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Genetic and Phenotypic Characteristics of Hb H Disease in the Azerbaijani Population

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Relevance

The Republic of Azerbaijan is among the countries with a high prevalence of hereditary anemias—hemoglobinopathies. Among this large group, β- and α-thalassemias are the most common. In the complex mechanism of anemia development in thalassemias, the main role is played by impaired synthesis of one or more globin chains, leading to reduced hemoglobin production and globin chain imbalance. Hb H disease is characterized by deletion of three α-globin genes, leading to an excess of β-chains in the form of β4 tetramers. Clinical manifestations of Hb H disease in Azerbaijan are highly polymorphic, which may be explained by the diversity of molecular defects underlying this condition. Currently, more than 500 point mutations and deletions affecting β- and α-globin genes have been identified worldwide, each population having its own mutation spectrum.

Objective

To identify the spectrum of α-thalassemic mutations characteristic of the Azerbaijani population and to study the phenotypic manifestations of their various combinations in Hb H disease.

Materials and Methods

The study included 80 patients diagnosed with Hb H disease showing varying clinical manifestations, and 105 α-thalassemia carriers (mainly close relatives). Hb H was detected by electrophoresis, and α-thalassemia mutations were identified using dot-blot hybridization (α-globin Strip Assay) and DNA sequencing.

Results

Fifteen α-thalassemic mutations were identified in the Azerbaijani population: 3.7 kb DEL, 4.2 kb DEL, 20.5 kb DEL, MED DEL, α2 Poly A-1, α2 Poly A-2, α2 IVS-1 5nt DEL, α2 Codon 142 (T>C) - Hb CS, α1 Codon 59 (G>A) - Hb Adana, c.389 (T>C), αααanti 3.7 triplication, c.134_135 insC, --THAI/αα, c.3G>A (p1:p.2?), c.45(G>A). The mutation spectrum was dominated by deletions, with double deletion 20.5 kb (n=100) and single deletion 3.7 kb (n=75) being the most frequent. Point mutations were much rarer.

Among patients with the heterozygous form of the disease, α+-thalassemia was found in 51 individuals and α0-thalassemia in 54. Two individuals showed homozygosity for α+-thalassemia (-α/-α). More than 30 different genotypes were identified in patients with Hb H disease. The most frequent was the combination of single and double deletions (--/-α) in 54 patients. In 21 patients, a combination of deletional and non-deletional mutations (--/ααT) was found, and in 5 cases homozygosity for non-deletional defects (αTα/αTα). This high genetic heterogeneity explains the variability in hematological and clinical parameters.

All patients with Hb H disease showed reduced hematological parameters (Hb, MCV, MCH) compared to controls, with lower values in homozygous and compound heterozygous mutations. RBC counts were elevated in deletional compounds but normal in point mutations. Patients with non-deletional mutations had lower HbA2 and higher Hb H levels.

Phenotypic Manifestations

Genotypic heterogeneity of Hb H disease in Azerbaijan is also reflected in the polymorphism of clinical presentation. The phenotype usually resembles intermediate thalassemia, with moderate hemolytic anemia of varying severity, hepatosplenomegaly, and occasional acute hemolytic crises triggered by oxidative drugs or infections.

In patients with deletional genotypes, the clinical course was mild, with disease onset in later life and often discovered incidentally. Many women were diagnosed during pregnancy, often with concurrent iron deficiency anemia. In contrast, patients with point mutations had early disease onset, more severe anemia, high reticulocytosis, frequent crises, and splenomegaly. These patients often required periodic or regular red cell transfusions. However, deletional genotypes are predominant in the local population, and severe clinical forms of Hb H disease are rare.