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SHORT COMMUNICATION



Compound Heterozygosity for Hb Adana (*HBA2*: c.179G>A) and the $-\alpha^{3.7}/\alpha\alpha$ Thalassemia Deletion in Greece: Clinical Phenotype and Genetic Counseling

Stamatia Theodoridou^a, Aikaterini Teli^b, Eleni Yfanti^c, Timoleon-Achilleas Vyzantiadis^d, Theodoros Theodoridis^e and Marina Economou^b

^aHaemoglobinopathy Prevention Unit, Hippokraton Hospital of Thessaloniki, Thessaloniki, Greece; ^bFirst Department of Paediatrics, Aristotelion University of Thessaloniki, Thessaloniki, Greece; ^cThalassaemia National Centre of Greece, Laikon General Hospital of Athens, Athens, Greece; ^dFirst Department of Microbiology, Medical School, Aristotelion University of Thessaloniki, Thessaloniki, Greece; ^eFirst Department of Obstetrics and Gynaecology, Aristotelion University of Thessaloniki, Thessaloniki, Greece

ABSTRACT

Hb Adana (*HBA2*: c.179G>A) is found worldwide but is extremely rare and carriers are asymptomatic, with red cell indices similar to α^+ -thalassemia (α^+ -thal) carriers. First line screening tests are unable to detect the unstable hemoglobin (Hb). Coinheritance with the α -thal ($-\alpha^{3.7}$) deletion is herein presented and the challenges involving genetic counseling of couples carrying the mutations are discussed.

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Hb Adana (*HBA2*: c.179G>A) in interaction with deletional and nondeletional α -thalassemia (α -thal) mutations leads to Hb H or, less commonly, to α -thal intermedia (α -TI) with clinical manifestations varying from asymptomatic forms to severe anemia [1,2]. Hb Adana carriers are asymptomatic with normal or nearly normal Hb levels and red cell indices similar to α^+ -thal carriers, whereas homozygous Hb Adana manifests as hydrops fetalis [3]. First line screening tests are unable to detect the highly unstable variant, which is the second most common nondeletional α -thal mutation in Southeast Asia, but also found in different parts of the world [4–10]. We report two cases of Hb Adana with a coinherited α -thal ($-\alpha^{3.7}$) deletion; the only α -thal and Hb Adana double heterozygosity cases diagnosed in subjects of Greek origin.

First case

The first case concerns a 3-year-old girl, born to parents referred for genetic counseling at the 11th week of a second gestation. The couple was referred because the mother's blood results showed a hemoglobin (Hb) level of 10.7 g/dL, red blood cell (RBC) count of $4.04 \times 10^{12}/L$, mean cell volume (MCV) 80.7 fL, mean cell Hb (MCH) 26.4 pg, Hb A₂ 2.8% and Hb F 1.0%, with positive inclusion bodies, while her ferritin level was 11.0 ng/mL and her ethnic and regional background was at high risk for thalassemia.

Her partner, who came from the same region, was screened and his blood test showed an Hb of 13.8 g/dL, RBC

$5.88 \times 10^{12}/L$, MCV 73.1 fL, MCH 23.5 pg, Hb A₂ 2.4% and Hb F 1.0%, while his ferritin level was 173.0 ng/mL with inclusion bodies found positive for α -thal. Carrier identification is carried out at all Thalassaemia Prevention Units following a standard scheme that includes all the above mentioned tests.

Molecular analysis for both α - and β -globin genes was requested for the couple. As mild anemia in their first offspring was reported, routine investigation was suggested for the 3-year-old girl demonstrating an Hb of 8.2 g/dL, RBC $3.82 \times 10^{12}/L$, MCV 70.0 fL, MCH 22.0 pg, Hb A₂ 1.9% and Hb F 2.3%. Her ferritin level was 226.0 ng/mL and inclusion bodies were found positive after incubation. On clinical examination, the child was found to be of normal weight and height for her age, albeit, paleness, icteric sclera and mild splenomegaly were noted. Genetic analysis revealed that the mother carried the most prevalent α -thal ($-\alpha^{3.7}$) deletion defect in Greece, reported in individuals from the Mediterranean area, the Middle East, Africa, and Asia. The father carried the rare nondeletional Hb Adana mutation [$\alpha 59(E8)Gly \rightarrow Asp$, *HBA2*: c.179G>A] on the $\alpha 2$ -globin gene, one among the severe nondeletional α -thal gene mutations known [1]. As suspected from the hematological data, the 3-year-old offspring was found to be a compound heterozygote for Hb Adana *in trans* to a 3.7 kb α^+ -thal deletion. The couple was counseled regarding the possibility of having another offspring with the same compound heterozygosity and was informed regarding the possible clinical phenotypes involved.

Second case

The second case concerns a 17-year-old boy followed at our Thalassaemia Clinic, First Department of Paediatrics, Aristotelion University of Thessaloniki, Thessaloniki, Greece, who was diagnosed at the age of 8 to carry Hb Adana on the $\alpha 2$ -globin gene in coinheritance with the $-\alpha^{3.7}$ α -thal deletion [8]. As mentioned by Economou *et al.* [8], the findings were compatible with a very mild phenotype, diagnosis being totally incidental, anemia being mild and growth not having been impaired.

Although the boy retained a mild hypochromic microcytic anemia until adolescence (Hb \sim 10.0 g/dL, MCV 71.0 fL, MCH 23.0 pg, RBC distribution width (RDW) 18.6%, reticulocyte count 5.1%), at the age of 11, it was decided that transfusions were needed due to marked splenomegaly, in addition to limited weight and height gain. For the following few years, the boy was transfused monthly, necessitating chelation therapy. Weight, height and pubertal development were normal by the age of 15, however, splenomegaly persisted. It was decided to perform a splenectomy and transfusions were stopped shortly afterwards. During the following months the boy retained an Hb of 9.5 g/dL but complained of constant fatigue and impaired physical activity and was once more put on a regular transfusion program, in accordance to his request.

The spectrum of α -thal determinants in Greece is variable, the relative incidence being approximately 5.0–10.0%. The correlation of phenotype with genotype in Hb H in Greece has been previously demonstrated [11], showing that the majority of Hb H disease patients present with a mild clinical course, only few genotypes being associated with a severe phenotype. According to this data, there is no indication for prenatal diagnosis of Hb H in the Greek population with the exception of specific genotypes. The Greek National Haemoglobinopathy Registry [12] has aimed to provide all available clinical information, while the ongoing National Screening Programme aims at continuous identification of different variant combinations so as to enable timely and correct genetic counseling of couples at risk. That is of great importance in countries that, as Greece, have a high frequency of hemoglobinopathies that can have a major impact on public health.

In view of the limited data available on such a rare coinheritance, we report the clinical phenotype of the only two cases of Hb Adana and $-\alpha^{3.7}/\alpha\alpha$ compound heterozygosity diagnosed in subjects of Greek origin. In both the cases described, diagnosis was incidental, highlighting the mild phenotype that usually accompanies coinheritance of α -globin gene mutations with unstable α chain variants [2]. However, α -thal presents with great clinical diversity and the experience in cases that are due to nondeletional mutations is limited. The coinheritance of Hb Adana, a very unstable α chain variant, with the $-\alpha^{3.7}$ α^+ -thal deletion is rare, the other two cases reported to date being of Albanian origin and presenting with a clinical phenotype of α -TI [5]. Hb Adana (on the $\alpha 2$ - or $\alpha 1$ -globin gene) coinherited with other α -thal mutations or deletions is

reported in only a few other families in Turkey [4], Southeast Asia [2], Philippines [7] and Indonesia [10]. As reported before, Hb Adana can lead to Hb H hydrops fetalis when associated with an α -thal-1 deletion *in trans* and in association with the α^0 -thal allele ($-\alpha^{\text{FIL}}$) [7] or to severe α -TI combined with a mutation at codon 24 (*HBA2*: c.75T>A) [10]. It seems that compound heterozygotes for Hb Adana on the $\alpha 2$ -globin gene manifest a more severe phenotype compared to Hb Adana on the $\alpha 1$ -globin gene, depending on the coinherited mutation (deletional or nondeletional).

Certain genotypes found in compound heterozygosity with thalassaemic genes do not always reflect a specific phenotype. Even compounds that normally lead to mild non transfusion-dependent thalassaemia intermedia can be associated with more severe and rare clinical phenotypes. It seems that other factors, besides the specific molecular mutation and the absolute hematological indices, determine the pathway between genotype and phenotype. In addition, phenotypes may change over time, as demonstrated by the second case described above. Long follow-up of such rare cases is necessary in order to gain as much information as possible, so as to offer the best management to the patients and the most accurate counseling to their families.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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