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## EDITORIAL



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

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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.<sup>1</sup>

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.<sup>2</sup> 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,<sup>3</sup> but also of cirrhosis. Though less prevalent, the *HFE* p.C282Y variant of hereditary haemochromatosis conferred a similar increase in the risk.<sup>4</sup> 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  $\alpha$ 1-antitrypsin deficiency had a large impact on the individual risk.<sup>5</sup>

These results reinforce the notion that hepatic fat and lipotoxicity are major drivers of liver disease.<sup>6,7</sup> 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.<sup>8</sup> The novelty of the study by Chen *et al.*<sup>2</sup> extended to the evaluation of the impact of risk variants on non liver-related traits. In line with independent findings,<sup>4,9,10</sup> 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.<sup>9,11</sup>

Concerning other mechanisms of liver damage, data suggest that even the mild hepatic iron accumulation typically favoured by carriage of *HFE* p.C282Y<sup>10</sup> 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.<sup>4,5</sup> In addition, hepatic

**TABLE 1** Common genetic causes of cirrhosis in Europeans<sup>2</sup>

Variant	Gene	Protein variation	AF	Beta	Main mechanism	Pleiotropic effects
Genome-wide analysis						
rs738409 C > G	<i>PNPLA3</i>	p.I148M	0.22-0.23	0.27-0.47	Lipid accumulation	Blood traits (lower platelets and leucocytes, higher haemoglobin), diabetes
rs1800562 G > A	<i>HFE</i>	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	<i>SERPINA1</i>	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  $\alpha$ 1-antitrypsin).

Main mechanisms are derived from the literature, pleiotropic effects are those identified by Chen *et al.*<sup>2</sup>

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

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fat has recently emerged as a major determinant of iron stores by facilitating iron absorption,<sup>10,12,13</sup> especially in carriers of *HFE* p.C282Y<sup>14</sup> and *SERPINA1* p.E342K.<sup>15,16</sup> Chen *et al* also highlighted that *HFE* p.C282Y favours haemoglobinization, thereby protecting against iron deficiency and anaemia,<sup>2</sup> which might have provided an evolutionary advantage to carriers.<sup>4,10,17</sup> 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.<sup>18,19</sup>

## 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, Diatch Pharmacogenetics and Intercept and having received research grants from: Gilead.

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