Partial Mispairing and Crossing-Over Between $\beta^0$ and $\delta$ Genes as the Origin of the $\delta \beta^0$ Thalassemia Gene

A Single Mutational Event Hypothesis

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Summary. Two double heterozygous $\beta^0/\delta \beta^0$ thalassemic sibs of Mexican descent were studied. The father had a $\beta/\beta^0$ genotype, while the mother, one sib and several maternal relatives were $\beta/\delta \beta^0$ heterozygotes. Parental consanguinity and an apparently low frequency of thalassemia among Mexicans suggested a possible common origin of both $\beta^0$ and $\delta \beta^0$ genes. A hypothesis to explain such a possibility is proposed on the basis of a partial mispairing between $\beta^0$ and $\delta$ genes followed by a crossing-over which would result in a $\delta \beta^0$ recombinant gene. This hypothesis could also be extended to explain the $\beta \ 22 \text{ glu} \rightarrow \text{ala}$, $\delta \ 22 \text{ ala} \rightarrow \text{glu}$ and $\delta \ 116 \text{ arg} \rightarrow \text{his}$ Hb variants as recombinants from double crossing-over between $\beta$ and $\delta$ mispaired genes for which the name "interstitial-Lepore" is proposed.

The $\beta$ thalassemias constitute a heterogeneous group of inherited hemoglobinopathies in which $\beta$-chain synthesis can either be reduced or absent (Weatherall, 1976). The latter form is known as $\beta^0$ thalassemia, which in some cases is due to the absence of $\beta$-globin messenger RNA ($\beta$-mRNA) as judged by hybridization to complementary DNA, prepared with viral reverse transcriptase (Forget et al., 1974), and by translation both in whole cells and in cell-free protein synthesis systems (Benz et al., 1975). In other cases the $\beta$-mRNA is present but not translated in the erythroid cell cytoplasm (Conconi et al., 1972; Kan et al., 1975; Weatherall, 1976). Although various types of $\beta^0$ thalassemia could be deduced from the heterogeneity of results of different investigators (Weatherall, 1976), Forget and Hillman (1977) have recently concluded that until specific structural differences in the $\beta$-globin gene of $\beta^0$-thalassemics are detected by gene mapping or nucleotide sequence studies, one cannot make any definitive conclusions as to the precise molecular basis of the varied forms of $\beta^0$-thalassemia. This assessment was supported by Ottolenghi et al. (1977), who only added that there are at least

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two different types of $\beta^0$-thalassemia, a $\beta$-mRNA negative type and a $\beta$-mRNA positive type.

Similar methods have been used to identify the defect in $\delta \beta^0$ thalassemias; the results suggest that it arises from a deletion of the $\beta$ globin gene (Ramírez et al., 1976; Weatherall, 1976).

The purpose of this paper is to describe a family in which two sibs were doubly heterozygous $\beta^0/\delta \beta^0$ thalassemics and to propose a hypothesis to explain the origin of $\delta \beta^0$ thalassemia from a $\beta^0$ gene after its mispairing with a $\delta$ gene followed by crossing-over. An abstract of this paper has already been published (Cantú et al., 1978).

Report of a Case

The 7-year-old propositus (VI-3 in Fig. 1) was the product of a 3rd uncomplicated pregnancy and normal delivery. At about eight months of age, he presented with symptoms of pallor, scleral jaundice, cholangia, diaphoresis and hepatosplenomegaly of 6 cm below the costal margin. At this time there was hypochromic anemia with 10.2% of reticulocytes. Later, he presented with several episodes of acute hemolytic anemia, including fever, pallor, jaundice and cholangia associated with leukocytosis. A gross diagnosis of Cooley's anemia was established when he was two years of age because of the absence of Hb A, the elevation of Hb F and the clinical manifestations. The patient has required repeated periodical transfusions and long-term folic acid therapy. The hepatosplenomegaly has persisted, although with variations from 3 to 12 cm below the costal margin. From 1972 to 1978 his Hb ranged between 5.3 and 11.3 g/dl and his PCV from 18 to 35%.

Fig. 1. Pedigree. Arrow indicates the propositus. White: $\beta$. Black: $\beta^0$. Strips: $\delta \beta^0$. (See text for details)