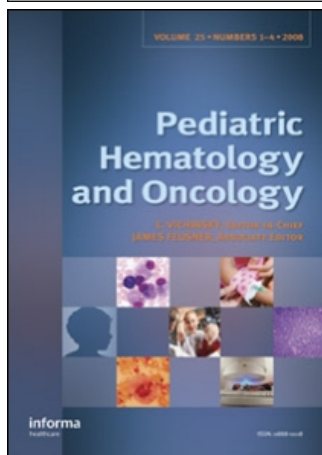


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A NEW CASE OF (TA)8 ALLELE IN THE UGT1A1 GENE PROMOTER IN A CAUCASIAN GIRL WITH GILBERT' SYNDROME

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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 $\mu\text{mol/L}$) 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 $\mu\text{mol/L}$), normal routine tests of liver function, and no overt hemolysis. The father and mother have normal bilirubin levels (14.2 and 9.4 $\mu\text{mol/L}$, 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 insertion [(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

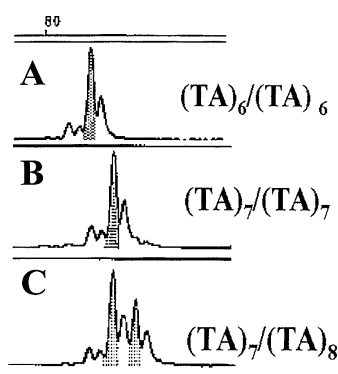


FIGURE 1 Screening for UGT1A1 promoter variants, performed by fluorescence-labeled PCR. The amplified DNA fragments were separated by automated capillary electrophoresis and analyzed with ABI GeneScan program (Applied Biosystems). (A) Homozygosity for the normal (TA)6 allele; (B) homozygosity for a mutant (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 $\mu\text{mol/L}$, 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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