Annals of Hepatology
The Official Journal of the Mexican Association of Hepatology, the Latin-American Association for Study of the Liver and the Canadian Association for the Study of the Liver

OPINION

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

Marcin Krawczyk,*,** Frank Lammert*

* Department of Medicine II, Saarland University Medical Center, Homburg, Germany.
** Laboratory of Metabolic Liver Diseases, Centre for Preclinical Research, Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland.

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.[1] Its pathogenesis is unclear and, apart from liver transplantation, no effective treatment of PSC has been established.[2] 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.[3,4] 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.[5] Of note, the PSC-causing exposome has yet to be defined.

Lately Alberts, *et al.*[6] aimed at detecting genetic modifiers of PSC progression.[6] To this end an extensive, multicentric cohort comprising a total of 3,402 patients with PSC was analyzed.[6] 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".[7] 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 3.[6] 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.*[6] 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.

Manuscript received: October 1, 2017. **Manuscript accepted:** October 1, 2017.

DOI:10.5604/01.3001.0010.5271

The study by Alberts, *et al.*[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),*[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),[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 approach –for example commencing the search for genetic modifiers in experimental models of chronic cholestasis using, for example quantitative trait locus (QTL) analysis,[9] and then replicating them in well-characterized cohorts of patients– might facilitate the systematic detection of additional modifiers of liver fibrosis. Future studies in patients with other chronic liver diseases such as primary biliary cholangitis (PBC), IgG4-associated cholangiopathy and cystic fibrosis-associated liver disease should be undertaken to evaluate the role of gene polymorphisms in the progression of cholestatic liver injury.

Given all uncertainties concerning the pathogenesis of PSC studies, which like the report by Alberts, *et al.*,[6] investigate the modulators of PSC are urgently needed. On one hand, they would improve our understanding of the pathogenesis of cholestatic liver conditions; on the other hand their results could be used to stratify patients according to their inherited risk for progressive liver disease. Indeed, robust genetic markers of deterioration of liver function in PSC might easily be implemented in the clinic. Given the development of new methods of analyzing not only the genetic but the full spectrum of modifiers of disease progression, we believe that the next years might provide answers to the many open questions concerning PSC. Stay tuned!

DISCLOSURE STATEMENT

There are no conflicts of interest.

REFERENCES

1. Karlsen TH, Folseraas T, Thorburn D, Vesterhus M. *J Hepatol.* In press.
2. Krawczyk M, Ligocka J, Ligocki M, Raszeja-Wyszomirska J, Milkiewicz M, Szparecki G, Ilczuk T, et al. Does transient elastography correlate with liver fibrosis in patients with PSC? Laennec score-based analysis of explanted livers. *Scand J Gastroenterol* 2017; 29: 1-6.
3. Wiesner RH, Grambsch PM, Dickson ER, Ludwig J, MacCarty RL, Hunter EB, Fleming TR, et al. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. *Hepatology* 1989; 10: 430-6.
4. Boonstra K, Weersma RK, van Erpecum KJ, Rauws EA, Spanier BW, Poen AC, van Nieuwkerk KM, et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology* 2013; 58: 2045-55.
5. Karlsen TH, Chung BK. Genetic Risk and the Development of Autoimmune Liver Disease. *Dig Dis* 2015; 33(Suppl. 2): 13-24.
6. Alberts R, de Vries EMG, Goode EC, Jiang X, Sampaziotis F, Rombouts K, Böttcher K, et al. Genetic association analysis identifies variants associated with disease progression in primary sclerosing cholangitis. *Gut*. In press
7. Liu JZ, Hov JR, Folseraas T, Ellinghaus E, Rushbrook SM, Doncheva NT, Weersma RK, et al. Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis. *Nat Genet* 2013; 45: 670-5.
8. Karlsen TH, Lammert F, Thompson RJ. Genetics of liver disease: From pathophysiology to clinical practice. *J Hepatol* 2015; 62(1 Suppl.): S6-S14.
9. Reichert MC, Hall RA, Krawczyk M, Lammert F. Genetic determinants of cholangiopathies: Molecular and systems genetics. *Biochim Biophys Acta*. In press.

Correspondence and reprint request:
Marcin Krawczyk, MD.
Department of Medicine II. Saarland University Medical Center.
Kirrberger Str. 100. 66424 Homburg. Germany.
Tel.: +49 6841 1615000. Fax: +49 6841 1623267
E-mail: marcin.krawczyk@uks.eu