Hemoglobin - Beta Locus

**Alternative Names**
HBB  
Beta-Thalassemia  
Beta-Thalassemias  
Methemoglobinemia, Beta-Globin Type  
Erythremia, Beta-Globin Type  
Cooley's Anemia

**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**
141900

**Mode of Inheritance**
Autosomal dominant for some such as methemoglobinemia, polycythemia, and Heinz body hemolytic anemia; Autosomal recessive for others such as sickle cell disease and thalassemia major

**Gene Map Locus**
11p15.5

**Description**
Beta-thalassemia is one of the most common single gene disorders affecting almost all the countries in the Mediterranean Basin, Australasia, the Americas and Africa. It is characterized by the deficiency or absence of beta-globin chain production. More than 200 mutations have so far been reported that result in beta-thalassemia.

The clinical severity of the beta-thalassemia syndromes depends on the extent of globin alpha chain/non-globin alpha chain imbalance. In beta thalassemia, excess alpha chains are produced, which bind to the red blood cell membranes and form toxic aggregates producing membrane damage and causing intravascular hemolysis. Clinical presentation of beta-thalassemia major occurs from six to 24 months of age. Affected infants fail to thrive and become progressively pale. Feeding problems, diarrhea, irritability, recurrent bouts of fever, and progressive enlargement of the abdomen caused by splenomegaly may occur. After the age of 10 years, affected individuals are at risk of developing severe complications related to iron overload, including growth retardation and failure of sexual maturation.

Clinical features of beta-thalassemia intermedia includes pallor, jaundice, cholelithiasis, liver and spleen enlargement, moderate-to-severe skeletal changes, leg ulcers, extramedullary masses of hyperplastic erythroid marrow, tendency to develop osteopenia and osteoporosis, and thrombotic complications.

**Molecular Genetics**
The human beta globin gene cluster is located on chromosome 11, spans about 45 kb, and includes 5 functional genes and 1 pseudogene. The beta-globin gene consists of three exons and two introns, with a total length of 1.6 kb. It is member of the beta-globin gene family, which includes beta, delta, A-gamma, G-gamma, and epsilon.

The genetic defect involved in beta thalassemia is usually a missense or nonsense mutation in the beta-globin gene, although occasional defects due to gene deletions of the beta-globin gene and surrounding regions have also been reported. The severity of the damage depends on the nature of the mutation. Some mutations (beta-zero) prevent any formation of beta chains; others (beta-plus) allow some beta chain formation to occur.

**Epidemiology in the Arab World**
**Algeria**
Lapoumeroulie et al. (1986) found the G-to-A change at position 5 of the donor site consensus sequence of IVS1 (CAG-GTTGGT to CAGGTTGAT) in an Algerian patient. Beldjord et
al. (1988) found a C-to-A change at position -8 in the acceptor splice site of IVS2 in an adult Algerian patient, presumably causing a decreased splicing.

Bouhass et al. (1990) studied 33 thalassemia chromosomes in Algerian patients. Of all patients seven carried the T-to-C transition at position 2 in IVS1. Thus, the mutation may be common in the Algerian population. They observed 2 patients who were homozygous for the substitution and had no detectable Hb A by standard electrophoresis procedures. Interestingly, the other 2 possible changes at this position have also been observed. Bouhass et al. (1990) found the frameshift, -A, codon 6, GAG to GG, mutation in one patient who was genetically heterozygote for a new mutation consisting of a T-to-A transversion at position 2 of IVS1.

In an Algerian family with hereditary persistence of fetal hemoglobin, Zertal-Zidani et al. (1999) identified a novel C-to-A transversion at position -114 in the distal CCAAT box of the G-gamma globin gene promoter. This substitution cosegregated with a unique beta-globin gene cluster haplotype. Individuals heterozygous for this mutation exhibited moderate rise in Hb F levels (0.6-3.5%). Much higher Hb F levels (3.8 -11.2%) were observed when a beta- thalassemia allele was present in trans to the hereditary persistence of fetal hemoglobin allele.

In a 66-year-old man born in Tizi-Ouzou in northeastern Algeria, Lacan et al. (2004) described abnormal hemoglobin with change of codon 29 in the first exon of the beta-globin gene from GGC (gly) to AGC (ser; gly29 to ser). The carrier showed hematologic abnormalities; the presence of microcytosis and hypochromia was explained by an additional homozygous 3.7 kb alpha(+) thalassemia deletion.

Bahrain

Dash et al. (1996) were the first to describe hemoglobin C (HbC) in a Bahraini family. HbC was detected in the pregnant mother, who was Egyptian in origin, by hemoglobin electrophoresis in acid agar gel and confirmation by the “Iso Lab-Hemocard” monoclonal antibody test for HbC. Hemoglobin quantitation was made by HPLC showing HbC 32.2%, HbA2 2.8%, HbF 0.5%, and HbA 64.5%. Her peripheral blood film showed microcytic hypochromic red cells with some target cells. One of her children, a boy, also had the HbC trait.

During the study of the incidence of cystic fibrosis in Bahrain, Al Arrayed and Abdulla (1996) detected 27 patients with cystic fibrosis (25 were Bahrainis). Of those, one patient had sickle/beta-thalassemia. Three years later, Al Arrayed et al. (1999) analyzed 500 formats for 500 clients taken at random. About 23.2% of the parents were first cousins, 1.5% were second cousins, and 3% were far relatives. The frequency of beta thalassemia was 2%. Average Hb A2 level in beta thalassemia trait was 5.6%.

Jassim et al. (1998) studied 80 individuals with beta-thalassemia alleles. Of those, 35 were transfusion dependent beta-thalassemia major patients, 37 were beta-thalassemia trait, and eight were sickle/beta-thalassemia patients. Jassim et al. (1998) used phenol-chloroform extraction method, reverse dot blot, PCR, denaturant gradient gel electrophoresis, and sequencing to examine 67 chromosomes with beta-thalassemia alleles. The results showed 12 different mutations, and [IVS-I 3' (-25bp)] mutation was largely predominant (36%) in Bahrain, compared to other Middle East countries. The other two prevalent mutations were the major Mediterranean allele [CD 39 (C-T)] (24.2%) and the Indian allele [IVS-I-5 (G-C)] (16.7%). These two mutations were probably introduced into Bahrain from the West and East, respectively. The other nine mutations were less frequent in Bahrainis and they were: [IVS-II-1 (G>A)], [IVS-I-1 (G>A)], [CD 44 (-C)], [nt -88 (C>A)], [CD 8/9 (+G)], [CD15 (G>A)], [IVS-I-110 (G>A)], [CD 35 (-C)], and [CD 41/42 (-TCTT)]. Jassim et al. (1998) concluded that Bahrain appears to be the epicenter for [IVS-I 3' (-25bp)] mutation in the Middle East. Soon later, Jassim et al. (2000) studied the molecular spectrum of beta-thalassemia mutations among Bahrainis by using denaturing gradient gel electrophoresis (DGGE), reverse dot blot (RDB), direct DNA sequencing, and haplotype analysis. Blood samples were taken from 87 Bahraini patients of 51 unrelated families. Those patients were divided into three groups: 33 clinically homozygote beta-thalassemia, 17 S-beta-thal, and 37 simple heterozygotes. A total of 70 beta-thal chromosomes were characterized in the study and 13 different beta-thal alleles were detected. However, three mutations comprised the majority of the alleles: 36% were of the Asian Indian mutation type [IVSI-3' end (-25 bp)], 26% were of the Mediterranean type [Cd 39 (C>T)], and 16% were of the Asian Indian mutation type [IVSI-5 (G>C)]. Further three mutations [IVSH-II-1 (G>A), Cd 44 (-C), and IVSI-1 (G>A)] were found to be less frequent with a total frequency of 13% and the remaining seven mutations were rare. Jassim et al. (2000) found similarities in mutation types among Bahrainis compared to those in neighboring countries, hence reflecting a genetic admixture among populations of the region. Haplotype analysis of the most common beta-thalassemia mutations in Bahrain showed each of them to be in
linkage disequilibrium with specific haplotype(s). However, each single mutation had a common framework background.

Jassim and Al Arrayed (2006) studied the different molecular determinants that might cause an extremely mild form of sickle cell/beta-thalassemia syndrome in the Bahraini population. Blood samples of two non-related Bahraini girls were tested by PCR-restriction fragment polymorphism (PCR-RFLP), denaturing gradient gel electrophoresis (DGGE), and differential PCR amplification. Three different molecular determinants were found in their beta globin gene. The first one was the compound heterozygosity for the sickle cell mutation and nt-88 (C-A) mutation. The second determinant was the presence of HbS haplotype associated high HbF expression. The third determinant was the co-inheritance of alpha thalassemia.

**Comoros**

Badens et al. (2000) reported the frequency of beta thalassemia trait in the Comorian community by performing prenatal screening in 283 immigrant women in Marseilles. Of those women, three (1%) were heterozygotes for beta thalassemia with allele frequency of 0.53%. Four different beta thalassemia mutations were identified in the six alleles analyzed from beta thalassemia heterozygotes: IVS 2-1 (G-A); beta 39 (C-T), IVS 1-110 (G-A), and Initiation Cd ATG-ACG. All but one of the beta thalassemia mutations characterized were typical Mediterranean mutations.

**Egypt**

Wong et al. (1989) found a C-to-A change at position -3 in the acceptor splice site of IVS2 (CAG to AA) an Egyptian patient.

In an Egyptian child with thalassemia major, Deidda et al. (1990) found heterozygosity for a G-to-A substitution at position -1 of IVS1, which altered the conserved dinucleotide AG present in the consensus acceptor sequence. The other chromosome carried the T-to-C mutation at position 6 of the first intervening sequence (IVS1). The latter mutation was associated with haplotype 6, frequently observed in Mediterranean areas; the new mutation was associated with haplotype 1.

El Kalla and Mathews (1997) studied beta thalassemia in the United Arab Emirates using gene amplification, hybridization with specific labeled oligonucleotide probes, sequencing of amplified DNA, restriction enzymes, and amplification refractory mutation system techniques. El-Kalla and Mathews (1997) identified a homozygous deletional mutation (AATAAA-AATAA) in a 6-year-old Egyptian boy, who was transfusion dependent with marked hepatosplenomegaly.

Sadek (1998) reported two females from a consanguineous family from Egypt with bilateral congenital choanal atresia. The patients also presented features of vitamin D resistant rickets. Their mother had beta-thalassemia minor.

Mahran et al. (1999) performed a prenatal diagnosis to identify mutations of the beta-globin gene in affected Egyptian families by using DNA PCR-amplification refractory mutation system (ARMS) and, therefore, achieving a preventive program. The study included 24 families, of which the at-risk couples, their diseased offspring(s) and 24 amniotic fluid samples from the ongoing pregnancies were tested (192 chromosomes) at molecular bases. The success rate of amniocentesis was 96%. Hematological studies were also performed. Consanguinity was observed in 13 families (54.16%). Of the total studied chromosomes, 122 were mutant (58 mutant chromosomes among patients, 48 for the heterozygote parents, 15 for the heterozygote fetuses, and only one chromosome of amniotic fluid samples was uncharacterized). The most common three mutations among 24 probands were beta-zero IVS 1 nt 1 (G-A), beta-plus IVS 1 nt 110 (G-A), and beta-plus IVS 1 nt 6 (T-C), which constituted 68.53% of all mutations. In 2% of the 24 probands the allele could not be characterized. It was found that homozygous beta-zero IVS 1 nt 1 (G-A) was the most frequent genotype among the 24 beta-thalassemia probands (30.76%). This mutation is followed by the homozygous beta-plus IVS 1 nt 110 (G-A; 23.07%), the compound heterozygote beta-zero IVS 1 nt 1 (G-A) with beta-plus IVS 1 nt 6 (T-C; 7.69% each). The highest mean of HbF level was in the beta-zero/beta-plus group (51.9%). The beta-zero/beta-zero group had the highest means of HbA level (81.5%), MCV level (80.9 fL), and MCH level (27.4 pg). Mahran et al. (1999) explained the correlation between phenotypes and genotypes on the basis that the clinical severity of beta-thalassemia was mainly dependant on the degree of beta-chain deficiency. Also, it was found that the coinheritance of hemoglobin Constant Spring could significantly reduce the severity of the disease.

[See also: Bahrain > Dash et al, 1996].

**Iraq**

Gutman et al. (1978) described two maternal male cousins in a Jewish Iraqi family with dyskeratosis congenita and megaloblastic bone marrow. One cousin had pancytopenia while the other had thrombocytopenia. The kindred displayed a
deficiency of glucose-6-phosphate dehydrogenase (G6PD) and a beta-thalassemia trait. Chromosomal studies showed a 46XY karyotype in both cases; however, nonspecific numerical aberrations and structural abnormalities were found in the first and in the second case, polyploidy was seen in four of 60 cells.

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. In the proband’s brother, this variant was associated with a beta-thalassemia nonsense mutation at codon 39.

In a family originating from Iraq, Deutsch et al. (1999) identified a novel beta-chain silent variant, a change of codon 10 from GCC to GTC (ala10 to val), in association with thalassemia. The variant, which they designated Hb Iraq-Halabja, gave a normal oxygenation curve, a normal heterotropic action of 2,3-DPG, and normal heat stability and isopropanol precipitation tests. The variant showed a clear difference in migration properties compared to normal beta chain only when run on PAGE urea Triton. The codon involved in Hb Iraq-Halabja is the same as that mutant in Hb Ankara, in which the substitution is ala10 to asp.

Al-Allawi et al. (2006) carried out a study to determine the molecular basis of beta-thalassemia in the Dohuk region of Iraq. Either of the parents of a total of 104 unselected beta-thalassemia major/intermedia which registered at the Dohuk Thalassemia Care Center, were included in this study. They included 50 males and 54 females with ages ranging between 20 and 46 years (median age of 35 years). Consanguinity was present in 67 of the parents (64%). Twelve mutations out of a total of twenty screened mutations were detected. The eight most frequent mutations in order of frequency were: IVS-II-1 (G>A; 18%), c.44 (-C; 12%), c.5 (-CT; 11%), IVS-I-1 (G>A; 9%), IVS-I-6 (T>C; 9%), c.39 (C>T; 9%), c.8/9 (+G; 8%), and IVS-I-5 (G>C; 7%). These mutations accounted for 82% of affected chromosomes in the studied individuals. The four less frequent mutations were: c.8 (-AA; 3%), IVS-I-110 (G>A; 2%), c.22 (-7 bp; 1%), and c.30 (G>C; 1%), whereas uncharacterized mutations constituted 12% of the studied chromosomes. Al-Allawi et al. (2006) observed that the frequencies of the c.44 (-C) and c.5 (-CT; 11%) mutations are much higher than have been reported before in Syria or in neighboring regions suggesting that these mutations may have arisen in Dohuk and was then transferred by gene-flow to surrounding countries. Al-Allawi et al. (2006) suggested that the IVS-I-110 mutation may have spread to Dohuk region through interaction with Arab tribes during the Islamic Empire. The variations in the values of the blood tests were not so remarkable, except in the much lower Hb A2 and Hb F and higher MCV and MCH level in the IVS-I-6 mutation, which is consistent with its mild nature.

Jalal et al. (2010) carried out a molecular study to determine the spectrum of beta-thalassemia (beta-thal) mutations in the Kurdish population of northeastern Iraq (Sulaimaniyah Province). A random 123 carriers of beta-thal (aged 17-56 years; mean: 26 years; 61 females and 62 males), identified by the Sulaimaniyah Provincial Premarital Screening Program in northeastern Iraq, were screened for beta-thal mutations. A total of 11 different beta-thal mutations were identified in the studied samples, of which eight represented 96% of the mutated beta-globin genes. The most common mutations among the studied patients were found to be as following: IVS-II-1 (G>A; 25%), IVS-I-110 (G>A; 20%), codon 8 (-AA; 15%), codons 8/9 (+G; 12%), IVS-I-5 (G>C; 8%), codon 5 (-CT; 7%), IVS-I-6 (T>C; 4%) and IVS-I-1 (G>A; 4%). Three other mutations were present at frequencies below 2%: codon 39 (2%), codon 44 (2%), and codon 15 (G>A; 1%). Thirty-nine out of 123 subjects (32%) were found to be carrier of beta+ (IVS-I-110, IVS-I-6, IVS-I-5), while the rest were found to be carriers of beta0 mutations. Jalal et al. (2010) found that there are some notable differences in frequencies of various mutations in comparison to other eastern Mediterranean populations, as well as with previous studies of Iraqi Kurds. Jalal et al. (2010) concluded that this finding illustrates the relative heterogeneity of the mutations distributed in Iraq, and the need to screen other areas of the country, to ensure the establishment of an effective prenatal diagnosis program.

[See also: Kuwait > Adekile et al., 2005].

Jordan
[See also: Kuwait > Mulla and Chrobak, 1973; Adekile et al., 2005].

Kuwait
Mulla and Chrobak (1973) reported the first Arab cases of hemoglobin C disease in Kuwait. The two cases consisted of two families, one Kuwaiti and the other Jordanian.

Kazazian and Boehm (1988) found a deletion of 17 nucleotides that removed the acceptor splice site from IVS1 in a Kuwaiti patient.

Adekile et al. (1994) characterized the beta thalassemia determinants among Kuwaiti Arabs. PCR, hybridization and DNA sequencing techniques were used to analyze 123 beta-
thalassemia chromosomes. Of the 12 mutations identified, six were Mediterranean alleles [IVS-II-1 (G>A), IVS-I-6 (T>C), CD 39 (C>T), IVS-I-110 (G>A), CD 8 (-AA) and IVS-I-1 (G>A)], which were responsible for 64% of the chromosomes. The four East Indian mutations [IVS-I-5 (G>C), IVS-I-3’ end -25nt del, CD8 8/9 (+G), and 619 –bp del] were seen in 25% of the cases. Two Kurdish-Iranian alleles [CD 44 (-C) and CD 36/37 (-T)] were observed in 11% of the chromosomes. Later, Adekile et al. (1996) studied the genetic epidemiology of β-thal in Kuwait. Data indicated that 40% of study subjects carried α-thal determinants, among these the -3.7 kb deletion [α-thal-2 trait] was the most prevalent (30%). The study identified 10 different β-thal mutations; the most common one among people of Saudi origin was IVS-II-1 (G>A), while the IVS-1 3’ 25 bp pair deletion was only detected in those of Iranian origin. Additionally three mutations; IVS-II-1 (G>A), IVS-I-1 (T>C), and codon 8 (-AA) were found in patients with thalassemia intermedia. Al Mazidi (1996) scanned 40 children with β-thal for various endocrine disorders. The patients’ age range was (14-30) and 60% of them were Kuwaitis. The list of disorders among these patients included short stature (45%), delayed and or arrested puberty (45%), hypoparathyroidism (15%), hypothyroidism (8%), diabetes mellitus (5%), and multiple endocrine disorders (38%).

Al-Fuzae et al. (1998) carried out a retrospective and prospective study of 129 patients with β-thalassemia major seen between 1965 and 1995 in a single hospital in Kuwait. About 80% of the patients were products of consanguineous unions. Bone marrow transplantation was performed in 11 of these patients. Although there was no BMT-related mortality, three cases of graft rejection and two of chronic graft-versus-host disease were noticed. With regard to hepatitis infection, 42 patients were found to be Hepatitis C seropositive, while nine were positive for HBsAg.

Adekile et al. (2005) conducted a molecular study to analyze beta-globin gene mutations associated with beta-thalassemia intermedia on 18 patients from Mubarak and Amiri Hospitals in Kuwait with a mean age of 12.7 ± 8.1. The patients were from 13 unrelated families, of them 3 siblings were identified using family screening and 15 were assigned for examination. The study involved 11 males and 7 females, 4 Jordanians, 1 Iraqi, and 13 Kuwaitis from 8 families, and none of these patients required a regular blood transfusion. Subjects were also screened for the deletion of alpha2 – globin gene (-3.7 kb). Out of the 18 patients, 4 were found to be homozygous for the IVS-I-II (G>A) and 4 for the IVS-I-6 (T>C) mutations, while the rest were found to be compound heterozygote with a combination of the subsequent mutations: CD 8 (-AA) and -101 (C>T); IVS-I-6 (T>C) and CD 19 (A>G); IVS-II-1 (G>A) and -28 (A>C); IVS-I-110 (G>A) and gammabeta0 deletion. Consequently, the patients’ genotype were reported to be 61% homozygote for two mild mutations (IVS-II-1 and IVS-I-6), indicating that patients from Kuwait showing beta-thalassemia should have an early screen for these two common alleles.

**Lebanon**

Makhoul et al. (2005) investigated the religious and geographic distribution of beta-thalassemia mutations in Lebanon and traced their origins. Sunni Muslims had the highest beta-thalassemia carrier rate and presented the greatest heterogeneity, with 16 different mutations. Shiite Muslims followed closely with 13 mutations, whereas Maronites represented 11.9% of all beta-thalassemic subjects and carried 7 different mutations. RFLP haplotype analysis showed that the observed genetic diversity originated from both new mutational events and gene flow from population migration.

**Morocco**

Baklouti et al. (1988) reported the association of Hb Dunn (alpha [A4] Asp----Asn) and Hb O-Arab (beta 121 [GH4] Glu----Lys) in a healthy Moroccan man. Hb O-Arab was easily recognized through its electrophoretic properties and was confirmed by the suppression of the Eco RI site located in exon 3 of the beta-gene. 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.

Among 598 children from the Berber population of the Mzab, Merghoub et al. (1997) found Hb C and Hb D (Ouled Rabah) in the same gene frequency (0.015). Hb D (Ouled Rabah) is considered a private marker of the Kel Kummer Tuaregs. Haplotype analysis suggested a single origin of the Hb Dunn chromosome. Genetic markers calculated from blood group data clustered Mozabites and Tuaregs with the other Berber-speaking groups, Arabic-speaking populations being more distant. However, they found no specific relationship between the Mozabites and Kel Kummers. Tuaregs in general exhibit features that tend to differentiate them from other Berber-speaking groups. Merghoub et al. (1997) concluded that Hb D (Ouled Rabah) may be specific for Berber-speaking populations and noted...
that the origin of the Berber people is not clearly established.

Wajcman et al. (2000) found a hemoglobin variant in a family in Morocco and designated it Hb Casablanca. It was found to be another example of a hemoglobin variant with 2 abnormalities in the same chain: the first was identical to that of Hb Bushey (phe122 to leu; 141900.0492) and the second to that of Hb J (Antakya) (lys65 to met; 141900.0121). The stability and oxygen-binding properties of Hb Bushey and Hb Casablanca were identical to those of Hb A.

North et al. (2001) found Hb Tsukumi in a Moroccan woman.

Oman
White et al. (1986) analyzed 5000 subjects from three major Peninsular Arab States and determined the frequency of beta thalassemia in Oman to be 2.4%.

In two members of an Arabian family from Oman, Ramachandran et al. (1992) discovered a leu-to-val replacement at position beta-32 by reversed phase high performance liquid chromatography. In one person, it occurred with Hb S and in the other with Hb A. Although Hb Muscat was slightly unstable, its presence had no apparent adverse effect on the health of its carriers.

White et al. (1993) re-estimated the frequency of high HbA2 Beta Thalassemia trait in Omanis to be 0.015.

El-Kalla and Mathews (1993) examined 199 beta-thalassemia patients, 16 of which were nationals of Oman. This group comprised patients with clinical diagnoses of typical transfusion-dependent thalassemia major. Mutations were detected by using the tools of gene amplification, dot-blot hybridization with synthetic probes, restriction enzyme analyses, and sequencing. 15 of the 16 Omani patients had the IVS-I-5 (G-C) Asian Indian mutation.

El-Kalla and Mathews (1997) studied the heterogeneity of beta thalassemia alleles in 37 Omani nationals residing in the United Arab Emirates. Eight mutations were identified: two splice junction mutations [IVS-I 25nt del3’ and IVS-II-1 (G-A)], three splice consensus sequence mutations [IVS-I-5 (G-C), IVS-I-6 (G-T), and IVS-I-1-I (G-C)], one nonsense mutation [CD39 (CAG-TAG)], one frameshift mutation [CD44 (-C)], and one RNA cleavage mutation [AATAAA-A (-AATAA)]. The Asian Indian IVS-I-5 (G-C) mutation was responsible for about 71% of the total chromosomes analyzed while IVS-I -1 (G-C) occurred only in one patient producing Hb Monroe.

Rajab et al. (2000) conducted a study to determine the birth prevalence of symptomatic hemoglobinopathies (with exclusion of alpha-thalassemia) in Oman through a national register which was obtained by gathering information (demographic and course of the disease) about the patients from hospital-based registers of all 17 regional hospitals and two tertiary care centers. In total, 781 cases of beta-thalassemia were included, but 548 cases (70%) were excluded after sorting out the duplicates and excluding those with wrong diagnosis. This register was then updated annually and new cases were added thereafter. By December 1995, 243 patients with homozygous beta-thalassemia (233 retrospectively from hospital records and 10 from one year prospective registration) were identified. The majority of beta-thalassemia cases were under the age of 16 years. The birth prevalence of symptomatic beta-globin disorders in Oman was 1 in 323 live births or 3.1 per 1000 live births in 1989-1992, which included 0.4 per 1000 live births of homozygous beta-thalassemia. Each year, it was calculated that 15 new cases of beta-thalassemia were expected to be born and the heterozygotes carrier frequency was 4% according to the national register. The regional distribution of beta-thalassemia revealed that it was more prevalent (more than 70% of cases) in the North Eastern coastal line of Oman in regions with smear-positive rates of malaria of 1% to more than 5% (parts of North Batna, Muscat and South Shargiya).

Al-Riyami et al. (2001) estimated the prevalence of hemoglobinopathies in Oman by interviewing members of households (6600 with response rate of 92.5%) randomly selected from a list prepared from a sample of 264 units chosen from all Oman districts. The 1993 national population census was used as a frame for the two-stage stratified probability sampling. Blood was withdrawn from 6342 children (aged 0-5 years) and analyzed for complete blood count and blood indices, and levels of hemoglobin S, A2 (values more than 3.5% confirmatory of beta-thalassemia trait in the absence of any hemoglobin abnormality) and F. The prevalence of beta-thalassemia trait was 2.2% and the mean level of HbS was 28.8% in 219 children with ages of 2 to 5 years (no regional variation). Beta-thalassemia trait showed significant association with mild anemia (detected in 3.2%) and showed significant regional variation, being more common in North Batinah (3.6%) and Muscat (3.0%), and least common in Dhofar (0.5%) and North Sharqiya (0.9%), but no association with age, gender, or history of blood transfusion (during
one year before the study) was detected. The prevalence of first cousin consanguinity was determined as 33.6%, and it was associated significantly with homozygous blood disorders. Upon comparison of the prevalence with that of other countries of the Gulf Cooperation Council (GCC), Oman lay in between, as that of United Arab Emirates was the lowest (1.7%) and Saudi Arabia had the highest prevalence (2.4%). On combing these results with the 1993 census, it was calculated that in Oman, 5392 children under the age of five years had beta thalassemia trait, and according to the authors’ results and the Hardy-Weinberg equation, the number of children born yearly with a major hemoglobinopathy was 2 per 1000 live births which increased to 3 per 1000 live births upon correction for consanguinity. Therefore, with a birth rate of 42,000/year, 125 children with a major hemoglobinopathy were calculated to be born yearly. As these numbers would increase the burden on health services, Al-Riyami et al. (2001) suggested that future health planning for Oman should be undertaken by improving and strengthening the national programs for detection, genetic counseling and health education.

Palestine
El-Kalla and Mathews (1997) identified the cryptic splice site mutation CD 27 (G>T), resulting in the production of Hb Knossos, in a Palestinian family residing in the United Arab Emirates.

Zlotogora (1997) conducted a survey of 2000 different Palestinian Arab families. In 601 cases, an autosomal recessive disease was diagnosed or strongly suspected. The distribution of these disorders was not uniform and some disorders, such as Krabbe disease, were found at high frequency in only a small part of the population. For some other disorders, a high prevalence was also reported among Palestinian Arabs living in other regions, for example, beta thalassemia, Bardet-Biedl syndrome, Meckel syndrome, autosomal recessive congenital hydrocephalus, and recessive osteopetrosis.

Qatar
Kamel et al. (1985) discovered a fast moving hemoglobin variant in a 24-year old Qatari female with post-partum anemia. Her mother and sister were also noted to have the same variant. This variant moved at the position of HbF upon citrate gel electrophoresis at pH 6.1, eluted in front of the minor HbA1 zone during cation exchange HPLC, and was retained at the top of the DEAE-cellulose column. Structural analysis of the variant revealed the beta chain to have an N-Met-Glu-His-Leu-Thr-Pro-Glu-Glu-Lys sequence at the N-terminal. Substitution of glutamic acid for valine at beta 1 apparently prevented removal of the initiator methionine, thus, extending the N-terminus by one residue to Met-Glu-His-Leu-Thr-. The N-terminal residue could not be detected, leading Kamel et al. (1985) to assume that it was blocked by a molecule that could not be completely identified. Direct probe electron impact mass spectrometry was used to identify the blocking group, but did not yield any specific results, other than suggest the presence of an acetyl moiety. Kamel et al. (1985) named this new variant Hb Doha, and speculated that the Val-Glu change in position beta1(NA1) could have prevented the removal of the N-terminal methionyl residue. They also noted that all three Hb Doha heterozygotes showed no deleterious effects in the functional properties of their hemoglobin.

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. Beta-thalassemia trait was revealed in 28% of the patients, whereas beta-thalassemia intermedia and major were detected in 0.11% and 0.76%, respectively. In addition, 1.53% of the patients were seen to have HbS/beta 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 two patients with comorbidity of dilated cardiomyopathy and thalassemia. The patients were 20 and 21-years old males. Both had reduced ejection fraction (14-21%), and died within 2-years. In the entire group studied, this association was found to have the shortest period between diagnosis and death.

Al-Obaidli et al. (2007) analyzed, for the first time, the molecular basis of beta-thalassemia in Qatar to define the beta-thalassemia mutational spectrum in Qatar. A total of 37 patients constituted the study population, of whom 28 were clinically recognized as transfusion-dependent beta-thalassemia carriers, three were sickle cell disease cases and six were referred for diagnosis of an unexplained microcytic anemia. The reverse dot-blot, denaturing gradient gel electrophoresis (DGGE), direct DNA sequencing technique and PCR-based procedures were used in this study. Al-Obaidli et al. (2007) found 12 different beta-thalassemia alleles in the
Qatari population. The most highly prevalent mutant allele was IVS-I-5 (G to C; a beta-plus type), followed by codons 8/9 (+G; a beta-zero type). They represented 35.4% and 26.1% of the total thalassemia alleles, respectively. Both these prevalent mutant alleles were found in large numbers in the homozygous state, likely due to the high rate of consanguinity in Qatar. The third mutant allele was IVS-II-1 (G to A; beta-zero; 9.2%), followed by 25 bp deletion (beta-zero; 6.2%) and IVS-I-110 (G to A; beta-zero; 6.2%).

The other rare mutations found in Qatar were codon 8 (-AA), followed by codon 15 (G to A), codon 44 (-C), codon 30 (G to C), codon 39 (C to T) and IVS-I-1 (G to A). Although the DNA sequencing of the entire beta-globin gene region was performed in two patients with typical thalassemia clinical features and transfusion dependency, Al-Obaidli et al. (2007) failed to reveal the second mutant alleles in these patients. This led Al-Obaidli et al. (2007) to suggest that mutations likely occurring elsewhere than in the beta-globin gene per se. Al-Obaidli et al. (2007) concluded that the spectrum of beta-thalassemia mutations is quite strikingly wide comparing to the small size of the population in Qatar. Two years later, Al-Obaidli et al. (2009) reported the molecular characterization of one of the two alleles which were remained uncharacterized in a 16-year-old Qatari girl reported earlier by Al-Obaidli et al. (2007). The allele is a novel deletional variant beta-thal allele, hitherto unreported in the literature. This deletion is a deletion of 192 bp within beta-globin gene and it spans 60 bases in exon 1, the entire intron 1 of 130 bases and the first two bases in exon 2, leading to predict that the mutant gene will direct the synthesis of a truncated polypeptide of 21 amino acids instead of the normal 146 amino acids due to a reading frameshift and the premature occurrence of a stop codon. The second mutation in the patient was found to be the IVS-I-5 mutation. Al-Obaidli et al. (2009) thus concluded that the patient is a compound heterozygote for the novel deletion and the IVS-I-5 mutation. Her parents and her similarly affected brother were not available for testing. Al-Obaidli et al. (2009) concluded that the presence of this novel deletional allele in a compound heterozygous state with a non-deletional allele warrant caution in a diagnostic setting, especially in the absence of family study.

Saudi Arabia
Wong et al. (1989) found a T>G change at position -3 in the acceptor splice site of IVS1 (TAG>GAG) in a Saudi Arabian patient.

Sudan
Vella and Hassan (1961) described a Northern Sudanese girl who presented at the age of 12 months with rickets associated with severe hypochromic anemia, aniso-poikilocytosis, and marked splenomegaly. Upon management of rickets, hypersplenism became clearly evident, by the rapid disappearance of transfused RBCs from circulation and thrombocytopenia. The patient’s condition improved following splenectomy. Two years later, she was readmitted, complaining of weakness in her right leg. The patient was chronically anemic. Paper electrophoresis of her hemoglobin detected an abnormal amount of fetal hemoglobin, suggesting thalassemia major. A study on her family showed both of her sisters to be hypochromic, with increase in erythrocyte osmotic resistance. The younger sister was pale with a palpable spleen. The parents were first cousins. The mother had thalassemia minor, and peripheral smears for the father showed hypochromia, moderate aniso-poikilocytosis, and microcytosis. The maternal grandmother and two of five siblings of the mother suffered from thalassemia minor. Vella and Hassan (1961) suggested that the lack of reports of beta thalassemia in the Northern Sudanese population is probably due to the disease being obscured by the presence of the prevalent endemic diseases and nutritional disorders.

Prehu et al. (2002) described a heterozygous hemoglobin variant that combined the change of Hb O-Arab and Hb Hamilton on the same beta-globin allele. The other allele carried the Hb S mutation. The patient was a child of Chad-Sudanese descent, suffering from a sickle cell syndrome. Compared to the classic description of the Hb S/Hb O-Arab association, the additional Hb Hamilton mutation did not seem to modify the clinical presentation.

Syria
Noguera et al. (2002) described Hb Agenogi in an Argentinean patient with Syrian and Hungarian ancestry.

Tunisia
Chibani et al. (1988) determined the spectrum of mutations producing beta-thalassemia in Tunisia by direct DNA analysis using hybridization with allele-specific oligonucleotide probes and restriction endonuclease assay. In the 34 unrelated beta-thalassemia patients included in the study, Chibani et al. (1988) identified four previously unreported haplotypes and found that this population differs from others in Mediterranean areas in the frequency of the beta-thalassemia haplotypes, the unexpected observation being the high frequency of haplotype IX. Six different point mutations were found, accounting for 62% of beta-thalassemia genes in this Tunisian population. The molecular defects known to be the most frequent in Mediterranean (nonsense codon 39, IVS1 nt 110,
United Arab Emirates. Seven mutations were thalassemia mutations in 50 patients from the Quaife et al. (1994) explored the spectrum of beta-sister from a local family in Dubai.

El-Kalla and Mathews (1993) also identified a novel beta-thalassemia mutation, namely CD37 (C-T), occurring at frequencies higher than 5%. Among the 12 remaining mutations CD 8/9 (+G), IVS-I-1 (-C), IVS-II-1 (G>A), CD 30 (G>C), and CD 15 (G>A) were present at frequencies between 2-8%. Quaife et al. (1994) proposed that the Asian Indian mutations, such as IVS-I-5 (G>C), were introduced into the UAE population by migration from Baluchistan.

In a young Arabian boy living in Tunisia, Molchanova et al. (1992) detected a leu48-to-pro substitution, causing Hb Bab-Saadoun, in the beta chain. Since the parents did not have the variant, it presumably occurred by spontaneous mutation. It was thought that the presence of Hb Bab-Saadoun unlikely results in a hemolytic anemia.

In a Tunisian patient with thalassemia intermedia, Jacquette et al. (2004) identified compound heterozygosity for mutations in the HBB gene: a change from AATAAA to AAAAAA in the polyadenylation site of the gene and a 2-bp insertion (25insTA) in codon 9, causing a frameshift with a premature termination at codon 19.

United Arab Emirates
White et al. (1986) analyzed 5000 subjects from three major Peninsular Arab States and determined the frequency of beta thalassemia in the United Arab Emirates to be 1.7%. [Note: data from other studies indicate that the actual frequency of beta-thalassemia in the UAE is higher than 8%; see below > Baysal, 2001].

El-Kalla and Mathews (1993) investigated the spectrum of various beta-thalassemia alleles prevalent in the United Arab Emirates population. El-Kalla and Mathews examined 199 beta-thalassemia patients, 93 of which were nationals of the UAE; consanguinity rate was 60%. This group comprised patients with clinical diagnoses of typical transfusion-dependent thalassemia major. Mutations were detected by using the tools of gene amplification, dot-blot hybridization with synthetic probes, restriction enzyme analyses, and sequencing. El-Kalla and Mathews found 13 mutations amongst UAE beta-thalassemia patients. The IVS-I-5 (G-C) Asian Indian mutation was the most common allele among UAE nationals at a frequency of 54.1%. Among the 12 remaining mutations Cd 8/9 (+G), IVS-I-25 nt deletion and Cd 39 (C-T) occurred at frequencies higher than 5%. El-Kalla and Mathews (1993) also identified a novel beta-thalassemia mutation, namely CD37 (-G). This frameshift mutation co-existed with beta-thalassemia mutation C8 (-AA) in a brother and sister from a local family in Dubai.

Quaife et al. (1994) explored the spectrum of beta-thalassemia mutations in 50 patients from the United Arab Emirates. Seven mutations were characterized. Of these, the mutation IVS-I-5 (G-C) was the most common (66%). The other six mutations, CD 8/9 (+G), IVS-I-1, 3’ end (-25bp), CD 5 (-CT), IVS-II-1 (G>A), CD 30 (G>C), and CD 15 (G>A) were present at frequencies between 2-8%. Quaife et al. (1994) proposed that the Asian Indian mutations, such as IVS-I-5 (G>C), were introduced into the UAE population by migration from Baluchistan.

De Leo et al. (1995) analyzed 70 beta-thalassemia patients for mutations in the beta-globin gene. Haplotype analysis for the beta-thalassemia chromosomes carrying the IVS-I-5 (G-C) mutation indicated that this allele could have an independent origin in the United Arab Emirates.

El-Kalla and Mathews (1997) studied the heterogeneity of beta-thalassemia alleles in 137 nationals of the United Arab Emirates. Methods utilized included gene amplification, hybridization with specific labeled oligonucleotide probes, sequencing of amplified DNA, restriction enzymes and amplification refractory mutation system techniques. El Kalla and Mathews (1997) characterized 19 different beta-thalassemia mutations in 253 chromosomes from beta thalassemia patients. Among these mutations were: one transcription mutation [-101 (C-T)], two splice junction mutations [IVS-I-1, 25nt del 3’ and IVS-II-1 (G-A)], five splice consensus sequence mutations [IVS-I-5 (G-C), IVS-I-6 (G-T), IVS-I-1 (G-C), IVS-I +1 (G-C), and IVS-I-1-848 (C-A)], one intrinsic cryptic splice site mutation [IVS-I-110(G-A)], two nonsense mutations [CD 15 (TGG-TAG) and CD 39 (CAG-TAG)], six frameshift mutations [CD 5 (-CT), CD 8 (-AA), CD 8/9 (+G), CD 36/37 (-T), CD 44 (-C), CD 82/83 (-G)], one RNA cleavage mutation (AATTTAA-AATAAG), and one dominantly inherited mutation [CD 110(T-C)]. The most common amongst these mutations was the IVS-I-5, which was responsible for more than 54% of the total mutations. El Kalla and Mathews (1997) identified two different point mutations at CD 30, producing variant hemoglobins. The first allele [IVS-I -1(G-C)] was identified in five patients, producing Hb Monro. The second was a rare European mutation [IVS-I +1(G-C)], which produced Hb Tacoma. This allele was characterized in a single 3-year-old girl, heterozygous for CD 36/37 (-T), and who’s father and sister were heterozygous for Hb Tacoma. The RNA cleavage mutation AATTTAA-AATAAG was identified in a brother and a sister, in a compound heterozygous condition with IVS-I-5 (G-C). The dominant inherited mutation CD 110 (CTG-CCG) was characterized in two transfusion dependent siblings of Irani Baluchi ethnic origin, in a compound heterozygous condition. Their mother
was also heterozygous for the mutation, but healthy
[See also: El-Kalla and Mathews, 1997 > Egypt, Oman, and Palestine].

El-Kalla and Baysal (1998) examined UAE nationals for their genotype-phenotype correlation of sickle cell disease. Eight different beta-thalassemia mutations were identified, existing in heterozygous condition with the HbS allele. Seven of these eight mutations were beta-zero and, their coexistence with the sickle gene, manifested severe clinical symptoms.

In a study on the hemoglobinopathies in the United Arab Emirates, Baysal (2001) examined beta thalassemia alleles in 280 transfusion dependent beta-thalassemia UAE nationals. The study showed beta-thalassemia (major, intermedia and HbE/beta-thal) to be the most prevalent hemoglobinopathy among UAE nationals (8.3%) with a molecular heterogeneity encompassing 44 different beta-thalassemia mutations. The frequency of homozygous mutations was found to be very high (45.5%), possibly because of the high degree of consanguinity in the population (50.5%). The most common beta-thalassemia homozygous mutation was the Arabian Indian IVS-I-5 (G-C) 66.1%). Baysal (2001) suggested that historical migrations from Baluchistan and the Indian subcontinent could have played a major role in establishing this mutation in the population.

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%; iron deficiency anemia 10%; glucose-6-phosphate dehydrogenase (G6PD) deficiency 9%; sickle cell trait 5%; and beta thalassemia 9%.

Baysal (2005) examined the molecular heterogeneity of beta thalassemia in the United Arab Emirates. Beta thalassemia alleles of 313 patients, all UAE nationals were characterized using column chromatography, isoelectric focusing, restriction enzyme analysis, beta strip hybridization, PCR and DNA sequencing. Of the 313 patients, 212 were homozygous and 101 were compound heterozygotes for the beta thalassemia gene. Baysal (2005) attributed the high incidence of homozygotes to the high degree of consanguinity in the UAE population. As in previous studies, the Asian Indian IVS-I-5 (G-C) mutation occurred in 47.6% of the beta-thalassemia patients from the UAE, of which 39% were homozygous for the mutation. Baysal (2005) suggested that the IVS-I-5 (G-C) mutation was introduced into the Arabian Peninsula across the straits of Hormuz. Baysal (2005) attributed the high level of heterogeneity observed in the patients analyzed to the roots of most UAE national families being in surrounding countries like Iran and Baluchistan and to the admixture of genes between the different populations in and around the Gulf area, Indian subcontinent, and Africa.

In an update on the status of beta-thalassemia in the UAE population, Dr. Erol Baysal (personal communication, April 2006) indicated that 51 beta-thalassemia mutations are found in 372 beta-thalassemia patients, nationals of the UAE. About two-thirds of the patients were homozygotes, and half of these were homozygous for the Arabian Indian IVS-I-5 (G-C) mutation.

Yemen
White et al. (1986) analyzed 5000 subjects from three major Peninsular Arab States and determined the frequency of beta thalassemia in Yemen to be 6.24%.

References


Jalal SD, Al-Allawi NA, Bayat N, Imanian H, Najmabadi H, Faraj A. Beta-Thalassemia
mutations in the Kurdish population of northeastern Iraq. Hemoglobin. 2010; 34(5):469-76. PMID: 20854121 [FT]


Molchanova TP, Wilson JB, Gu LH, Guemira F, Tattoum S, Huisman TH. Hb Bab-Saadoun or alpha 2 beta (2)48(CD7)Leu----Pro, a mildly unstable variant found in an Arabian boy from Tunisia. Hemoglobin. 1992; 16(4):267-73. PMID: 1517103


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Contributors
Abdul R Hamzeh: 6.1.2015
Pratibha Nair: 6.1.2015
Abdul R Hamzeh: 8.1.2013
Abdul R Hamzeh: 7.1.2013
Pratibha Nair: 3.4.2012
Pratibha Nair: 10.5.2011
Tasneem Obeid: 27.3.2011
Tasneem Obeid: 7.11.2010
Lina Walid: 15.7.2010
Lina Walid: 6.5.2010
Tasneem Obeid: 8.4.2010
Pratibha Nair: 26.5.2009
Pratibha Nair: 10.5.2009
Tasneem Obeid: 13.8.2008
Tasneem Obeid: 3.7.2008
Pratibha Nair: 27.7.2008
Tasneem Obeid: 25.12.2007
Eiman Ibrahim: 1.9.2007
Eiman Ibrahim: 7.8.2007
Abeer Fareed: 6.5.2007
Abeer Fareed: 18.4.2007
Abeer Fareed: 9.4.2007
Abeer Fareed: 25.3.2007
Abeer Fareed: 22.1.2007
Abeer Fareed: 8.10.2006
Ghazi O. Tadmouri: 8.10.2006
Pratibha Nair: 21.5.2006
Abeer Fareed: 20.5.2006
Ghazi O. Tadmouri: 17.5.2006
Abeer Fareed: 25.10.2006
Pratibha Nair: 16.5.2006
Sarah Al-Haj Ali: 16.5.2006