



King's Research Portal

DOI:

[10.1016/j.jhep.2017.04.012](https://doi.org/10.1016/j.jhep.2017.04.012)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Grammatikopoulos, T., & Thompson, R. J. (2017). Reply to: Doublecortin domain containing protein 2 (DCDC2) genetic variants in primary sclerosing cholangitis. *Journal of Hepatology*.
<https://doi.org/10.1016/j.jhep.2017.04.012>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Accepted Manuscript

Letter to the Editor

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

Tassos Grammatikopoulos, Richard J. Thompson

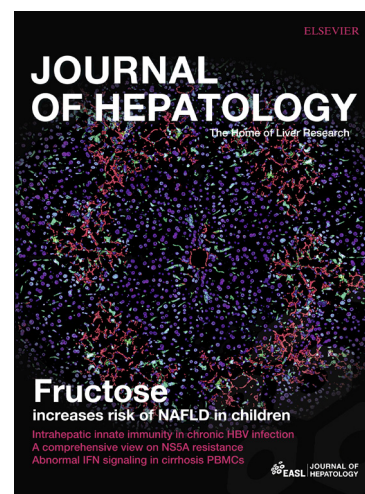
PII: S0168-8278(17)30253-2
DOI: <http://dx.doi.org/10.1016/j.jhep.2017.04.012>
Reference: JHEPAT 6506

To appear in: *Journal of Hepatology*

Received Date: 9 April 2017
Accepted Date: 22 April 2017

Please cite this article as: Grammatikopoulos, T., Thompson, R.J., Reply to: Doublecortin domain containing protein 2 (*DCDC2*) genetic variants in primary sclerosing cholangitis, *Journal of Hepatology* (2017), doi: <http://dx.doi.org/10.1016/j.jhep.2017.04.012>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Letter to the editor

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

Tassos Grammatikopoulos^{1,2}, Richard J Thompson^{1,2}

1. Paediatric Liver, GI & Nutrition Centre, King's College Hospital, London, UK
2. Institute of Liver Studies, Division of Transplantation Immunology and Mucosal Biology, King's College London, London, UK

Word count: 341/800

Corresponding author: Dr Tassos Grammatikopoulos
Paediatric Liver, GI & Nutrition Centre
King's College Hospital,
Denmark Hill, London, SE5 9RS, UK
Tel: +44 20 3299 1162
Fax: +44 20 3299 4228
Email: t.grammatikopoulos@nhs.net

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 sequelae 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.

1. Fausa O, Schrumpf E, Elgjo K. Relationship of inflammatory bowel disease and primary sclerosing cholangitis. *Semin Liver Dis* 1991;11:31-39.
2. Grammatikopoulos T, Sambrotta M, Strautnieks S, Foskett P, Knisely AS, Wagner B, Deheragoda M, et al. Mutations in DCDC2 (doublecortin domain containing protein 2) in neonatal sclerosing cholangitis. *J Hepatol* 2016;65:1179-1187.
3. Gradilone SA, Masyuk AI, Splinter PL, Banales JM, Huang BQ, Tietz PS, Masyuk TV, et al. Cholangiocyte cilia express TRPV4 and detect changes in luminal tonicity inducing bicarbonate secretion. *Proc Natl Acad Sci U S A* 2007;104:19138-19143.
4. Masyuk AI, Huang BQ, Radtke BN, Gajdos GB, Splinter PL, Masyuk TV, Gradilone SA, et al. Ciliary subcellular localization of TGR5 determines the cholangiocyte functional response to bile acid signaling. *Am J Physiol Gastrointest Liver Physiol* 2013;304:G1013-1024.
5. Masyuk AI, Masyuk TV, Larusso NF. Exosomes in the pathogenesis, diagnostics and therapeutics of liver diseases. *J Hepatol* 2013;59:621-625.
6. Masyuk TV, Masyuk AI, LaRusso NF. TGR5 in the Cholangiociliopathies. *Dig Dis* 2015;33:420-425.
7. Yee LE, Garcia-Gonzalo FR, Bowie RV, Li C, Kennedy JK, Ashrafi K, Blacque OE, et al. Conserved Genetic Interactions between Ciliopathy Complexes Cooperatively Support Ciliogenesis and Ciliary Signaling. *PLoS Genet* 2015;11:e1005627.