



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 [α 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 α 88(F9) Ala for a Ser results in increased oxygen affinity and decreased n_{50} 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 α -globin gene defect, as reported earlier for the Saudi Arabian population.

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 α thalassemia. Foamy macrophages and vacuolated 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 α -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 α -thalassemia was likely to be very frequent in the Comorian population.

Kuwait

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

Mauritania

In 1989, Wajcman et al. described Hb Nouakchott [α 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 38.9%.

El-Kalla and Baysal (1998) undertook a study on four alpha-thalassemia patients from Oman. One of the patients had the --MED-I/-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.

Saudi Arabia

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

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 microcytosis 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 thalassaemic 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-thalassaemia 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 thalassaemia 8.7%. Miller et al. (2003) further indicated that there was likely to be a high prevalence of alpha-thalassaemia 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 thalassaemia in Yemen to be 6.5%.

References

Abbes S, M'Rad A, Fitzgerald PA, Dormer P, Bloquit Y, Kister J, Galacteros F, Wajcman H. HB Al-Ain Abu Dhabi [alpha 18(A16)Gly-Asp]: a new hemoglobin variant discovered in an Emirate family. *Hemoglobin* 1992; 16(4):355-62. PMID: 1428941

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

Adekile AD, Gu LH, Baysal E, Haider MZ, al-Fuzae L, Aboobacker KC, al-Rashied A, Huisman TH. Molecular characterization of alpha-thalassaemia determinants, beta-thalassaemia alleles and beta S haplotypes among Kuwaiti Arabs. *Acta Haematol*. 1994; 92(4):176-81. PMID: 7701914

Al-Mukharraq HJ. Hemoglobin H disease in Bahrain. *J Bahrain Med Soc*. 1999; 11(3):7-11.

Badens C, Martinez di Montemuros F, Thuret I, Michel G, Mattei JF, Cappellini MD, Lena-Russo D. Molecular basis of haemoglobinopathies and G6PD deficiency in the Comorian population. *Hematol J*. 2000; 1(4):264-8. PMID: 11920200

Baklouti F, Baudin-Chich V, Kister J, Marden M, Teyssier G, Poyart C, Delaunay J, Wajcman H. Increased oxygen affinity with normal heterotropic effects in hemoglobin Loire [alpha 88(F9)Ala----Ser]. *Eur J Biochem*. 1988a; 177(2):307-12. PMID: 3142772

Baklouti F, Francina A, Dorleac E, Baudin-Chich V, Gombaud-Saintonge G, Plauchu H, Wajcman H, Delaunay J, Godet J. Asymptomatic association of hemoglobin Dunn (alpha 6[A4]Asp----Asn) and hemoglobin O-Arab (beta 121[GH4]Glu----Lys) in a Moroccan man. *Am J Hematol*. 1988b; 27(4):253-6. PMID: 3354560

Baysal E. Hemoglobinopathies in the United Arab Emirates. *Hemoglobin* 2001; 25(2):247-53. PMID: 11480786

Darbellay R, Mach-Pascual S, Rose K, Graf J, Beris P. Haemoglobin Tunis-Bizerte: a new alpha 1 globin 129 Leu-->Pro unstable variant with thalassaemic phenotype. *Br J Haematol*. 1995; 90(1):71-6. PMID: 7786798

El-Kalla S, Baysal E. Alpha-thalassaemia in the United Arab Emirates. *Acta Haematol*. 1998; 100(1):49-53. PMID: 9691147

Miller CJ, Dunn EV, Berg B, Abdouni SF. A hematological survey of preschool children of the United Arab Emirates. *Saudi Med J*. 2003; 24(6):609-13. PMID: 12847588

Mohammad AM. Alpha-thalassaemia in Bahrain: haemoglobin H disease - not so benign. *Bahrain Med Bull* 1991; 13(2):49-51.

Shome DK, Al-Jishi E, Greally JF, Malik N, Zainaldeen HA, Das NS. The Middle-East connection of Wolman Disease. *Saudi Med J*. 2002; 23(5):597-601. PMID: 12070591

Wajcman H, Belkhdja O, Labie D. Hb Setif: G1 (94) Asp-Tyr. A new chain hemoglobin variant with substitution of the residue involved in hydrogen bond between unlike subunits. *FEBS Lett*. 1972; 27(2):298-300. PMID: 4667378



Wajcman H, Delaunay J, Francina A, Rosa J, Galacteros F. Hemoglobin Nouakchott [alpha 114(GH2)Pro----Leu]: a new hemoglobin variant displaying an unusual increase in hydrophobicity. *Biochim Biophys Acta.* 1989; 998(1):25-31. PMID: 2790052

Wajcman H, Kister J, M'Rad A, Marden MC, Riou J, Galacteros F. Hb Val de Marne [alpha 133(H16)Ser-->Arg]: a new hemoglobin variant with moderate increase in oxygen affinity. *Hemoglobin.* 1993; 17(5):407-17. PMID: 8294200

White JM, Byrne M, Richards R, Buchanan T, Katsoulis E, Weerasingh K. Red cell genetic abnormalities in Peninsular Arabs: sickle hemoglobin, G6PD deficiency and alpha and beta thalassemia. *J Med Genet* 1986; 23(3):245-51. PMID: 3723553

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-](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=846)

[bin/OC_Exp.php?Lng=GB&Expert=846](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=846)

<http://www.sos.se/SMKH/2005-110-15/2005-110-15.htm>

Contributors

Abeer Fareed: 25.3.2007

Abeer Fareed: 10.1.2007

Ghazi O. Tadmouri: 8.1.2007

Ghazi O. Tadmouri: 8.10.2006

Pratibha Nair: 20.5.2006

Ghazi O. Tadmouri: 17.5.2006

Abeer Fareed: 17.5.2006

Pratibha Nair: 17.5.2006

Sarah Al-Haj Ali: 17.5.2006

