Hb Évora [α2-35, Ser→Pro], a novel hemoglobin variant associated with an α-thalassemia phenotype

Haematologica 2007; 92:(5)e68

Gomes and colleagues recently reported a missense mutation involving amino acid codon 35 of the α2-globin gene (TCC→CCC, Ser→Pro).[1] This mutation was found in members of two unrelated families, both of Portuguese Caucasian background. The carriers had an α^+-thalassemia phenotype with mild microcytosis and hypochromia. The authors postulated that the mutation gives rise to a highly unstable Hb variant, which was named Hb Évora. This mutation was first reported by us in 2001.[2] The affected infant was a compound heterozygote for the codon 35 TCC→CCC mutation and the Filipino α^0-thalassemia deletion, and was afflicted with the Hb H hydrops fetalis syndrome. The newborn was delivered at 34.5 weeks of gestation because of fetal distress. He had severe anemia, pericardial effusion, hepatosplenomegaly, bilateral inguinal testes and ambiguous genitalia. The infant had a stormy postnatal course and was transfused six times during the first four months of life. Both his parents were of Filipino descent, living in California (USA). The father was heterozygous for the codon 35 TCC→CCC mutation and had mild microcytosis and hypochromia, absence of Hb H inclusion bodies, and normal level of Hb A_2. An abnormal Hb could not be detected by IEF or HPLC. Furthermore, synthesis of a variant Hb could not be demonstrated by *in vitro* labeling of newly synthesized globin chains with [^{3}H]-leucine.[2] Taken together, these observations are consistent with hyperinstability of the mutant globin chain or Hb.

We have subsequently developed a multiplex PCR-ARMS diagnostic test to detect the codon 35 TCC→CCC mutation and five other α2-globin gene mutations (Hb Constant Spring, Hb Quong Sze, initiation codon ATG→A-G, codon 30 DGAG, codon 59 GGC→GAC). All have been associated with severe Hb H disease phenotypes or Hb H hydrops fetalis syndrome.[3] We have since identified a Canadian woman of Filipino descent who was heterozygous for the codon 35 TCC→CCC mutation. She too had the phenotype of α^+-thalassemia trait.

The frequency and population distribution of the α2-globin gene codon 35 TCC→CCC mutation remain to be ascertained. The mutation has now been reported in at least four unrelated families, two originating from the Philippines and two from Portugal. Given the historical relationship between the Portuguese and Filipino populations, it is tempting to speculate a common western Mediterranean origin for this mutation.

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