Letter: sleep and psychological disorders in patients with inflammatory bowel diseases; another potential role of vitamin D deficiency

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Sirs, We read with great interest the comprehensive review study of Mouli and Ananthakrishnan.[1] The authors have evaluated and discussed current evidence regarding the roles of vitamin D deficiency in the pathogenesis and progression of inflammatory bowel disease (IBD). In this regard, different cellular and molecular mechanisms are discussed in this review.

However, as mentioned by the authors, there is a strong role for environmental factors in the pathogenesis and progression of IBD. There is growing evidence that psychological factors, including psychological stress and depression, are influential in the pathogenesis and clinical course of IBD.[2, 3] Growing evidence also indicates the importance of sleep disorders in the clinical course of IBD. It has been shown that sleep disturbance increases the risk of disease flares in patients.[4–6]

It is therefore interesting that vitamin D deficiency has been shown to play a role in both psychological[7] and sleep disorders[8] in non-IBD populations, although the underlying mechanisms are still unknown. There is no study till now evaluating the effects of vitamin D deficiency on psychological health or sleep quality in IBD patients. Although several factors can affect psychological health and sleep quality in IBD patients including demographic- and disease-related factors,[2, 4] a role for vitamin D deficiency is also plausible.

Therefore, the 'optimal role of vitamin D supplementation as a therapeutic modality in patients with IBD' is not only the induction and maintenance of remission as mentioned by Mouli and Ananthakrishnan[1] but may also include treatment of psychological and sleep disorders in IBD patients. These issues should be added to the remaining unanswered questions regarding the role of vitamin D in IBD, and warrant evaluation in future studies.

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Letter: does the *IFNL4* gene discovery really provide a causal role for the *IL28B* haplotype blocks?

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Sirs, Stättermayer *et al.*[1] reported on the accuracy of the recently discovered interferon-λ4 (*IFNL4*) ss469415590 variant (TT or ΔG) in conjunction with the two widely studied interleukin 28B (*IL28B*) single-nucleotide polymorphisms (SNPs), rs12979860 and rs8099917, for predicting the likelihood of a response to pegylated IFN-α-2a (PEG) and ribavirin (RBV) in a large set (n.754) of chronic hepatitis C virus (HCV) patients.

While *IFNL4* variant was strongly associated with a sustained virological response in both HCV genotypes 1 and 4, and thus confirmed previous findings by Prokunina-Olsson *et al.*[2] and Bibert *et al.*,[3] the study confirms a strong linkage between ss469415590 and rs12979860 variants ($\rho = 0.988$) compared with the modest correlation between rs8099917 and *IFNL4* ($\rho = 0.598$). These findings therefore do not support an additional clinical benefit of *IFNL4* in the prediction of a response to PEG/RBV in Caucasian patients.

Recently, the finding that recombinant IFNL4 protein exerts a potent antiviral activity against both HCV and human coronaviruses[4] works against the assumption that the same protein does inhibit clearance of HCV, i.e. negatively interfering with HCV infection, while being endowed with a strong anti-HCV activity. This suggests the existence of a complex relationship between IFNL4 and HCV in humans, similar to that recently described for IFN-1 and lymphocytic choriomeningitis virus in mice,[5] where chronic IFN-I signalling due to persistent infection drives immunosuppression and disease progression.

Although validation studies in large cohorts of patients, like the one investigated by Stättermayer *et al.*,[1] may help understand the clinical utility of IFNL4, these studies have so far failed to demonstrate any causal relationship between IFNL4 protein and nonresponse to interferon therapy in chronic HCV patients. Among other approaches, the assessment of the missense variants previously described in the *IFNL4* coding region,[2] may help unravel this issue.

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Letter: does the *IFNL4* gene discovery really provide a causal role for the *IL28B* haplotype blocks? Authors' reply

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Sirs, We thank Dr Galmozzi and Dr Lampertico for their comment on our recently published paper on the effect of the dinucleotide frameshift variant in ss469415590 in the interferon (IFN)-λ4 gene on interferon/ribavirin treatment and its relationship with the two commonly used single nucleotide polymorphisms (SNP) in *IL28B* (rs12979860, rs8099917).[1, 2]

We agree that our study does not provide insights on the causal relationship between *IFNL4* and treatment response in patients with chronic hepatitis C virus (HCV) infection. Nevertheless, our study was designed to investigate the clinical usefulness of the different SNPs in *IL28B* and *IFNL4* in a large cohort of Caucasian patients infected with chronic HCV.

Hamming *et al.* demonstrated that *IFNL4* encodes an active type III interferon with potent anti-viral activity against both HCV and coronaviruses.[3] Galmozzi and Lampertico therefore conclude that this strong anti-viral activity works against the assumption of an inhibition of the IFNL4 protein of treatment-induced HCV clearance. We would like to remind them that up-regulation of intrahepatic interferon-stimulated genes (ISG) is associated with treatment failure in patients with chronic HCV, and levels of ISG are differently distributed according to different *IL28B* genotypes.[4] Furthermore, Prokunina-Olsson and her collaborators demonstrated that IFNL4 induces ISG expression in HepG2 hepatoma cells.[5] Thus, high baseline ISG levels might be associated with poor response to exogenous IFN, by exhausting the IFN response pathways.[6]