

Double heterozygosity of the thalassemic mutations term. Cd +6 C→G and IVS-I-110 in a Greek woman: A case presentation

Yunan bir kadında çift heterozigozit talasemik mutasyonlar terimi Cd +6 C → G ve IVS-I-110: Bir olgu sunumu

Stamatia Theodoridou, Vasilios Perifanis, Stella Kotsiopoulou, Olga Karakasidou, Vasiliki Aletra, Michael Alemayehou

Haemoglobinopathy Prevention Unit, Hippokration Hospital of Thessaloniki, Greece

To the Editor

The phenotypic and molecular diversity of compound heterozygosity for thalassemic genes in Greece is extensive. The interaction of silent and classic β -thalassemia results in the clinical phenotype of thalassemia intermedia.

We report the clinical and hematological findings in an 18-year-old female referred to our hemoglobinopathy prevention unit that was observed to be compound heterozygote for the β -thalassemia mutations termination Cd +6 C→G and IVS-I-110. Her parents were heterozygous for 1 of the 2 thalassemia genes. Termination Cd +6 C→G in the 3' untranslated region (3'UTR of the β -globin gene (+1480 C→G) mutation is very rare and was previously reported in only a few Greek families [1,2].

The young woman had been followed-up since childhood for anemia, prior to the definitive characterization of her β genotype. Her clinical phenotype was mild, with anemia and slight splenomegaly, but without jaundice or the need for transfusion. Her

growth and development as a child were satisfactory. Hematological data of the propositus were as follows: Hb: 8.2 g/dL; Hct: 25.2%; MCV: 60.4 fL; MCH: 19.5 g/dL; RBC: $4180 \times 10^3 \mu\text{L}$. Her ferritin level was 27 ng/mL and HPLC hemoglobin variant analysis showed Hb A2 was 6.6% and Hb F was <2%. Microscopic examination of a stained peripheral blood smear showed severe anisocytosis, microcytosis, and basophilic stippling. No erythroblasts were noted. Written informed consent was obtained from the patient.

Hematological findings in the mother were as follows: Hb: 12.2 g/dL; Hct: 38.1%; MCV: 67 fL; MCH: 21 g/dL; RBC: $5690 \times 10^3 \mu\text{L}$; Hb A2: 5%; Hb F: <2%. Her father's hematological data were within normal limits (with the exception of an Hb A2 level of 3.4%), as follows: Hb: 14.9 g/dL; Hct: 45.3%; MCV: 87 fL; MCH: 28.6 g/dL; RBC: $5190 \times 10^3 \mu\text{L}$.

Molecular examination showed that the mother carried the typical β -thalassemia mutation IVS-I-110, which is the most common β -thalassemia mutation in the Greek population [3] and the father carried

the rare β -thalassemia (++) silent mutation termination Cd +6 C→G. Previously reported data show that the C→G mutation at position 6 3' to the termination codon is a mild β -thalassaemia mutation that causes a slight reduction in the level of β -globin mRNA and β -globin chain synthesis. In accordance with the literature, hematological findings in the heterozygous father with this mutation were within the normal range, except for a slightly elevated Hb A2 level. As reported by Maragoudaki et al. [2], heterozygotes for the mutation +1480 C→G have normal red cell indices, morphology, and osmotic fragility. Hb A2 and F values are within the normal range and globin-chain synthesis is slightly unbalanced. They also reported 5 cases of compound heterozygosity for +1480 C→G and IVSI-110 that had the mild clinical phenotype; their hemoglobin levels varied from 8 to 10.5 g/dL and Hb F ranged between 2.6% and 10.3%.

In conclusion, the clinical phenotype of the combination of the 2 mutations is a mild disease with a non-transfusion-dependent thalassemia intermedia phenotype. According to the literature [1] the C→G mutation at position 6 3' is characterized by a slight decrease in the stability of mRNA, which becomes clinically important only when beta chain synthesis in trans is severely decreased or completely elimi-

nated. Identification of such combinations is important for the genetic counseling of couples at risk in countries such as Greece, in which the high frequency of hemoglobinopathies has a major impact on public health.

Conflict of interest statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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