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### **TATA-Box polymorphism in the uridine diphosphate glucuronosyl transferase gene in Portuguese patients with clinical diagnosis of Gilbert Syndrome**

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Gilbert Syndrome (GS) is an inherited form of mild unconjugated hyperbilirubinemia characterized by decreased bilirubin UDP-glucuronosyl transferase (UGT1A1) activity. GS is the most common alteration of the hepatic bilirubin metabolism, occurring in 2-12% of the population.<sup>1-5</sup> A nonsense mutation of the UGT1A1 gene was identified in a patient with Crigler-Najjar Syndrome in 1992, but it was only in 1995 that mutations in UGT1A1 that caused GS were discovered. The most common genetic variant of the UGT1A1 gene is a TA insertion in the repetitive TATA-Box of the gene promoter, which normally consists of six repeats.<sup>2</sup> The TA(7) allele causes reduced expression of the gene, and homozygosity of this allele is typically associated with a mild form of GS1. The aim of our study was to determine the frequency of UGT1A1 gene variants in Portuguese patients with clinical diagnosis of GS. We screened 25 Portuguese patients with clinical diagnosis of GS: 6 females, ages 4-30 years, and 19 males, ages 1-35 years. The diagnosis of GS was based on the standard criteria<sup>6</sup>. The mean (+/- SD) total bilirubin concentration was 45,15 +/- 25,18 mmol/L. Genomic DNA was extracted from peripheral blood leukocytes using standard methods. Screening of the variants in the promoter of the UGT1A1 gene was performed by polymerase chain reaction with primers described by Bancroft et al.<sup>7</sup> Analysis of the amplified DNA fragments was performed by automated capillary electrophoresis. Analysis of UGT1A1 promoter variants (Figure 1) revealed that 22 (88%) of the GS patients were homozygous for the mutant allele (TA(7)/TA(7)), and 3 (12%) were heterozygotes (TA(6)/ TA(7)). The high frequency of SG patients presenting this mutation is similar to that found in other populations, namely in the Italian population where the homozygote frequency was seen to be 80%.<sup>3</sup> Based on the frequency observed in Caucasians, in several studies of small series, Beutler et al.<sup>5</sup> calculated a homozygote frequency of 15%. This predicted value is higher than that of patients with a clinical diagnosis of GS, which probably reflects the existence of other inherited or acquired factors affecting bilirubin metabolism, in addition to reduced glucuronidation caused by the TA insertion.<sup>2</sup> Male

element had a more significant elevation in serum bilirubin than the females. This is possibly due to the greater bilirubin load per kilogram of body weight in males or the inhibition of enzymatic glucuronidation by androgenic steroids, or both.<sup>2</sup> The higher levels may explain the sample bias of 19:6 (men/women) in our group of GS patients. In conclusion, our results suggest that the insertion of the TA dinucleotide in the promoter region of the gene of the UGT1A1 is the main cause of GS in the Portuguese population.

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