



Hemoglobin, Gamma G

Alternative Names

HBG2

Hemoglobin--Gamma Locus, 136 Glycine

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

Unknown

OMIM Number

142250

Mode of Inheritance

Autosomal dominant

Gene Map Locus

11p15.5

Description

The solution to the fetus's problem of getting oxygen from its mother's blood involves the development of a fetal hemoglobin. The hemoglobin in fetal red blood cells differs slightly from that in adult corpuscles. Two of the four peptides of the fetal and adult hemoglobin chains are identical - the alpha chains - but adult hemoglobin has two beta chains, while the fetus has two gamma chains. Normal beta-chains bind the natural regulator diphosphoglycerate, which assists in the unloading of oxygen. The gamma-chain isoforms do not bind diphosphoglycerate as well and therefore have a higher affinity for oxygen. In the low-oxygen environment of the placenta, oxygen is released from adult hemoglobin. In this same environment, fetal hemoglobin does not give away oxygen, but binds it. This small difference in oxygen affinity mediates the transfer of oxygen from the

mother to the fetus. Within the fetus, the myoglobin of the fetal muscles has an even higher affinity for oxygen, so oxygen molecules pass from fetal hemoglobin for storage and use in the fetal muscles. Fetal hemoglobin is not deleterious to the newborn, and in humans, the replacement of fetal hemoglobin-containing blood cells with adult hemoglobin-containing blood cells is not complete until about 6 months after birth.

Molecular Genetics

The gamma locus determines the gamma chain of fetal hemoglobin (alpha-2/gamma-2). Two types of gamma polypeptide chains do exist. Although not distinguishable by most of the physical methods used, sequencing has shown at least 1 amino acid difference: at position 136 one type has glycine (G-gamma) and the second type has alanine (A-gamma). The ratio of G-gamma to A-gamma is fairly constant (about 7:3) during the fetal period. The ratio declines progressively during the postnatal gamma-to-beta switch, leading to an average value of 2:3 in the small residual amount of Hb F detectable in normal adult blood. In a normal human genome there are usually four gamma structural loci, two on each autosome that presumably arose by gene duplication.

A number of mutations have been identified that interfere with the normal process of hemoglobin switching and result in hereditary persistence of fetal hemoglobin. Several single-base substitutions located within the promoter regions of the gamma genes appear to be responsible for the hereditary persistence of fetal hemoglobin phenotype.

Hematologic correlations with restriction mapping suggest that a region of DNA near the 5-prime end of the delta gene may be involved in the cis-suppression of gamma-globin gene expression in adults. The beta-globin locus control region is a powerful regulatory element required for high-level globin gene expression. Nucleotide sequences of the beta-



globin locus control region were originally described as a cluster of DNase I hypersensitive sites 6 to 18 kb upstream to the epsilon-globin gene. The hemoglobin beta locus control region is thought to organize the entire 60-kb beta-globin gene cluster into an active chromatin domain and allows a high level of position-independent, copy number-dependent, and erythroid-specific globin gene expression.

Epidemiology in the Arab World

Algeria

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.

Saudi Arabia

Wood et al. (1980) studied fetal hemoglobin (HbF) synthesis in 22 cases of sickle cell anemia from Saudi Arabia and compared with an equal number of cases of African origin. Among the Saudi Arabs gamma chain synthesis ranged from 4.0% to 19.9% of the total non-alpha chain synthesis (mean 8.1%) while the corresponding range for the Negro cases was < 0.3% to 4.6% (mean 1.7%). In both groups the peripheral blood HbF level was on average 3-4 times higher than the proportion synthesized, indicating that the selective survival of HbF containing cells (F cells) was an important factor in determining the final HbF levels. Among the Saudi Arab cases there was a significant negative correlation between the degree of F cell enrichment and either the HbF level of the percentage gamma chain synthesis. No such correlation was observed among the Negro cases. Wood et al. (1980) realized that a high proportion of the cases in both groups were carriers of alpha thalassemia in addition to sickle cell, but did not observe any effect of alpha thalassemia on HbF production.

Patients from the eastern province of Saudi Arabia who have sickle cell anemia have high circulating levels of fetal hemoglobin, 17% Hb F on the average, and, as a consequence, have a mild form of the disease. Miller et al. (1987) found a single-base cytosine-to-thymidine substitution at the 158 bp 5-prime to the cap (preinitiation) site of the G-gamma-

globin gene of the high-hemoglobin-F chromosome. The substitution was present in nearly 100% of patients with sickle cell disease or trait and in 22% of normal Saudis. Homozygosity for this mutation had no demonstrable effect on hemoglobin F production in the normal Saudi population. Miller et al. (1987) concluded that 'the substitution appears to be necessary for the production of high levels of hemoglobin F, but is not sufficient alone.'

United Arab Emirates

In a hematologically normal newborn baby originating from the United Arab Emirates, Abbas et al. (1995) identified a rapidly migrating fetal hemoglobin variant and showed by miniaturized techniques of protein chemistry that the mutation resided in the G-gamma chain and resulted in a lys59-to-glu substitution.

References

- Abbas S, Fitzgerald PA, Varady E, Girot R, Pic P, Blouquit Y, Ducrocq R, Drupt F, Wajcman H. Two fetal hemoglobin variants affecting the same residue: Hb F-Emirates [G gamma 59(E3)Lys->Glu] and Hb F-Sacromonte [G gamma 59(E3)Lys->Gln] Hemoglobin. 1995; 19(3-4):173-82. PMID: 7558873
- Miller BA, Olivieri N, Salameh M, Ahmed M, Antognetti G, Huisman TH, Nathan DG, Orkin SH. Molecular analysis of the high-hemoglobin-F phenotype in Saudi Arabian sickle cell anemia. N Engl J Med. 1987; 316(5):244-50. PMID: 2432426
- Wood WG, Pembrey ME, Serjeant GR, Perrine RP, Weatherall DJ. Hb F synthesis in sickle cell anaemia: a comparison of Saudi Arab cases with those of African origin. Br J Haematol. 1980; 45(3):431-45. PMID: 6158984
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Related CTGA Records

Fetal Hemoglobin Quantitative Trait Locus 1

Hemoglobin--Beta Locus

Sickle Cell Anemia

External Links

<http://globin.cse.psu.edu/html/huisman/variants/>

<http://harvester.embl.de/harvester/P620/P62027.htm>



Contributors

Ghazi O. Tadmouri: 15.5.2006

Ghazi O. Tadmouri: 30.10.2005

Ghazi O. Tadmouri: 22.9.2004

