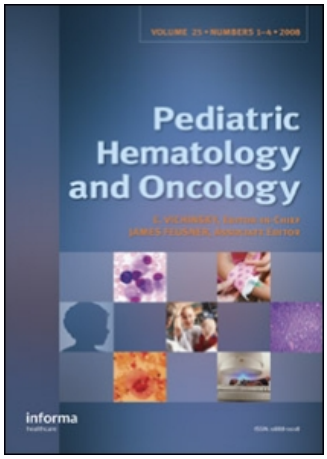

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A NEW CASE OF (TA)8 ALLELE IN THE UGT1A1 GENE PROMOTER IN A CAUCASIAN GIRL WITH GILBERT' SYNDROME

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□ *The authors describe a 5-year-old Caucasian girl, referred to their hospital for evaluation of an unconjugated hyperbilirubinemia (57.9 μmol/L) detected from blood analysis during an episode of fever. The molecular analysis of the TATA-box region of the UGT1A1 gene revealed that the patient was a compound heterozygote for two insertions, one TA and the other TATA [$(TA)_7/(TA)_8$]. This is the first case of (TA)8 allele found in a Portuguese Caucasian patient and the third found in the literature.*

Keywords. bilirubin, Gilbert syndrome, hyperbilirubinemia, UGT1A1

Gilbert syndrome (GS) is characterized by a chronic, nonhemolytic unconjugated hyperbilirubinemia in the absence of liver disease or overt hemolysis. On the basis of serum bilirubin levels, 3–10% of the general population are estimated to have GS. Serum bilirubin levels vary according to time, intercurrent illness, or fasting [1–4].

Hepatic glucuronization of bilirubin is catalyzed by isoenzyme 1A1 of UDP-glucuronosyltransferase (UGT1A1). The first mutation in this gene was described in 1992 [5]. It was a nonsense mutation found in homozygosity in a patient with Criegler–Najar syndrome (CNS) [6]. Only in 1995 were mutations in this gene found to be correlated with GS [2]. To date, more than 50

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mutations causing GS or CNS have been described. However, the main cause of GS in all studied populations is a TA insertion in the repetitive TATA box of the gene promoter, which normally consists of 6 repeats. This (TA)7 allele is extremely common, occurring with a frequency of 38% in Caucasians [1–3, 5]. This TATA-box region is the binding site for the transcription factor IID, and for this reason plays an important role in the initiation of the transcription [2]. A variation in this sequence results in a reduction of the efficiency and accuracy of gene expression leading to higher bilirubin levels [2, 7].

The authors report on a Caucasian girl with GS, who was found to be a compound heterozygote for the (TA)7 and (TA)8 alleles.

CASE REPORT

In November 2002, a 5-year-old girl was referred to our hospital for evaluation of an unconjugated hyperbilirubinemia detected by blood analysis during an episode of fever. The girl had been born of a full-term pregnancy and had a clinical history of prolonged neonatal jaundice (5 weeks) considered a result of breast feeding. Neither sclera icterus nor liver or spleen enlargement was observed on clinical examination. The laboratory evaluation revealed a low-grade unconjugated hyperbilirubinemia (57.9 μmol/L), normal routine tests of liver function, and no overt hemolysis. The father and mother have normal bilirubin levels (14.2 and 9.4 μmol/L, respectively).

Molecular analysis of the TATA-box region of the UGT1A1 gene was performed by fluorescence-labeled polymerase chain reaction using the primers described by Bancroft et al. [8] and the conditions previously described [9, 10]. The analysis revealed that our patient was a compound heterozygote for two insertions, one TA and the other TATA [$(TA)_7/(TA)_8$] (Figure 1). The father was heterozygote for the TATA insersion [$(TA)_6/(TA)_8$] and the mother for the TA ones [$(TA)_6/(TA)_7$].

DISCUSSION

Traditionally, GS has been a diagnosis of exclusion. Routine biochemistry measurement of enzymatic activity has never been possible but genetic testing for GS has the potential to provide a positive diagnosis.

To date, we have studied the promoter region of the UGT1A1 gene in 60 patients referred to our center with clinical diagnosis of GS. Fifty-two were found to be homozygotes, 7 were heterozygotes for the (TA)7 allele, and only the case described here has the (TA)8 allele. In fact, no other Portuguese patients were described as having the present mutation. In the literature, only 2 further cases of (TA)8 allele have been described in Caucasian patients. The first [7] was a girl from Taranto (Apulia), Italy, with

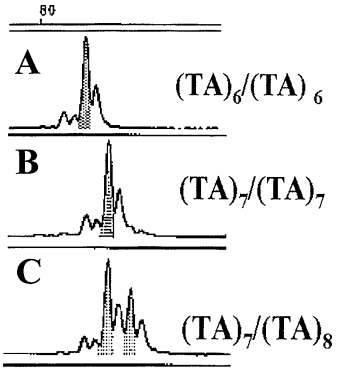

FIGURE 1 Screening for UGT1A1 promoter variants, performed by fluorescence-labeled PCR. The amplified DNA fragments were separated by automated capillary electrophoresis and analyzed with ABI GeneScan program (Applied Biosystems). (A) Homozygosity for the normal (TA)6 allele; (B) homozygosity for a mutant (TA)7 allele; (C) our patient with (TA)7 and (TA)8 alleles.

the presence of the same compound heterozygosity. Besides the similarity in terms of age and gender, this case presented a bilirubin level of 60 μmol/L, comparable to that found in our case. Taken together, these cases provide evidence toward a correlation between phenotype and genotype. The second case [11] was a 3-year-old boy from Greece who was found to be heterozygous for the (TA)6 allele [(TA)6/(TA)8].

In Caucasian populations the (TA)8 allele is extremely rare [6, 7]. However, in African populations this allele is more common, with a frequency of 6.9%. The presence of this rare allele in the Caucasian population was suggested by Iolascon et al. [7] and Tsezou et al. [11] to be a result of a recent genetic event and not derived from a common ancestral mutation. In effect, repeated sequences are extremely unstable and may be lengthened or shortened by a variety of mechanisms, such as unequal crossing over in meiosis.

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