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LETTERS TO THE EDITOR

Role of *ABCC2* common variants in intrahepatic cholestasis of pregnancy

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Abstract

The pathogenesis of intrahepatic cholestasis of pregnancy (ICP), a disorder that adversely affects maternal wellbeing and fetal outcome, is unclear. However, multiple factors probably interact along with a genetic predisposition. We would like to add some comments on a paper recently published concerning the role of *ABCB11* and *ABCC2* polymorphisms in both ICP and contraceptive-induced cholestasis, especially in the light of our recently published findings about a positive association between ICP and *ABCC2* common variants.

Key words: Intrahepatic cholestasis of pregnancy; ABCC2; MRP2; Gene variants

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TO THE EDITOR

We read with great interest the article of Meier *et al.* about the role of *ABCB11* and *ABCC2* polymorphisms in both intrahepatic cholestasis of pregnancy (ICP) and contraceptive-induced cholestasis[1]. The authors observed an association between the *ABCB11* 1331T > C polymorphism and the above mentioned cholestatic disorders. Additionally, the authors claimed of a lack of association with 3 single nucleotide polymorphisms (SNPs) in *ABCC2* gene, concluding that common *ABCC2* polymorphisms are not associated with the development of ICP.

We would like to make several comments on these findings, particularly concerning to the lack of association with *ABCC2* gene variants. First of all, a note of caution should be added to the reported findings, as the markers assumed by the authors as common variants (rs2273697, rs17222723 and rs8187710), except for rs2273697, include one allele at a very low frequency, as the rs17222723-A allele frequency is 0.067 and the rs8187710-A allele frequency is 0.059, at least for data from the HapMap project for Caucasians and from a rough estimation of own author's data[1]. Consequently, in the group of patients included by the authors only 5 out 33 patients showed either the rs172227234 or rs8187710 heterozygous AT or AG genotype, respectively, and none of them showed the homozygous AA genotype. The same happened in the pregnant control group. Thus, in this frame, the statistical power of the study even taking into account the additive genetic model is very low (less than 20%) owing to the lower MAF of these variants.

Second, we wish to note that we recently published[2] a candidate gene association study showing the contribution of six *ABCC2* gene variants to the risk of ICP. The study involved promoter, coding and non-coding regions of *ABCC2* (4 tag SNPs representing 46 polymorphic sites located in 70 kb of the gene, in addition to the rs17222723 and rs8187710), and showed that, at least, one of the *ABCC2* variants (rs3740066) at the exon 28 was significantly associated with ICP being the estimated risk of disease for homozygous AA subjects 4-fold higher in comparison with homozygous GG subjects (OR, 4.44; 95% CI, 1.83-10.78; $P < 0.001$). Although more studies are necessary to establish whether rs3740066 is the causal variant or one linked to it, our results suggest that ICP may be associated with common variants of *ABCC2*. Interestingly, we also included in the analysis rs172227234 and rs8187710, and we did not observe significant differences in genotype frequencies of the 2 SNPs in ICP and controls.

In conclusion, we consider that the pathogenic involvement of *ABCC2* (*MRP2*) in ICP is still an open issue, particularly in the frame of a small number of studies about the role of the *ABCC2* gene variants in cholestatic disorders, with the exception of the Dubin Johnson phenotype.

Although the major physiological function of ABCC2 is to transport conjugated metabolites into the bile canaliculus, previous data demonstrated that a major metabolite of human estrogen metabolism, estradiol-17-β-D-glucuronide (E$_2$17βG), has been shown to be transported by both MRP2 and MRP3[3]. These findings support that ABCC2 represents an alternative candidate protein involved in the pathogenesis of hormonal cholestasis. Additionally, it was shown that MRP2 is regulated by three distinct nuclear receptor signaling pathways that converge on a common response element in the 5'-flanking region of this gene[4]. Hence, the intimate mechanism, by which gene variants including *ABCC2* may influence ICP susceptibility, is not fully explored and a complex network involving nuclear receptors and other transcription factors may be the cause of liver injury in cholestatic disorders[5].

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