Search for Genetic Modifiers of PSC:
Time to Increase the Number of Needles in the Haystack

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ABSTRACT

Primary sclerosing cholangitis (PSC) belongs to the most obscure liver diseases. Patients with progressive PSC require liver transplantation as only therapeutic option. Previously several HLA- and non-HLA-associated PSC risk variants have been discovered, however their involvement in the development of PSC seems to be minor in comparison to environmental determinants. Lately, variant rs853974 at the RSPO3 gene locus has been shown to modulate the course of PSC. Here we briefly discuss the phenotypes related to this polymorphism and propose alternative directions of research that might help to identify new genetic modifiers of PSC progression.

Key words: Cholestasis. Liver transplantation. RSPO3. Stellate cells.

Primary sclerosing cholangitis (PSC) is a rare progressive cholestatic liver disease. Its pathogenesis is unclear and, apart from liver transplantation, no effective treatment of PSC has been established. Furthermore, we lack reliable biomarkers that could predict which PSC patients are at-risk of progression and deterioration of liver function. Hence, the prognosis of patients who suffer from PSC is often unfavourable. Since genetic predisposition is known as potential trigger of PSC, numerous genetic association studies in large cohorts of patients were undertaken. They led to the identification of several PSC-predisposing variants, many of which are involved in crosstalk between immune cells and cholangiocytes; however their contribution to the disease risk is relatively small and currently the notion that exogenous factors (which might be termed exposome) have stronger influence on the odds of developing PSC prevails. Of note, the PSC-causing exposome has yet to be defined.

Lately Alberts, et al. aimed at detecting genetic modifiers of PSC progression. To this end an extensive, multicentric cohort comprising a total of 3,402 patients with PSC was analyzed. The patients were followed-up for a median time of 8.7 years, and during this period 26% underwent liver transplantation, 11% developed hepatobiliary cancer, and 5% died of PSC-related complications. All patients were genotyped using the “Immunochip.” Among 130,422 tested variants, a single highly significant \( (P = 6.1 \times 10^{-9}) \) association was identified between the single nucleotide polymorphism rs853974 and liver transplant-free survival. Moreover, carriers of the rs853974 genotype [AA] had increased odds of PSC-related death as compared to patients bearing the genotype [GG]. rs853974 is localized on chromosome 6, and the authors reported that the effects might be conferred by variation of the RSPO3 gene encoding R-spondin. This notion was supported by expression analyses demonstrating lower mRNA levels of Rspo3 in cholangiocytes from cholestatic mice as compared to healthy cholangiocytes. Cholangiocyte-like-cells and primary bile duct cells were, in turn, characterized by increased RSPO3 expression as compared to human-induced pluripotent stem cells. Finally, RSPO3 was also detected in human hepatic stellate cells, at least by quantitative PCR. Given these observations and the known role of RSPO3 in Wnt signaling, Alberts, et al. postulated that RSPO3 might be one the modifiers of the PSC progression; at the same time they underscored the need of performing further studies investigating the functional roles of RSPO3 in the setting of cholestatic liver diseases.
The study by Alberts, et al.\textsuperscript{6} moves the attention of PSC research from triggers to modifiers of the liver disease. Although one could argue that there is no clear difference between genetic modifiers and triggers (i.e. each trigger of the disease might modify its progression and vice versa),\textsuperscript{8} here the focus was placed on identifying variants that affect the progression of PSC. By defining end-points (e.g. transplantation or death), the authors detected a new PSC-related polymorphism and this might shed a new light on the pathogenesis of one of the least-understood disease of the liver. On the other hand, this report opens several new questions. First of all, the study investigated only a set of clinical phenotypes recorded in the large consortium (such as PSC subtype, dominant strictures, concomitant inflammatory bowel disease, cancer and liver transplantation) but not detailed histopathological phenotypes or the full spectrum of pathobiological markers that are nowadays available through systems medicine technologies. Should we test rs853974 in patients with PSC to detect ones who could have a more aggressive progression of the disease? Given the fact that detected hazard ratio for requiring liver transplantation or PSC-related death among carriers of the risk rs853974 variant is low, namely 2.1 (95% confidence interval 1.7 - 2.8),\textsuperscript{6} this polymorphism is not informative in clinical practice. Finally, it has to be mentioned that only one polymorphism was detected and most likely other variants also modulate liver injury in patients with PSC. We consider that studies with a different disease might modify its progression and vice versa,\textsuperscript{8} provide answers to the many open questions concerning PSC. Stay tuned!

**DISCLOSURE STATEMENT**

There are no conflicts of interest.

**REFERENCES**


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