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INFLUENCE OF GENETIC AND ACQUIRED FACTORS THAT MODIFY SERUM BILIRRUBIN LEVELS IN THE PORTUGUESE POPULATION

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Introduction: The isoenzyme UDP-glucuronosyltransferase 1A1 (UGT1A1) catalyzes bilirubin glucuronidation by converting bilirubin in water-soluble glucuronides that then undergo biliary or renal elimination. During the last years, molecular studies have suggested that the presence of two extra bases in the repetitive promoter TATA box region of the *UGT1A1* gene, described as $(TA)_7$ allele, are responsible for the reduced UGT1A1 activity leading to hyperbilirubinemia. Homozygosity for the $(TA)_7$ allele have been associated with Gilbert's syndrome (GS), that is a genetic recessive disorder characterized by a mild unconjugated hyperbilirubinemia occurring in the absence of haemolysis or of liver disease. Several studies establish that unconjugated hyperbilirubinemia exhibits a mode of inheritance where the "major" recessive gene (*UGT1A1*) accounts for only a part of the serum bilirubin concentration. More recently, it was described that increased red cell mass probably plays a role in the pathogenesis of GS.

Objective: The aim of this study is to determine the influence of the $(TA)_7$ allele, some environmental factors and increased red cell mass in serum bilirubin levels in Portuguese population.

Material and Methods: We include in this study 165 young adults with average age (19.5 ± 2.1 years). All volunteers give their written informed consent to participate in this study. In all individuals, after an overnight fasting, venous blood samples were collected in order to determine total and direct-reacting bilirubin, blood cell count and surrogate markers, and isolate genomic DNA to perform the molecular study of *UGT1A1* promoter region. At the same time, a standardized interviewer-administered questionnaire was also performed that included questions about smoking habits, oral contraceptive therapy, caloric intake, fasting time and physical activity.

Results: For the *UGT1A1* polymorphism, we found that 15%, 79% and 71% individuals were (TA_7/TA_7) , (TA_6/TA_7) and (TA_6/TA_6) , respectively. Estimated frequency of $(TA)_7$ allele was 33%, close to the 38,7% previously described for caucasians. A trend to higher bilirubin levels, without statistical significance, was found in males, in non-smoking subjects and in female subjects that were under oral contraceptive therapy. Statistically significant correlations were found between bilirubin serum levels and fasting time ($p=0.001$) and caloric intake ($p=0.03$), haemoglobin ($p=0.03$), hematocrit ($p=0.001$), mean corpuscular haemoglobin ($p=0,006$) and mean corpuscular hemoglobin concentration ($p=0,001$). No significant association was found between serum bilirubin levels and physical activity.

Conclusions: Our results strongly suggest that genetic background plays a major role in serum bilirubin levels variation as well as other factors like red blood mass and fasting time which also contribute to this inter-individual variation.