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# Compound Heterozygosity for Silent Cap +1570 (T>C) *(HBB:* c*96T>C), Codon 39 (C>T) (*HBB*: c.118C>T) and the Presence of $\alpha\alpha\alpha^{anti-3.7}/\alpha\alpha$ in Greece. A Case Presentation

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SHORT COMMUNICATION



# Compound Heterozygosity for Silent Cap +1570 (T>C) (*HBB:* c*96T>C), Codon 39 (C>T) (*HBB*: c.118C>T) and the Presence of $\alpha\alpha\alpha^{anti-3.7}/\alpha\alpha$ in Greece. A Case Presentation

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**ABSTRACT**

The rare point mutation Cap +1570 (T>C) (*HBB*: c*96T>C) has been reported in families of Czech, Greek, Turkish and Italian origin. The mutation contributes to a reduction of the β-globin chain synthesis, and in heterozygous carriers, it causes a silent phenotype, while in compound heterozygosity with severe β-thalassemia (β-thal) mutations, it leads to a non transfusion dependent β-thal intermedia (β-TI) state. We report a case of compound heterozygosity for codon 39 (C>T) (*HBB*: c.118C>T) and Cap +1570, in addition to the presence of $\alpha\alpha\alpha^{anti-3.7}/\alpha\alpha$.

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β-Thalassemia (β-thal) is one of the most extensively studied genetic diseases with remarkably different clinical phenotypes. The molecular basis of the phenotypic diversity of β-thal is reported in existing databases [1]. Understanding the relationship between genotype and phenotype is very beneficial in clinical practice for the appropriate treatment in homozygous or compound heterozygous patients as well as for the prediction of the phenotype in genetic counseling of at-risk couples.

The very rare point mutation Cap +1570 (T>C) (*HBB*: c*96T>C) has been reported in families of Czech [2], Greek [3], Turkish [4] and Italian [5] origin. The mutation contributes to a reduction of the β-globin chain synthesis. In heterozygous carriers, it causes a silent phenotype, while in compound heterozygosity with severe β-thal mutations, it leads to a β-thal intermedia (β-TI) state.

The coinheritance of the silent Cap +1570 defect and severe β-thal mutations has been previously reported in Italy by Vinciguerra *et al.* [5]. Although the phenotypic and molecular variety of compound heterozygosity for thalassemic genes is excessive in Greece, to the best of our knowledge, only seven cases of Cap +1570 have been reported in Greece [3]. We report the first observed case of a compound heterozygosity for codon 39 (C>T) (*HBB*: c.118C>T) and Cap +1570, in addition to the presence of $\alpha\alpha\alpha^{anti-3.7}/\alpha\alpha$ in a Greek patient.

## Case report

A 51-year-old Greek female, with a history of β-TI presented at the Thalassaemia Unit, Hippokration Hospital of Thessaloniki, Thessaloniki, Greece, for further investigation due to worsening of her anemia. As a child, growth and development were satisfactory and presented neither bone deformities nor thalassemic facies. She had been followed up since her youth with the clinical phenotype of β-TI with the need of occasional blood transfusions during pregnancy and infections (six units).

At presentation, clinical examination revealed splenomegaly with a longitudinal measure of 220 mm (normal <130 mm) and extramedullary hematopoiesis with a paraspinal mass of 3 cm. Hematological findings of the proband were as follows: hemoglobin (Hb): 8.2 g/dL, hematocrit [or packed cell volume (PCV)]: 0.27 L/L, mean cell volume (MCV) 69.0 fL, mean cell Hb (MCH) 21.0 pg, while high performance liquid chromatography (HPLC) variant analysis showed Hb $A_2$: 5.1% and Hb F: 19.0%. Severe anisocytosis, microcytosis, basophilic stippling and erythroblasts (25.0%) were noted in her blood smear. Her ferritin levels before blood transfusion were of 800.0 ng/mL and liver magnetic resonance imaging (MRI) T2* was 4.7 msec (normal value <6.3 msec), liver iron concentrate (LIC) 11 mgr/g dry weight and heart MRI T2* 33 msec (normal values >20 msec). Bone marrow examination showed erythroblastic reaction.

Molecular examination showed that she carried the codon 39 mutation and Cap +1570, in addition to the presence of $\alpha\alpha\alpha^{anti-3.7}/\alpha\alpha$. Compound heterozygosity for Cap +1570 and $\alpha\alpha\alpha^{anti-3.7}/\alpha\alpha$ was found in her mother and compound heterozygosity for codon 39 and $\alpha\alpha\alpha^{anti-3.7}/\alpha\alpha$ was also found in both her father and her

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**Table 1.** Hematological and molecular findings in the studied family members.

| Parameters | Proband | Father | Mother | Son |
|---|---|---|---|---|
| Sex-age (years) | F-52 | M-88 | F-77 | M-29 |
| RBC ($10^{12}$/L) | 3.86 | 4.98 | 4.78 | 5.49 |
| Hb (g/dL) | 8.2 | 10.7 | 14.3 | 10.8 |
| MCV (fL) | 69.0 | 67.1 | 87.9 | 62.1 |
| MCH (pg) | 21.0 | 33.4 | 42.0 | 34.1 |
| Hb $A_2$ (%) | 5.1 | 6.4 | 3.0 | 6.5 |
| Hb F (%) | 19.0 | 3.1 | <2.0 | 2.3 |
| α Gene mutation | $\alpha\alpha\alpha^{anti-3.7}/\alpha\alpha$ | $\alpha\alpha\alpha^{anti-3.7}/\alpha\alpha$ | $\alpha\alpha\alpha^{anti-3.7}/\alpha\alpha$ | $\alpha\alpha\alpha^{anti-3.7}/\alpha\alpha$ |
| β Gene mutation | c.118C>T/c*96T>C | c.118C>T | c*96T>C | c.118C>T |

RBC: red blood cell count; Hb: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular Hb; c.118C>T: codon 39 (C>T); c*96T>C: Cap +1570 (T>C).

son. The laboratory findings of the patient and the family are shown in Table 1.

She started receiving hydroxycarbamide and was advised to start either regular transfusions or have a splenectomy or both, but she refused. She receives occasional deferasirox (according to the results) as it is anticipated that even without transfusions, patients with β-TI present liver iron overload due to low hepsidine levels and the need for chelation therapy [6].

The spectrum of β-thal determinants in Greece is variable with the relative incidence being approximately 5.0-10.0% [3]. The Cap +1570 is a very rare silent mutation located 12 nucleotides upstream of the polyadenylation signal in the 3′ untranslated region (3′UTR) of the β-globin gene.

The presence of this defect in heterozygous carriers is probably misdiagnosed as the carriers have normal red cell indices and morphology as well as Hb $A_2$ and Hb F levels [5]. As this mutation contributes to a slight reduction of the β-globin chain synthesis, the coinheritance of a severe β-thal may lead to a state of β-TI phenotype, depending on the specific molecular mutations.

The presented case is the first reported in Greece with this rare combination with a phenotype of β-TI and the need for sporadic transfusions. In view of the rarity of such cases, it is useful to report the presented data. Vinciguerra *et al.* [5], have reported the case of a 71-year-old woman with the same molecular defects and the clinical phenotype of β-TI without requiring regular transfusions.

The molecular heterogeneity of thalassemia in Greece is well defined. The identification of combinations of silent defects with severe thalassemia mutations is essential for the genetic counseling of at-risk couples in countries such as Greece where the high frequency of hemoglobinopathies has a major impact on public health. Greece is a pioneering Mediterranean country in the implementation of both a national hemoglobinopathy prevention program and a structured patient management plan. As this silent mutation cannot be detected with first-line screening tests, an option could be to screen the partners of β-thal carriers for the severe mutation, as well as for the silent β-globin gene mutations, in order to provide the appropriate genetic counseling for the couples at-risk. It appears that even if the indication of prenatal diagnosis is not strictly accurate for co-heredity of the silent Cap +1570 mutation with severe β-thal defects as it leads to a β-TI state, parents must be informed if the result is the clinical phenotype and of the need of occasional blood transfusions for their offspring.

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## 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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