

Thalassemia intermedia in HbH-CS disease with compound heterozygosity for β -thalassemia: Challenges in hemoglobin analysis and clinical diagnosis

Abstract

Co-inheritance of α -thalassemia with homozygosity or compound heterozygosity for β -thalassemia may ameliorate β -thalassemia major. A wide range of clinical phenotypes is produced depending on the number of α -thalassemia alleles ($-\alpha/\alpha\alpha$, $--/\alpha\alpha$, $--/-\alpha$). The co-inheritance of β -thalassemia with α -thalassemia with a single gene deletion ($-\alpha/\alpha\alpha$) is usually associated with thalassemia major. In contrast, the co-inheritance of β -thalassemia with two α -genes deleted in cis or trans ($--/\alpha\alpha$ or $-\alpha/-\alpha$) generally produces β -thalassemia intermedia. In Southeast Asia, the most common defect responsible for α -thalassemia is the Southeast Asian (SEA) deletion of 20.5 kilobases. The presence of the SEA deletion with Hb Constant Spring (HbCS) produces HbH-CS disease. Co-inheritance of HbH-CS with compound heterozygosity for β -thalassemia is very rare. This study presents a Malay patient with HbH-CS disorder and β^0/β $+$ -thalassemia. The SEA deletion was confirmed in the patient using a duplex-PCR. A Combine-Amplification Refractory Mutation System (C-ARMS) technique to simultaneously detect HbCS and Hb Quong Sze confirmed HbCS in the patient. Compound heterozygosity for CD41/42 and Poly A was confirmed using the ARMS. This is a unique case as the SEA α -gene deletion in cis ($--$ SEA/ $\alpha\alpha$) is generally not present in the Malays, who more commonly possess the two α -gene deletion in trans ($-\alpha/-\alpha$). In addition, the β -globin gene mutation at CD41/42 is a common mutation in the Chinese and not in the Malays. The presence of both the SEA deletion and CD41/42 in the mother of the patient suggests the possible introduction of these two defects into the family by marriage with a Chinese.

Keyword: Amplification refractory mutation system; CD41/42; Duplex-PCR; Hb constant spring; Poly A; Thalassemia intermedia