DOI: 10.1111/liv.14333

EDITORIAL

Liver INTERNATIONAL WILEY

# Uncovering the genetics of cirrhosis: New plots for the usual suspects

See Article on Page 405

Cirrhosis is the end-stage and the turning point in the natural history of liver disease, as is the major determinant of hepatic decompensation and cancer. Chronic viral hepatitis, alcohol abuse and dysmetabolism are the major causes of this condition. However, individuals respond differently to liver damage triggers, and inherited factors and family history have a large role in explaining this variability.[1]

In this issue of *Liver International*, Chen *et al*. examined, by unbiased genome-wide screening coupled with the validation of strong candidates, the main common genetic variants predisposing to cirrhosis in Europeans.[2] The study was conducted in a large population-based cohort, namely UK Biobank including 1088 individuals with and 407 873 without cirrhosis, and validated in the Michigan Genomic initiative cohort of 875 surgical patients with and 31 221 without cirrhosis. The most important findings are reported in Table 1.

Genome-wide analysis highlighted that, considering the prevalence and effect size, the *PNPLA3* p.I148M variant is not only the main genetic cause of fatty liver,[3] but also of cirrhosis. Though less prevalent, the *HFE* p.C282Y variant of hereditary haemochromatosis conferred a similar increase in the risk.[4] Furthermore, by a candidate approach it was possible to confirm in both study cohorts that the low-frequency *SERPINA1* p.E342K variant responsible for most cases of α1-antitrypsin deficiency had a large impact on the individual risk.[5]

These results reinforce the notion that hepatic fat and lipotoxicity are major drivers of liver disease.[6,7] Indeed, besides the major role played by *PNPLA3*, variants in *TM6SF2*, *MBOAT7* and *HSD17B13* regulating this pathway were also associated with cirrhosis in UK Biobank. The same variants in *PNPLA3*, *TM6SF2*, *HSD17B13* and *SERPINA1* predisposed to alcoholic and metabolic cirrhosis in the Geisinger Health Study including 46 544 European individuals.[8] The novelty of the study by Chen *et al*[2] extended to the evaluation of the impact of risk variants on non liver-related traits. In line with independent findings,[4,9,10] both the *HFE* and *SERPINA1* variants decreased circulating lipids, thereby possibly contributing to fatty liver by inducing endoplasmic reticulum stress and impairment of lipoprotein secretion.[9,11]

Concerning other mechanisms of liver damage, data suggest that even the mild hepatic iron accumulation typically favoured by carriage of *HFE* p.C282Y[10] predisposes to cirrhosis. Confirmation of the impact on liver outcomes in participants stratified by genotypic data, concurrent risk factors, and iron status is still required. However, this interpretation is consistent with new evidence indicating that heterozygous carriage of *HFE* p.C282Y and *SERPINA1* p.E342K variants, previously deemed as autosomal recessive traits, favours liver disease.[4,5] In addition, hepatic

**TABLE 1** Common genetic causes of cirrhosis in Europeans[2]

| Variant | Gene | Protein variation | AF | Beta | Main mechanism | Pleiotropic effects |
|---|---|---|---|---|---|---|
| Genome-wide analysis | | | | | | |
| rs738409 C > G | *PNPLA3* | p.I148M | 0.22-0.23 | 0.27-0.47 | Lipid accumulation | Blood traits (lower platelets and leucocytes, higher haemoglobin), diabetes |
| rs1800562 G > A | *HFE* | p.C282Y | 0.06-0.08 | 0.30-0.45 | Iron overload | Lipid metabolism (lower circulating lipids), iron overload-related traits and higher haemoglobin |
| Replicated candidate variants | | | | | | |
| rs28929474 C > T | *SERPINA1* | p.E342K | 0.02-0.02 | 0.46-0.73 | ER stress | Lipid metabolism (lower circulating lipids), increased adiposity, emphysema |

Abbreviations: AF, allelic frequency in the included cohorts; Beta, effect on the risk of cirrhosis per risk allele; ER, endoplasmic reticulum; *HFE*, haemochromatosis gene; *PNPLA3*, Patatin-like phospholipase domain-containing 3; *SERPINA1*, Serine protease inhibitor 1 (encoding for α1-antitrypsin).

Main mechanisms are derived from the literature, pleiotropic effects are those identified by Chen *et al*[2].

Causal variants, which were significant at genome-wide level and/or replicated in the two study cohorts, are reported.

Handling editor: Alessio Aghemo

**Editor perspective:** Comment on '*Genetic variants that associate with liver cirrhosis have pleiotropic effects on human traits*', Chen et al https://doi.org/10.1111/liv.14321. PMID: 318153

fat has recently emerged as a major determinant of iron stores by facilitating iron absorption,[10,12,13] especially in carriers of *HFE* p.C282Y[14] and *SERPINA1* p.E342K.[15,16] Chen *et al* also highlighted that *HFE* p.C282Y favours haemoglobinization, thereby protecting against iron deficiency and anaemia,[2] which might have provided an evolutionary advantage to carriers.[4,10,17] An intriguing finding was that cirrhosis risk variants in *PNPLA3*, *TM6SF2* and *HSD17B13* were also associated with higher haemoglobin levels, as well as with other blood traits.

Whether the impact of cirrhosis risk variants on this wide spectrum of biological pathways has a causal role in determining liver damage, conferred some evolutionary advantage that became detrimental in affluent societies, or is an unrelated pleiotropic effect remains to be determined. Furthermore, it will be important to investigate the genetic causes of cirrhosis in even larger cohorts and in non-European populations, as for example the *HFE* and *SERPINA1* variants are rare in other ethnic groups.

Notwithstanding, recent studies have demonstrated that 'old' genetic causes of liver disease have a wider than expected impact on the risk of cirrhosis, and act through new and diverse biological pathways, highlighting derangement of the fat-iron axis as one possible common driver of liver disease. These conclusions have clinical relevance for risk stratification and targeted prevention of liver-related mortality through reduction of liver fat and lipotoxicity. They also suggest that iron reduction approaches should perhaps be reconsidered in those with evidence of high stores.[18,19]

## KEYWORDS

anaemia, cirrhosis, fatty liver, genetics, iron metabolism, risk stratification, steatosis

## CONFLICT OF INTEREST

The author declares that he does not have any conflict of interest relevant to this manuscript. He reports having received during the last 5 years speaking fees from MSD, Gilead, AlfaSigma, AbbVie, having served as a consultant of: Gilead, Pfizer, Astra Zeneca, Novo Nordisk, Diatech Pharmacogenetics and Intercept and having received research grants from: Gilead.

Luca Valenti[1,2]

[1]*Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy*
[2]*Translational Medicine – Department of Transfusion Medicine and Hematology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

**Correspondence**
Luca Valenti, MD MSc, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Translational Medicine – Department of Transfusion Medicine and Hematology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
Email: luca.valenti@unimi.it

## ORCID

*Luca Valenti* https://orcid.org/0000-0001-8909-0345

## REFERENCES

1. Long MT, Gurary EB, Massaro JM, et al. Parental non-alcoholic fatty liver disease increases risk of non-alcoholic fatty liver disease in offspring. *Liver Int*. 2019;39(4):740-747.
2. Chen VL, Chen Y, Du X, Handelman SK, Speliotes EK. Genetic variants that associate with liver cirrhosis have pleiotropic effects on human traits. *Liver Int*. 2019; in press. https://doi.org/10.1111/liv.14321 [Epub ahead of print]
3. Eslam M, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: Clinical impact. *J Hepatol*. 2018;68(2):268-279.
4. Pilling LC, Tamosauskaite J, Jones G, et al. Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank. *BMJ*. 2019;364:k5222.
5. Strnad P, Buch S, Hamesch K, et al. Heterozygous carriage of the alpha1-antitrypsin Pi*Z variant increases the risk to develop liver cirrhosis. *Gut*. 2019;68(6):1099-1107.
6. Pelusi S, Valenti L. Hepatic fat as clinical outcome and therapeutic target for nonalcoholic fatty liver disease. *Liver Int*. 2019;39(2):250-256.
7. Dongiovanni P, Stender S, Pietrelli A, et al. Causal relationship of hepatic fat with liver damage and insulin resistance in nonalcoholic fatty liver. *J Intern Med*. 2018;283(4):356-370.
8. 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(12):1096-1106.
9. Hamesch K, Mandorfer M, Pereira VM, et al. Fibrosis and metabolic alterations in adults with alpha-1-antitrypsin deficiency caused by the Pi*ZZ mutation. *Gastroenterology*. 2019;157(3):pp. 705-719 e18.
10. Wilman HR, Parisinos CA, Atabaki-Pasdar N, et al. Genetic studies of abdominal MRI data identify genes regulating hepcidin as major determinants of liver iron concentration. *J Hepatol*. 2019;71(3):594-602.
11. Valenti L, Dongiovanni P, Fracanzani AL, et al. Increased susceptibility to nonalcoholic fatty liver disease in heterozygotes for the mutation responsible for hereditary hemochromatosis. *Dig Liver Dis*. 2003;35(3):172-178.
12. Ryan JD, Armitage AE, Cobbold JF, et al. Hepatic iron is the major determinant of serum ferritin in NAFLD patients. *Liver Int*. 2018;38(1):164-173.
13. Rametta R, Dongiovanni P, Pelusi S, et al. Hepcidin resistance in dysmetabolic iron overload. *Liver Int*. 2016;36(10):1540-1548.
14. Valenti L, Fracanzani AL, Bugianesi E, et al. HFE genotype, parenchymal iron accumulation, and liver fibrosis in patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2010;138(3):905-912.
15. Schaefer B, Haschka D, Finkenstedt A, et al. Impaired hepcidin expression in alpha-1-antitrypsin deficiency associated with iron overload and progressive liver disease. *Hum Mol Genet*. 2015;24(21):6254-6263.
16. Valenti L, Dongiovanni P, Piperno A, et al. alpha1-Antitrypsin mutations in NAFLD: High prevalence and association with altered iron metabolism but not with liver damage. *Hepatology*. 2006;44(4):857-864.
17. Heath KM, Axton JH, McCullough JM, Harris N. The evolutionary adaptation of the C282Y mutation to culture and climate during the European Neolithic. *Am J Phys Anthropol*. 2016;160(1):86-101.
18. Dongiovanni P, Fracanzani AL, Fargion S, Valenti L. Iron in fatty liver and in the metabolic syndrome: a promising therapeutic target. *J Hepatol*. 2011;55(4):920-932.
19. Valenti L, Fracanzani AL, Dongiovanni P, et al. A randomized trial of iron depletion in patients with nonalcoholic fatty liver disease and hyperferritinemia. *World J Gastroenterol*. 2014;20(11):3002-3010.