morphological features of a Bahraini infant with Wolman disease. The patient was 11-week old male who was presented to the hospital with a one day history of fever, watery diarrhea, and vomiting. He was noticed to have abdominal distention with umbilical hernia, hepatomegaly, splenomegaly, and severe anemia. Hemoglobin electrophoresis and HPLC revealed 6% hemoglobin Bart’s that was associated with alpha thalassemia. Foamy macrophages and vaculated leukocytes were observed in marrow aspirate. The baby passed away six weeks after admission.

**Comoros**

Badens et al. (2000) studied the molecular basis of hemoglobinopathies in the Comorian population. A total of 467 newborns (246 females and 221 males) were screened. Hemoglobin Bart’s was detected by isoelectrofocalisation in nine (1.9%) newborns. In addition, 21 subjects were screened for alpha-3.7 kb deletion. Among those 21, there were three homozygotes and nine heterozygotes corresponding to 15 mutated alleles out of 42 (36%). Badens et al. (2000) concluded that alpha-thalassemia was likely to be very frequent in the Comorian population.

**Iraq**

Al-Allawi et al. (2009) carried out the first study to address the molecular basis of alpha-thalassemia in Iraq. A total of 51 unrelated individuals (25 males and 26 females, age range: 1 to 55 years, median: 25 years) with unexplained hypochromia and/or microcytosis, as well as nine patients with documented Hb H disease, were studied. All the studied individuals are from the Dohuk region in northern Iraq. In cases with unexplained hypochromia and/or microcytosis revealed the following genotypes: -alpha(3.7)/alpha alpha in 26 (51%) of these subjects, followed by - (MED-1)/alpha alpha in 12 (23.5%) cases, then - alpha(3.7)/-alpha (3.7) in five (9.8%) cases. Other genotypes identified sporadically were -alpha(4.2)/alpha alpha in two (3.9%) cases, one case each of the alpha(poly A1)alpha/alpha alpha (AATAAA->AATAAG) and alpha(Adana)alpha/alpha alpha [Hb Adana, codon 59 (Gly>Asp) or HBA1:c.179G>A] (1.96% each),
pentanucleotide (GAGGTGAGG -GAGG) deletion.

and III were found to be mean corpuscular volumes different from those in other eastern Mediterranean populations. Al-Allawi et al. (2009) concluded that the findings of this study are rather different from those existing in the adult.

Kuwait
Screening hemoglobin Bart's in 345 cord blood samples from newborn Kuwaitis revealed an incidence rate of 4.6% for alpha-thalassemia. However, upon investigating the sensitivity of this screening method Sismek et al. (1993) described it as “inadequate” because of the high prevalence of samples having one gene deletion [- alpha/alpha alpha] with no detectable Hb Bart's among Kuwaitis.

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%). Later, Adekile et al. (1996) studied spleen function in a set of 20 Kuwaiti sickle cell anemia (SS) patients aged 2 to 12 years through employing 99mTc-labeled tin colloid scintigraphy. The subjects underwent a combined prospective and retrospective study to explore the influence of coexistent alpha-thalassemia feature on the prevalence of gallstones in 45 SS patients from Kuwait. The cohort consisted of 30 males and 15 females with a mean age of 7.2 +/- 3.1, with the majority of subjects being homozygous for the Saudi Arabia/India (SAI) haplotype (87%) and the remaining were SAI/Ben compound heterozygote (11%). Seven patients (4 males and 3 females) with a mean age of 10.5 +/- 5.5 years, were found to suffer from gallstones and a lower Hb (8.4 +/- 0.8 g/dl) when compared to the group of lower mean age (6.8 +/- 3.2 years) lacking gall stones (9.5 +/- 1.3 g/dl). Moreover, gallstones were not present in the 4 alpha-thalassemia homozygotes, but occurred in 2 out of 13 heterozygotes and 5 out of 23 subjects without coexistent alpha-thalassemia, revealing a statistically significant difference with a chi2 value of 20.4. Haider et al. (1998) proposed that coexistent alpha-thalassemia might play a role in reducing the possibility of developing gall stones and hemolysis in Arab SS subjects.

Mauritania
In 1989, Wajcman et al. described Hb Nouakchott [alpha 114(GH2)Pro---- Leu] in a patient from Mauritania. The most striking fact in Hb Nouakchott was the highly increased hydrophobicity of the abnormal chain. Even though the substitution concerned a proline residue, it was without consequences on the oxygen binding and the stability of the molecule.

Morocco
Baklouti et al. (1988b) reported the association of Hb Dunn (alpha 6[A4]Asp----Asn) and Hb O-Arab (beta 121 [GH4]Glu----Lys) in a healthy Moroccan man. The identification of Hb Dunn was based on sequence determination of the alpha T1 peptide. The percentages of the various hemoglobins showed that the doubly mutated hemoglobin Dunn/O-Arab has a normal stability and suggested that the Dunn mutation is carried by the alpha 1-gene. In cord blood of the propositus's son, the output of the alpha Dunn gene was found equivalent to that existing in the adult.
Oman
White et al. (1986) analyzed 5000 subjects from three major Peninsular Arab states and determined the frequency of alpha thalassemia in Oman to be 39%. Later, White et al. (1993) estimated the frequency of alpha thalassemia in Oman by studying 1,000 Omani subjects. The frequency of homozygous alpha+ thalassemia (-alpha/-alpha) was found to be 0.45, showing that the alpha+ (-alpha/) thal gene was pandemic in this population.

El-Kalla and Baysal (1998) undertook a study on four alpha-thalassemia patients from Oman. One of the patients had the --MED-1/-alpha-3.7. A 3-year-old boy presented with early anemia from early childhood, without any requirement for blood transfusion. The other three patients showed the genotype alpha-PA-1 alpha/ alpha-PA-1 alpha.

Baysal (2001) examined three Omani patients with HbH disease. One of the patients, a 2-year-old boy, was characterized with –alpha-3.7/-MED-1.

Qatar
Fawzi et al. (2003) undertook a hospital-based study, in which they studied 1,702 Qatari nationals (905 females and 797 males) referred for investigation on suspicion of a hemoglobinopathy. All patients were subjected to analysis through hemoglobin electrophoresis and full blood count, sickling, and other screening studies. Of these, 16.9% showed a normal electrophoresis pattern, while in another 8.6%, the pattern was considered inconclusive, either due to the presence of iron deficiency anemia or due to a recent blood transfusion. Alpha thalassemia trait was revealed in 8.05% of the patients, whereas alpha-thalassemia intermedia was detected in 0.99%. In addition, 3.23% of the patients were seen to have HbS/alpha-thalassemia.

In a study by El-Menyar et al. (2006) analyzing data pertaining to all patients less than 50-years of age, who were hospitalized between 1996 and 2003 with cardiomyopathy in Qatar, a rare association was noticed in one patient leading to comorbidity of dilated cardiomyopathy and Hb H Disease. The patient was a 50-year old female with a reduced ejection fraction (30%), as well as HCV infection.

Saudi Arabia
Abdo (1989) described Hb Setif [alpha 94(G1)Asp- ---Tyr] in a family from Saudi Arabia.

As part of the hemoglobinopathies’ neonatal screening program in Qatif and Al Hasa, Saudi Arabia, Nasserullah et al. (1998) carried out a molecular study on a total of 12,220 infants, including 11,313 (92.6%) Saudis, to estimate the frequency of alpha-thalassemia disease. The study group included 4,744 males (4,410 Saudi, 334 non-Saudi) and 4,722 females (4,378 Saudi, 344 non-Saudi); and 1,370 males (1,254 Saudi, 116 non-Saudi) and 1,279 females (1,172 Saudi and 107 non-Saudi), in Al Hasa and Qatif, respectively. This target population included all babies born in Qatif Central hospital, Qatif, and King Fahad Hospital, Al Hasa, from December 1992 to December 1993. In addition, babies delivered at home in the Qatif and Al Hasa areas, and coming to primary health care centers for vaccination, were also included. The diagnosis of alpha-thalassemia was based on cellulose acetate electrophoresis and confirmed by agar gel electrophoresis. The common phenotypes detected in these infants included AF, AF Bartâs, SFA, SFA Bartâs, FS and FS Bartâs. Forty-seven samples (0.4%) were found with rare hemoglobin variants. These were not characterized further. The prevalence of alpha-thalassemia of Saudi infants was found very high (28% and 16.3% in Qatif and Al Hasa, respectively). Nasserullah et al. (1998) believed that this figure is even less than the actual figure, due to the method used in this study for the diagnosis of alpha-thalassemia (presence of more than 2% of Hb Bart’s) which is known to miss many cases. The prevalence of alpha-thalassemia among non-Saudi infants was found to be 1.8% and 1.9% in Qatif and Al Hasa, respectively. Nasserullah et al. (1998) concluded that the Saudi populations in Qatif and Al Hasa are at risk for alpha-thalassemia.

Sudan
El-Kalla and Baysal (1998) undertook a study on an 8-year-old alpha-thalassemia patient from Sudan. He showed the compound heterozygous genotype [alpha-5nt del alpha/-alpha-3.7]. The patient was an active and healthy boy, who was investigated for microcystosis and hypochromia, without iron deficiency and normal Hb A2 levels.

Tunisia
In 3 members of a Tunisian family, Darbellay et al. (1995) identified a leu129- to-pro substitution in the HBA1 gene by sequencing the entirety of the HBA2 and HBA1 genes. In the heterozygous state, the variant was manifested by microcytosis, whereas the homozygous state showed moderate anemia with marked microcytosis.

United Arab Emirates
White et al. (1986) analyzed 5000 subjects from three major Peninsular Arab states and determined the frequency of alpha thalassemia in the UAE to be 16.5%. [Note: data from other studies indicate that the actual frequency of alpha-thalassemia in the
UAE is much higher than that reported by White et al. (1986); see below > Baysal, 2001].

During a routine program of hemoglobin screening performed in the United Arab Emirates, Abbes et al. (1992) found an electrophoretically fast-moving variant in a 9-month-old girl and in several members of her family. Amino acid sequencing demonstrated that the new variant, HB Al-Ain Abu Dhabi, had a gly18-to-asp substitution. The variant had normal functional properties.

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 using microcolumn chromatography, isoelectric focusing, alkali denaturation, spectrophotometry, PCR, hybridization and DNA sequencing. The frequency of alpha-thalassemia among these neonates was very high (49%). The most common mutation was the 3.7 Kb deletion (68.6%, frequency 0.2847). One newborn was found to be compound heterozygous for the 3.7 Kb and the 4.2 Kb deletions. Four different non-deletional alpha globin mutations (alpha-T) were also identified; which were responsible for about 6% of the total mutations. These were: alpha-PA-1, alpha-PA-2, HbCS, and alpha-5nt del. Hb Barts was found in all cases with alpha-T mutations. Baysal (1998) also studied the genotype-phenotype correlation of 17 UAE nationals with HbH disease or Hb like conditions, and characterized five different alpha-thalassemia determinants (--MED-I, 3.7 Kb deletion, alpha-PA-1, alpha-CS, alpha-5nt del). Two brothers, both with alpha-CS alpha/alpha-CS alpha presented with totally different conditions. One was symptomatic from early infancy, while the other was completely asymptomatic.

In a study on the hemoglobinopathies in the United Arab Emirates, Baysal (2001) examined the alpha globin genes of 418 cord blood samples from newborn UAE nationals using PCR, hybridization and DNA sequencing. The frequency of alpha-thalassemia among these neonates was very high (49%). Additionally, Baysal (2001) identified four non-deletional mutations in 3% of the chromosomes (alpha-T). Baysal (2001) studied 28 alpha thalassemic UAE nationals, with HbH. The poly a-1 mutation [alpha-PA-1 (AATAAA-AATTAAG)] was the most common mutation (47.4%). In total, nine different alpha-thalassemia genotypes were identified.

Miller et al. (2003) carried out a cross-sectional community clinic-based capillary blood survey to produce a hematological profile of preschool national children of the United Arab Emirates. The sample included 1-5-year-old Emirati children attending a Primary Health Care Center in Al-Ain from April 2000 to October 2000. Those children with capillary hemoglobin (Hb) and mean corpuscular volume (MCV) values below predetermined cutoffs were offered venous blood hematological workup. A random sample of children with values above those cutoffs was also offered the same workup. In total, 496 children were surveyed. The mean Hb and adjusted MCV rose with increasing age but were not significantly different by gender. Two hundred and sixty-two children with Hb or MCV below the cutoffs and 50 children above the cutoffs were venous blood tested. The estimated abnormalities for this population of children were as follows: anemia 36.1%; iron deficiency anemia 9.9%; glucose-6-phosphate dehydrogenase (G6PD) deficiency 9.1%; sickle cell trait 4.6%; and beta thalassemia 8.7%. Miller et al. (2003) further indicated that there was likely to be a high prevalence of alpha-thalassemia in the population and emphasized the importance of DNA studies in this regard.

[See also: Oman > Baysal, 2001]

Yemen

White et al. (1986) analyzed 5000 subjects from three major Peninsular Arab states and determined the frequency of alpha thalassemia in Yemen to be 6.5%.

References


Abdo MZ. Hb Setif [alpha 94(G1)Asp---- Tyr] in a Saudi Arabian family. Hemoglobin. 1989; 13(7-8):737-42. PMID: 2634670


Related CTGA Records
Glucose-6-Phosphate Dehydrogenase
Hemoglobin--Alpha Locus 2
Hemoglobin--Beta Locus
Wolman Disease

External Links
http://www.emedicine.com/MED/topic2259.htm
http://www.genetests.org/profiles/a-thal
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=846

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