8. Visentini M, Cagliuso M, Conti V, et al. Clonal B cells of HCV-associated mixed cryoglobulinemia patients contain exhausted marginal zone-like and CD21 low cells overexpressing Stra13. *Eur J Immunol*. 2012;42:1468-1476.

DOI: 10.1111/apt.14901

Editorial: surviving your genes—the role of *PNPLA3* variation in end-stage liver disease

Nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) not only represent leading causes of chronic liver damage[1,2] but share significant pathophysiological pathways of disease.[3] Current evidence suggests that NAFLD has ostensibly incremented not only the burden of long-term complications of end-stage liver damage, including cirrhosis and hepatocellular carcinoma, but also liver- and non-liver-related mortality.

While it is difficult to accurately predict which NAFLD patients will clinically evolve more dramatically, it is clearly known that the presence and severity of liver fibrosis[4,5] are major determinants of the natural history of the disease. Other concurrent factors that may modify the clinical course of NAFLD predisposing to more aggressive and severe damage include age, sex, ethnicity, comorbidities, and genetic and epigenetic factors (Figure 1). The weight of each of these factors in determining the risk of progression to cirrhosis and decompensation in either NAFLD or ALD is only partially understood, particularly the size of the effect of the genetic influence.

In a recent issue of *AP&T*, Mandorfer and colleagues retrospectively evaluated the impact of the missense *PNPLA3*-rs738409 C>G variant on liver-related mortality in a cohort of patients with different underlying diseases and portal hypertension at the time of diagnosis.[6] The authors observed that homozygous status of the risk G-allele (rs738409-GG) substantially increased mortality rates among patients with NAFLD/ALD two-fold without influencing survival rates in patients with viral hepatitis. Altogether, these interesting results require some reflection. First, mortality rates were significantly influenced by *PNPLA3* variant only in the recessive model of inheritance, indicating that two copies of the G-allele seem to be required for increasing the risk of death. One might presume, however, that owing to the small sample size of the included cohort, the effect of the variant under the additive model, which is the model that has been largely replicated as a modifier of the presence of NASH and fibrosis,[7] could not be properly assessed. Second, while the authors have correctly adjusted their results by competing covariates, one might still argue what the specific role of *PNPLA3* variant is in determining mortality rates as the variant is undeniably a strong modifier of the severity of liver steatosis and fibrosis - the initial and final outcomes, respectively (Figure 1). The lack of association between the variant and a surrogate of steatosis may indicate the loss of a substantial proportion of functional organ mass in these patients with end-stage hepatic disease. In this particular scenario, it is difficult to explain the lack of effect of the *PNPLA3* variant on mortality due to viral hepatitis.

Finally, one might speculate that higher mortality rates in NAFLD/ALD are indeed explained by yet unexplored gene-by-gene interaction(s) with variant(s) located in gene(s) that may potentially modify the course of cirrhosis and portal hypertension, then amplifying the presence of deadly complications. For example, regulators of hepatic and systemic vasomotor activity, hemodynamic circulation and vascular remodelling, such as members of the angiotensin system,[8] might open further avenues for exploration novel gene-gene interaction networks and therapeutic options.

ACKNOWLEDGEMENTS

Declaration of personal interests: None.

FUNDING INFORMATION

Agencia Nacional de Promoción Científica y Tecnológica, Fondo para la Investigación Científica y Tecnológica (*FonCyT*) (PICT 2014-0432 and PICT 2015-0551 to SS and PICT 2014-1816 to CJP).

ORCID

C. J. Pirola http://orcid.org/0000-0001-8234-4058
S. Sookoian http://orcid.org/0000-0001-5929-5470

LINKED CONTENT

This article is linked to Mandorfer et al papers. To view these articles visit https://doi.org/10.1111/apt.14856 and https://doi.org/10.1111/apt.14932.

C. J. Pirola[1,2]
S. Sookoian[1,3]
[1]*Institute of Medical Research A Lanari, University of Buenos Aires, Ciudad Autonoma de Buenos Aires, Argentina*
[2]*Department of Molecular Genetics and Biology of Complex Diseases, Institute of Medical Research (IDIM), National Scientific and Technical Research Council (CONICET), University of Buenos Aires, Ciudad*

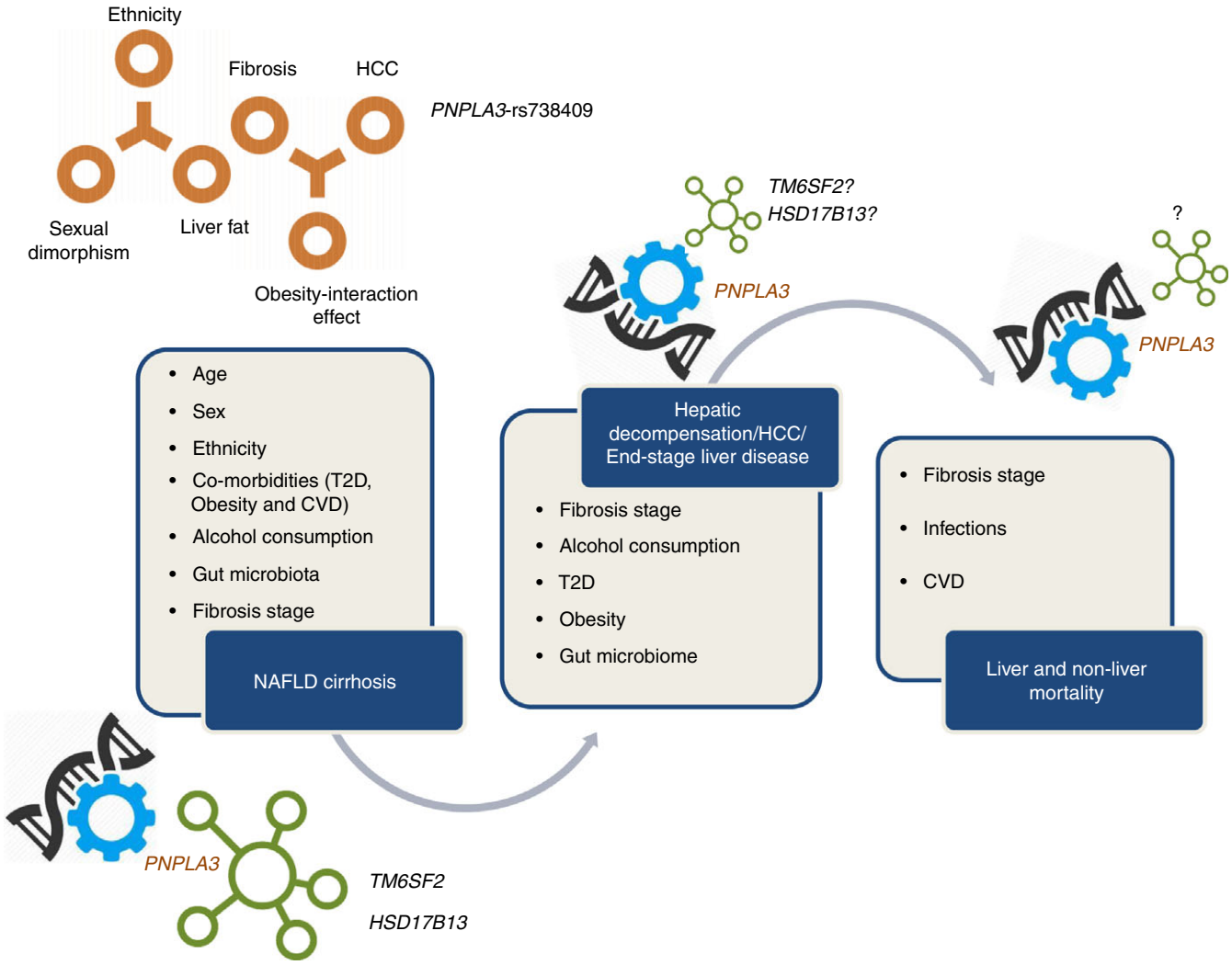

FIGURE 1 The role of *PNPLA3*-rs738409 in the Natural History of Progressive NASH. The figure depicts known risk factors involved in modulating the aggressive course of NAFLD from NASH (nonalcoholic steatohepatitis)-cirrhosis→hepatic decompensation, hepatocellular carcinoma (HCC) to→ all causes of death. Genetic factors: *PNPLA3* –missense rs738409 variant (I148M p.Ile148Met, based on the position of the variant on the protein) modulates the susceptibility of NAFLD (5.3% of the total variance),[7] the progression into NASH and the severity of liver fibrosis (OR 1.88 per G allele),[7] and potentially, the development of HCC.[9] The variant also modulates other factors, including sex (there is a negative correlation between male sex and the effect of the rs738409 on liver fat content[7]) and adiposity,[10] and presents large population diversity (from 12% in African population to 48% in South American and Mexican population) (http://browser.1000genomes.org/Homo_sapiens/Variation/Population). The natural course of NAFLD, particularly the progression to severe histological stages is modulated by other variants as well, including *TM6SF2*-rs58542926 and the newly discovered insertion variant in *HSD17B13* (rs72613567:TA),[11] the later conferring protection from chronic liver damage. Nevertheless, is still uncertain the role of these two variants in the development of HCC and decompensated liver disease. What is still poorly known is the burden of genetic influence in determining mortality and survival from aggressive NASH. Fibrosis is a strong covariate that associates with both, the genetic predisposition (*PNPLA3*-rs738409) and the course of the disease. Therefore, fibrosis is a strong confounding factor as it seems to be the consequence of the exposure as well. Hence, the association between the variant and the covariate-fibrosis could bias the estimated effect of rs738409 on hepatic decompensation and mortality in-patients with NAFLD-cirrhosis and portal hypertension. Information regarding gene-gene interaction and proper design in future studies, including longitudinal studies are essential to uncovering the role of genetic factors in survival and mortality from NASH-cirrhosis

Autonoma de Buenos Aires, Argentina
[3]*Department of Clinical and Molecular Hepatology, Institute of Medical Research (IDIM), National Scientific and Technical Research Council (CONICET), University of Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina*
Email: sookoian.silvia@lanari.fmed.uba.ar

REFERENCES

1. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67:328-357.

2. Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH. ACG clinical guideline: alcoholic liver disease. *Am J Gastroenterol*. 2018;113:175-194.
3. Sookoian S, Pirola CJ. Systems biology elucidates common pathogenic mechanisms between nonalcoholic and alcoholic-fatty liver disease. *PLoS ONE*. 2013;8:e58895.
4. Hagstrom H, Nasr P, Ekstedt M, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. *J Hepatol*. 2017;67:1265-1273.
5. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun W, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease. *Gastroenterology*. 2018; https://doi.org/10.1053/j.gastro.2018.04.034
6. Mandorfer M, Scheiner B, Stättermayer AF, et al. Impact of patatin-like phospholipase domain containing 3 rs738409 G/G genotype on hepatic decompensation and mortality in patients with portal hypertension. *Aliment Pharmacol Ther*. 2018;48:451-459.
7. Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. *Hepatology*. 2011;53:1883-1894.
8. Sookoian S, Castano G, Garcia SI, Viudez P, Gonzalez C, Pirola CJ. A1166C angiotensin II type 1 receptor gene polymorphism may predict hemodynamic response to losartan in patients with cirrhosis and portal hypertension. *Am J Gastroenterol*. 2005;100:636-642.
9. Trepo E, Nahon P, Bontempi G, et al. Association between the PNPLA3 (rs738409 C>G) variant and hepatocellular carcinoma: evidence from a meta-analysis of individual participant data. *Hepatology*. 2014;59:2170-2177.
10. Stender S, Smagris E, Lauridsen BK, et al. Relationship between genetic variation at PPP1R3B and levels of liver glycogen and triglyceride. *Hepatology*. 2018;67:2182-2195.
11. Abul-Husn NS, Cheng X, Li AH, et al. A protein-truncating HSD17B13 variant and protection from chronic liver disease. *N Engl J Med*. 2018;378:1096-1106.

DOI: 10.1111/apt.14932

Editorial: surviving your genes—the role of *PNPLA3* variation in end-stage liver disease. Authors' reply

EDITORS,

We thank Drs. Pirola and Sookoian for reviewing the role of the *rs738409 C>G p.I148M* variant in the patatin-like phospholipase domain containing 3 (*PNPLA3*) gene and its interaction with other genetic and nongenetic factors in modulating the course of (non-alcoholic) fatty liver disease as well as for their insightful comments on our manuscript.[1,2]

Drs. Pirola and Sookoian argue that it remains unclear whether the *PNPLA3 G* allele directly impacts liver-related mortality, since the *G* allele is linked to liver fibrosis, which drives the development of complications in fatty liver disease. Importantly, patients were characterised by hepatic venous pressure gradient (HVPG) measurement, which shows a good correlation with quantitative measures of liver fibrosis, such as collagen proportionate area (CPA).[3] Both HVPG and CPA allow for sub-classification of advanced chronic liver disease (ACLD; ie, advanced liver fibrosis/cirrhosis), and thus, have important prognostic implications.[4] However, in addition to the structural component (eg, liver fibrosis), there is also a dynamic component contributing to increased intrahepatic resistance,[5] which is particularly relevant in the presence of ongoing hepatic injury/inflammation[6,7] and might also be affected by *PNPLA3* genotype due to its implications on hepatic stellate cell activation.[8] Thus, HVPG, as a function of both the structural and dynamic component of intrahepatic resistance as well as the severity of splanchnic vasodilatation and hyperdynamic circulation,[9] might even be a better indicator of liver disease severity than liver fibrosis. For instance, in non-abstinent patients with alcoholic liver disease (ie, ongoing hepatic injury/inflammation), HVPG predicted clinical outcomes, while CPA (only indicative of the structural component, ie, liver fibrosis) did not.[10]

Importantly, all patients included in our study had portal hypertension, indicating ACLD.[2] Moreover, we accounted for potential differences in the severity of liver disease at baseline by adjusting all our survival analyses for HVPG. Thus, the observed association between *PNPLA3 G/G* genotype and hepatic decompensation/(liver-related) mortality in patients with fatty liver disease cannot be explained by a more rapid progression to ACLD or more severe liver fibrosis/portal hypertension at baseline. Interestingly, similar observations were made in *PNPLA3 G* allele carriers with alcoholic liver disease listed for liver transplantation,[11] or survivors of an episode of severe alcoholic hepatitis harbouring the *PNPLA3 G/G* genotype.[12] It is easily conceivable that harbouring the *PNPLA3 G/G* genotype worsened prognosis in patients with fatty liver disease by propagating the progression of liver fibrosis and portal hypertension during follow-up. Nevertheless, the exact pathophysiological mechanisms, which seem to be unrelated to hepatic steatosis,[2] as well as the contribution of other unexplored factors (eg, gene-gene interactions, as suggested by Drs. Pirola and Sookoian), clearly warrant further study.

ACKNOWLEDGEMENT

The authors' declarations of personal and financial interests are unchanged from those in the original article.[2]