A Novel Mutation of the δ -Globin Gene in an Asymptomatic 30-Year-Old Female

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δ -Thalassemia (OMIM No. 142000) resulting from mutations on the HBD gene usually has no clinical consequences, but it may cause a reduced rate of hemoglobin A₂ (HbA₂) [1, 2]. Human HbA₂ ($\alpha_2\delta_2$), which contains δ -globin, represents a minor fraction of the Hb found in human adults. In normal individuals, it constitutes between 2.5 and 3.3% of the total adult Hb content as measured by high-performance liquid chromatography [3].

Although genetic defects (δ -thalassemia or HbA₂ variants) that decrease HbA₂ levels (2% in heterozygote or $\leq 0.6\%$ in homozygote subjects) do not affect health, they can

hinder the diagnosis of the β -thalassemia trait [4]. Values of HbA₂ $>3.2\%$ associated with microcytosis characterize the β -thalassemia trait [3]. However, the coinheritance of β -globin and δ -globin gene mutations can decrease HbA₂ values to normal or lower levels due to a decreased δ -chain production. As iron deficiency anemia is also characterized by low HbA₂ levels, this disease must firstly be ruled out by evaluating iron parameters. Subsequently, a δ -globin mutation screening should be performed, especially in subjects from geographic areas with a high incidence of β -thalassemia carriers.

Here, we report a novel mutation of the δ -globin gene which was found in an asymptomatic 30-year-old female from Messina (Sicily, Italy) during a routine screening for thalassemia. We performed biochemical and genetic tests after informed consent was provided by the patient. Hematological parameters and serum ferritin were normal. We found low HbA₂ levels on high-performance liquid chromatography screening (HbA₂ 1.4%). However, as the patient was from a geographic area with a high prevalence of β -thalassemia, we performed automatic sequencing of the β -globin gene (ABI 3130 analyzer, Applied Bio-

Fig. 1. Electropherogram showing the novel δ -globin gene mutation: cd147 T>C.

systems, Foster City, CA, USA). DNA extraction was performed according to standard methods. No mutations of the β -globin gene were found.

Therefore, we amplified DNA samples by polymerase chain reaction to analyze the entire δ -globin gene (promoter region, all exons, and exon-intron junctions) [5]. The amplified samples were subjected to automatic sequencing (ABI 3130 analyzer; Applied Biosystems, Foster City, CA, USA) utilizing the BigDye Terminator Cycle Sequencing kit v3.1 (Applied Biosystems).

We found a novel TGA>CGA (stop to Arg) mutation at cd147 of the δ -globin

gene in a heterozygous state (Fig. 1). Previously, Alkindi et al. [6] described for the first time a TGA>TTA (stop to Leu) mutation at cd147 in a heterozygous state in a subject who was also homozygous for $-\alpha^{3.7}$ allele. The subject was also asymptomatic and was identified during a screening for β -thalassemia screening.

Thus, to the best of our knowledge, only 2 mutations have been found in cd147: TGA>CGA (stop to Arg) and TGA>TTA (stop to Leu). Both mutations cause an elongation of 15 amino acids in the protein carboxy terminal. We hypothesize that this elongated δ -globin, similarly to the elon-

gated polypeptides α -globin and β -globin, would be unstable [6]. Certainly, the number of mutations on the δ -gene has increased greatly and about 117 δ -globin gene mutations have been reported so far (<http://globin.cse.psu.edu/hbvar/menu.html>) [7].

The presence of HBD mutations could compromise the diagnosis of β -thalassemia carriers as it produces a lower HbA₂. Therefore, the molecular screening of δ -globin gene mutations could be useful for the genetic counseling of at-risk couples from geographic areas in which thalassemia is common.

References

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