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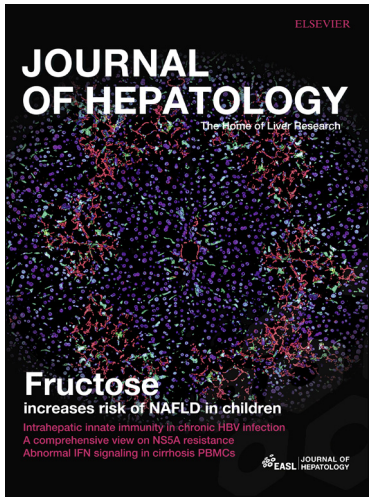

Letter to the Editor

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Letter to the editor

Reply to: Doublecortin domain containing protein 2 (*DCDC2*) genetic variants in primary sclerosing cholangitis

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We would like to thank Cheung et al. for their comments on possible genetic associations between neonatal sclerosing cholangitis (NSC) and primary sclerosing cholangitis (PSC). Cheung et al., through whole exome sequencing in a group of 67 (30 under 18 years old) patients diagnosed with PSC identified three missense variants in doublecortin domain containing 2 (*DCDC2*) gene [c.1368A>T; p.(Lys456Asn), c.661A>G; p.(Ser221Gly) and c.454C>G; p.(Pro152Ala)] with minimal predicted effect on protein function. These are all common variants, with c.661G in fact being more common than c.661A in all populations examined. PSC does not behave as Mendelian trait. There is however an increased occurrence of other autoimmune diseases in families [1]. Relatively common variants in cilial genes might still predispose bile ducts to being the target of autoimmunity in a particular individual. It would be important to examine the frequency of these variants compared to matched controls, or possibly use other forms of association studies such as the Transmission Disequilibrium Test, if trios were available,

In our cohort of NSC patients [2] we identified the same 3 missense variants in patients with or without disease-causing mutations in *DCDC2*. Immunohistochemical studies in NSC patients with only the above-mentioned missense variants showed preservation of DCDC2 protein and acetylated alpha-tubulin.

Although no disease causing variants in cilia related genes have been so far identified in patients with PSC the altered expression and mislocalisation of cilial proteins could still be implicated in the disease pathogenesis of PSC [3-5]. It has been suggested though that this effect is more likely part of a secondary sequalae of changes in the biliary microenvironment rather than the primary cause [6].

The pathophysiological mechanisms, by which common genetic variants with minimal isolated functional effect, can play a contributory role in the ciliopathy phenotype should remain under investigation. Such a mechanism is the one suggested in animal models of Meckel, Nephronophthisis and Bardet-Biedl syndromes [7] where all 3 complexes contribute synergistically to variability in ciliogenesis. The complexity of the interactions amongst different ciliary structures and their function remains a challenging field for researchers.

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