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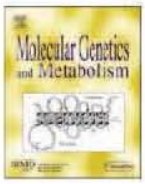

661

GENETIC AND ACQUIRED FACTORS THAT MODULATE SERUM BILIRUBIN LEVELS

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The isoenzyme UDP-glucuronosyltransferase 1A1 (UGT1A1) catalyzes bilirubin glucuronidation. Molecular studies suggest that the presence of two extra bases in the repetitive promoter TATA box region of the UGT1A1 gene, described as (TA)7 allele, is responsible for the reduced UGT1A1 activity that leads to hyperbilirubinemia. In fact, patients with Gilbert's syndrome (GS), a recessive disorder characterized by a mild unconjugated hyperbilirubinemia, are often homozygous for the TA duplication. The "major" recessive gene (UGT1A1) and other non-genetic factors are also associated with the inter-individual variation of bilirubin concentration.

To establish the influence of genetic and non-genetic variables in serum bilirubin concentration, we recruit 81 young adults (62 females and 19 males with average age 20,2 ±1,7 years) that give their written informed consent. A standardized questionnaire inquiring about smoking habits, oral contraceptive therapy, caloric intake, fasting time and physical activity was performed to select the participants without liver and/or haematological disorders. After an overnight fasting, venous blood samples were collected to determine total and direct-reacting bilirubin and to analyze the UGT1A1 promoter region in genomic DNA.

From UGT1A1 genotyping, we identified 6 homozygous for the (TA)7 allele, 40 were heterozygous and 35 were homozygous for the normal allele. Mean (± SD) serum bilirubin levels were 10.60 ± 4.46 μmol/L, but trend to higher bilirubin levels was found in males than in females (12.7 ± 6.33 μmol/L *vs.* 10,3 ± 5.5 μmol/L). Higher bilirubin concentrations were found in non-smoking subjects (11.2 ± 6.07 μmol/L *vs.* 9.7 ± 2,6 μmol/L) and in females taken oral contraceptives (11.9 ± 7.9 μmol/L *vs.* 9.5 ± 3,3 μmol/L). Statistically significant correlations were found between bilirubin serum levels and fasting time ($r=0,421$, $p=0.001$), as well as caloric intake ($r=-0.255$; $p=0.021$). Multiple regression analysis identified fasting time ($\beta=0.36$; $p=0.01$), under oral contraceptive therapy ($\beta=0.232$; $p=0.024$) and TA polymorphism ($\beta=0.480$; $p=0.001$) as independent variables that account for 41,9% of total serum bilirubin levels variation ($R^2=0.419$). No significant association was found between bilirrubin concentrations and physical activity.

Our results suggest that beyond the genetic information, the caloric intake, fasting time, smoking status and oral contraceptive therapy also contribute to the inter-individual variation of serum bilirubin levels.