RESEARCH OF NEW MUTATIONS IN ABCB11 AND ABCB4 GENES IN ICP ITALIAN PATIENTS.

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The Intrahepatic cholestasis of pregnancy (ICP) is a multifactorial disorder of pregnancy associated with a genetic background occurring during the second or third trimester of pregnancy and persists until delivery. Subjects with ICP have been shown to present mutations of genes coding for proteins regulating hepatobiliary transport of bile acids and phospholipids, ABCB11 and ABCB4 respectively.

This project investigates the genetic contribution of ABCB4 and ABCB11 genes in the development of ICP in a sample of Italian patients, and the relationship between genotype and phenotype, correlating the different mutations with biochemical indices of cholestasis.

33 women with a history of ICP was enrolled and 19 was screened for gene mutation. Genomic DNA was extracted from peripheral blood by standard methods; a polymerase chain reaction was performed in order to amplify the 28 exons of both genes; the presence of mutations was assayed by DNA sequencing techniques.

We found three new non-synonymous heterozygous mutations in exons 6, 9, 15 (E135K, V284D, Q558H respectively) in ABCB11 gene; a new non-synonymous heterozygous mutation in exon 13 (N510S), and a frameshift mutation in exon 14 (I587fsX604) in ABCB4 gene. The Q558H and N510S mutations are localised in the Nucleotide Binding Domain (NBD), a functional domain of protein, involved in the bond and hydrolysis of ATP; the I587fsX604 mutation causes the generation of truncated protein; using the Polyphen predicting program the V284D variant was reported to cause a probably damage on the protein function. No one of the previous mutations was found for any of the 100 control subjects screened. Moreover the V444A polymorphism, found on BSEP protein, was associated with all mutations. This polymorphism was reported in literature as a predisposing factor to develop ICP in presence of other mutations in ABCB11 and ABCB4 genes.

In all patients with ABCB11 and ABCB4 mutations was observed elevated bile acids and transaminase levels.

Further studies are required to amplify the cohort of subjects in order to estimate the mutation frequency in the Italian population and to analyse the effects of mutations on protein expression and function.