

Nonalcoholic fatty liver disease: is the IFNL4 rs368234815 variant protective from liver damage?

Enrico Galmozzi, Roberta D'Ambrosio

"A. M. and A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy

Correspondence to: Enrico Galmozzi. "A. M. and A. Migliavacca" Migliavacca Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy. Email: enrico.galmozzi@gmail.com.

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Comment on: Petta S, Valenti L, Tuttolomondo A, *et al.* Interferon lambda 4 rs368234815 TT> δ G variant is associated with liver damage in patients with nonalcoholic fatty liver disease. *Hepatology* 2017;66:1885-93.

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Nonalcoholic fatty liver disease (NAFLD) consists of a spectrum of disorders characterized predominantly by hepatic steatosis in the absence of significant alcohol consumption, potentially evolving to nonalcoholic steatohepatitis (NASH), with increased hepatocellular injury and inflammation with or without fibrosis. Factors promoting deposition of fat in the liver include obesity, diabetes, insulin resistance, and alcohol ingestion (1). Racial and ethnic differences have been reported in the prevalence of NAFLD, which is most common in East Asian Indians followed by Hispanics, Asians, Caucasians, and less frequently in African Americans (2-4). Although the reasons for these ethnic differences are still unknown, inherited factors has been found play a major role in the susceptibility to NAFLD and in its severity. Indeed, genetic elements such as the common variants in the patatin-like phospholipase domain-containing protein 3 (PNPLA3) and transmembrane 6 superfamily member 2 genes (TM6SF2) have been strongly associated not only with the development but also with the histological progression of liver damage in NAFLD patients (5,6). However, the variants in the interferon lambda (IFNL) 3/4 locus were associated with the liver fibrosis progression in hepatitis C virus (HCV) patients only (7), while contrasting results have been reported in subjects with NAFLD (8,9). In this context, the study by Petta *et al.*, conducted on a large cohort of Italian patients, adds important information about the independent

role of IFNL4 variants in the pathogenesis of NAFLD-related liver damage (10). The IFNL4 gene harbors the rs12979860 C>T polymorphism (commonly referred to as *IL28B*) in strong linkage with the causal variant rs368234815 TT/ Δ G, whose Δ G allele generates the open reading frame for the IFNL4 protein associated with either spontaneous or IFN-induced HCV clearance (11,12). Petta and colleagues reported a similar distribution rate of the IFNL4 variants among the 946 patients with a histological diagnosis of NAFLD and the 379 healthy controls, thus suggesting that IFNL4 polymorphisms do not confer per se a risk toward hepatic fat accumulation. However, in the cohort of NAFLD patients after correction for clinical/metabolic risk factors and for PNPLA3 genotype as well as for NASH, the common IFNL4 rs368234815 TT allele emerged as a major determinant of liver damage in terms of severity of fibrosis (F3-F4 by Kleiner classification). As expected, similar results were observed also for the linked common rs12979860 C allele. Furthermore, the IFNL4 variants were independently associated with secondary histological outcomes as moderate to severe lobular inflammation, with severe steatosis and NASH, especially in non-obese patient. Finally, when analyzing gene expression in 24 patients with available frozen samples, the authors found that NAFLD patients carrying the rs368234815 TT/TT genotype had more severe liver damage but decreased hepatic expression of selected interferon-stimulated genes (ISG). In particular,

among the 16 ISG analyzed, they observed a significant downregulation of IL10 receptor subunit beta (a subunit of IFNL3/4 receptor), tyrosine kinase non-receptor 1 and tyrosine kinase 2 (kinases involved in the phosphorylation of IFNL3/4 receptor subunits), as well as both STAT2 and IRS9 (part of the IFN-stimulated gene factor 3 complex). Based on these results, the authors speculate that lower hepatic expression of ISG in NAFLD patients not carrying the rs368234815 Δ G allele, could expose them to a higher risk of liver damage by reducing the ISG-mediated anti-inflammatory response. Nevertheless, the study by Petta *et al.* leaves open an important issue, i.e., what could be the molecular link between the IFNL4 protein expression, the poor response to IFN observed in HCV infection and the protection against hepatic damage found both in HCV and NAFLD patients. In this regard, recent publications showed that IFNL4 protein induces a strong long-term expression of the ubiquitin specific peptidase 18 (USP18) protein in chronic hepatitis C patients (13) and in primary human hepatocytes (14), leading to an attenuated response to IFN- α by inhibition of the Janus kinase (JAK)-signal transducers and activators of transcription (STAT) cascade. Moreover, another study demonstrated that the USP18 expression in hepatocyte ameliorates hepatic steatosis by deubiquitinating the transforming growth factor β -activated kinase 1 (TAK1), which in turns suppressed the downstream c-Jun N-terminal kinase and nuclear factor kappa B inflammatory signaling pathways (15). Taken together, these results provide a convincing molecular explanation of how the IFNL4 protein, through the induction of the multifunctional ISG-encoded peptidase USP18, can link the inhibition of the IFN response to the protection against hepatic damage observed in various liver disorders such as the HCV infection and NAFLD.

In conclusion, the identification of IFNL4 variants as relevant players in the pathogenesis of NAFLD, represents an important step forward in the study of genetic factors involved in this emerging leading cause of chronic liver disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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