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Cholestasis with normal gamma-glutamyltransferase from management to molecular investigation with novel mutations in ATP8B1 and ABCB11: Tunisian study

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Introduction: Cholestasis with normal gamma-glutamyltransferasis (GGT) is a heterogeneous group. ATP8B1 and ABCB11 two genes implicated on the respectively phenotypes PFIC1, BRIC1 and PFIC2 BRIC2, lithiasis, and drug cholestasis.

Aims: The aim of this study is to report the phenotype and the outcome and to determine the profile of mutations of the studied patients.

Methods & Materials: Eleven patients with persistent normal GGT cholestasis were studied from 93 patients with liver disease referred to us from 2007 to 2014. Eight patients were studied for ATP8B1, five for ABCB11, one family, with two patients, was studied for both genes. Polymerase chain reaction (PCR) was performed using a set of selected primers and direct sequencing by Applied Biosystems. Intronic variants were analyzed by the Human Splicing Finder program.

Results: Patients: the age at the diagnosis was ranged from neonatal to 12 months. Consanguinity was found in 10/11 of the patients. The constant features were pruritus and hepatomegaly. Short stature was found in 60%. No one developed portal hypertension (3 to 22 years). Two patients presented asthma with high level of IgE with negative sweat test. Two patients developed intense pruritus despite ursodesoxycholic acid (UDCA) and rifadin with severe lichenification of the skin, they were successfully treated by sertraline with a considerable improve of the skin. In one patient, we observed a relapse of the pruritus after two months requiring biliary derivation and in one patient, frequent crisis of crazy laughs, sertraline was stopped. Two patients developed liver failure respectively at the age of six months (hepatocarcinoma was found in explant liver) and six years old, received liver transplant. Molecular Study Results: For ATP8B1, we found two novel exonic mutations, the V310F and D379RfsX51 and two known variants the F305I and R952, seven novel intronic mutations, three silent mutations: two new mutations one of them D234D was near splicing site. For ABCB11, we found three exonic mutations: Y354X and two novel mutations N372YfsX23, A986P and two novel intronic variants. The analysis of the seven intronic variants by splicing Finder Program showed the possible role of four of them in the disease.

Conclusions: This study is the first to be performed in Tunisia for patients with normal GGT cholestasis. The molecular results were preliminary, but did not find founder effect. We report both novel exonic and intronic mutations. Most patients have more than two related variants, which may be due to high consanguinity and heterogeneity of the Tunisian population-by-population migration and civilizations. This study should be completed by the transcriptional study for the novel intronic and silent mutations.

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