UGT1A1 gene variations in individuals with and without clinical diagnosis of Gilbert Syndrome

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1 – INTRODUCTION

Bilirubin is a non-polar metabolite, results from catabolism of haemoglobin and is bound to glucuronic acid in the liver by the uridine diphosphate glucuronosyltransferase (UGT1A1). Molecular studies showed that the presence of two extra bases [A(TA)2]TAA in the promoter region of the UGT1A1 gene is responsible for the reduced UGT1A1 glucuronization activity and is the main cause of unconjugated hyperbilirubinemia observed in patients with Gilbert Syndrome (GS). However, individuals with normal bilirubin levels and no clinical symptoms of SG may also present this polymorphism in homozygosity. This polymorphism is not sufficient to explain the inter-individual variation and the presence of hiperbilirubinemia.

The aim of this work is to determine the presence of other mutations in the UGT1A1 gene, downstream of the TA duplication, and how they may contribute towards the inter-individual variation of serum bilirubin levels.

3 - RESULTS

Fig. 1. Partial sequence around the c.1423C>T mutation site, exon 5 of the UGT1A1 gene. (A) Normal sequence; (B) Heterozygous patient.

Table 1. UGT1A1 TA polymorphism and other sequence variations of coding regions, in GS patients and in Controls.

3 – DISCUSSION

In the group without GS, TA polymorphism is also responsible for different bilirubin concentrations. In this group no mutations were detected in the 6/7 and 7/7 clusters, but in the 6/6 group two new mutations were found in heterozygosity. These mutations are not associated with increased bilirubin levels. However, they could be associated with GS in the presence of other UGT1A1 mutations. Most of the patients clinically diagnosed with GS, were homozygous and only one as a normal number of repeats. Molecular analysis showed that one (3,6%) of the 7/7TA patients had another mutation in the UGT1A1 gene (c.674T>G). Comparing the 6/7TA group, one additional mutation was also found in three patients (43%) two of which had been previously described (c.674T>G; c.923G>A) and a new one (c.1423C>T; Fig. 1). As shown in Fig.2B mutations in coding regions are associated with increased serum bilirubin levels. Additionally, 4 polymorphisms were found (c.864+89C>T; c.997-37T>C; c.997-82A>C; c.997-87A>C) and are not associated with increased serum bilirubin levels.

Fig. 2. Differences between total bilirubin concentration (mg/dL) according to: (A) Genotypes 6/6, 6/7, and 7/7 in individuals without GS. (B) between individuals without GS and genotype 7/7 and for the two GS patients groups (with homozygosity for [TA] allele, and with one allele [TA] and the other with a mutation in coding region).

3 – CONCLUSIONS

Our study showed:

1) Homozygosity for the TA duplication is associated with GS.

2) TA polymorphism is also responsible for the interindividual variation observed among individuals in general population. Statistical differences occur within genotype 6/6 and 6/7 (p<0.0001) and is more pronounced between 6/6 and 7/7 genotype.

3) We found homozigous for the TA polymorphism, without further mutations in coding regions, that have normal ranges of serum bilirubin concentration. Probably other genetic and non-genetic factors could contribute to the bilirubin variation in Portuguese population.

4) In the GS group with heterozygosity for the TA duplication, we found variants in 43% of the patients, and mutations in UGT1A1 coding region are associated with more pronounced hiperbilirubinemia. This two observations emphasize the importance of complete UGT1A1 sequence analysis.


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