



Thesis Abstract

Influence of $\delta\beta$ -thalassemia or regulatory elements in individuals with increased fetal Hb levels in the São Paulo northwest population

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Fetal hemoglobin (Hb F), formed by two alpha globin chains (α) and two gamma chains (γ) ($\alpha_2\gamma_2$), has reduced expression in adults, ranging from 0 to 1% of total hemoglobin. Increased levels of Hb F are due to mutations in the β -globin family, which cause hereditary persistence of fetal hemoglobin (HPFH) and delta-beta thalassemia ($\delta\beta$ -thalassemia). The control of the production takes place by the regulatory region and regions outside the β -globin family, among them 2q16, 6q23, 8q, and Xp22.2. The aims of this study were to determine the presence and frequency of two mutations for $\delta\beta$ -thalassemia, the *XmnI* polymorphism and β -globin haplotypes in healthy individuals with increased Hb F in the State of São Paulo. We analyzed 60 samples of peripheral blood of healthy adults, without complaints of anemia. The samples were separated into two groups according to Hb F level: group I - 34 samples with Hb F ranging from 2 to 15% and group II - 26 samples with Hb F over 15%. In relation to the polymorphisms examined, we found three heterozygous individuals (5%) for Spanish $\delta\beta$ -thalassemia, belonging to group I, whose Hb F levels were within the normal range. The Sicilian $\delta\beta$ -thalassemia mutation was not found, indicating the need to study other polymorphisms related to the increase of Hb F in adult life. The frequency of *XmnI* polymorphism was 33.3% and the mean Hb F levels were $15.48 \pm 11.69\%$. The frequency observed in our study for this polymorphic site is higher than that found in the literature for healthy subjects. This polymorphism was more prevalent in individuals with Hb F levels below 15%. For four samples positive for this polymorphism, the Hb F levels were explained by the presence of HPFH and Spanish $\delta\beta$ -thalassemia mutations, so that the presence of the *XmnI* polymorphic site was not a determinant in the overexpression of γ -globin genes. Regarding β -globin haplotypes, 18 alleles and 27 distinct genotypic patterns were found. The pattern Atp1/Atp2 was the most

frequent genotype (13.72%). Of the 18 alleles, 13 showed atypical patterns. The results show that the haplotype V was the most frequent (27.45%), followed by atypical Atp2 (13.72%) and Atp1 (11.76%), and that there was a higher correlation with the presence of HPFH and *XmnI* polymorphism. The high frequency of haplotype V in our samples and high frequency of atypical haplotypes may reflect a high rate of miscegenation in this population, suggesting an ethnic characteristic for the Brazilian population, requiring the evaluation of population genetic markers to corroborate this hypothesis.

Key words: Hb F; $\delta\beta$ -thalassemia; *XmnI* polymorphism; β -globin haplotypes