

# A vaccine for Beethoven's vulnerable liver

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**Keywords:** Alcoholic liver disease, HBV, Liver cirrhosis

Dear EJCI Editor,

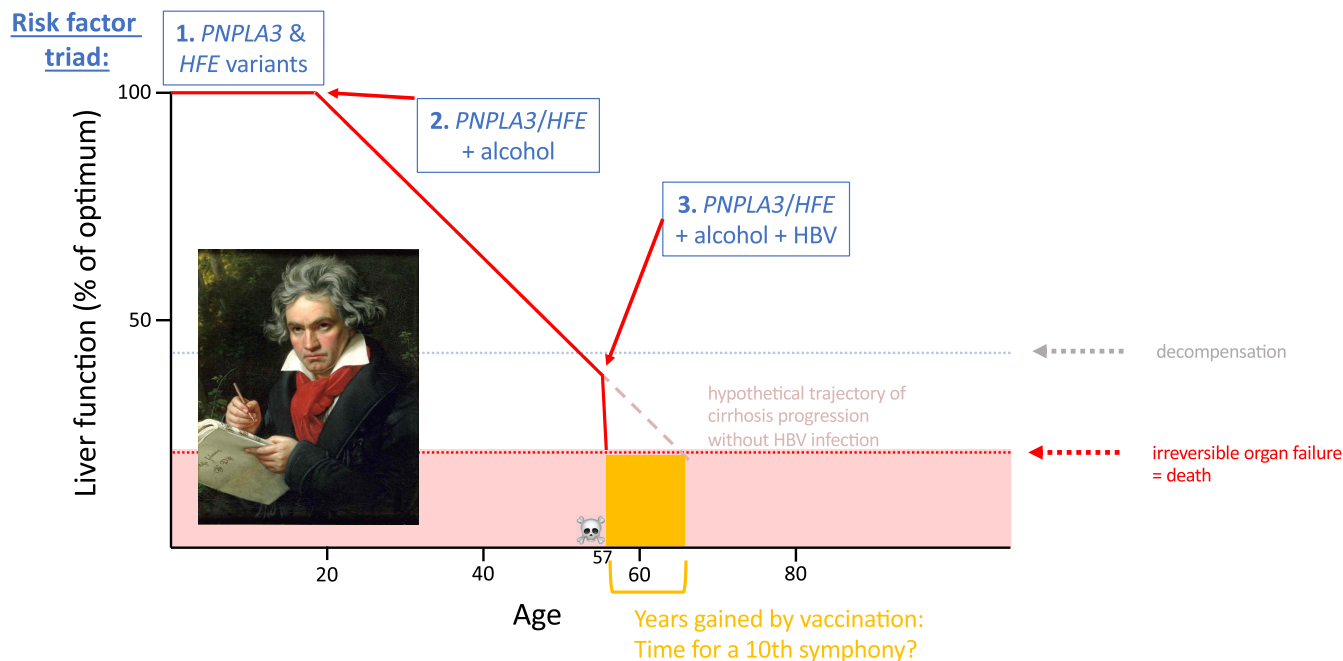
The recent report<sup>1</sup> presenting a thorough analysis of Ludwig van Beethoven's genome has made headlines in scientific and non-scientific journals. The famous composer is known to have suffered, among other ailments, from cirrhosis, and the study by Begg et al.<sup>1</sup> adds a few exciting new details to this picture. In brief, the authors showed that Beethoven carried a combination of genetic variants (i.e. *HFE* p.His63Asp and p.Cys282Tyr as well as *PNPLA3* p.I148M) that rendered his liver particularly vulnerable to external noxae, here iron, alcohol and caloric overload.<sup>2</sup> Hence, regular alcohol consumption, probably combined with rich food over many years is likely to represent the major cause for his chronic liver disease. Interestingly, Begg et al.<sup>1</sup> also performed a metagenomic analysis of Beethoven's hair locks and found that in the last months of his life, he might have suffered from hepatitis B virus (HBV) infection.

Although the mass media and the authors of the report<sup>1</sup> seem to have focused on the analysis of Beethoven's genome, the detection of HBV infection should not be overseen as it might be highly relevant to Beethoven's death, but also to our everyday liver patients. Apparently, the composer experienced a first episode of jaundice 6 years before his death in 1827, possibly a first sign of decompensation. The fact that it took a couple of decades of chronic alcohol consumption on the background of his high-risk genotype to develop clinical liver disease shows the organ's

enormous regenerative capacity. This proverbial resilience has been known for a long time and features prominently in the Prometheus saga from 800 BC, which Beethoven refers to in his ballet 'The Creatures of Prometheus Op. 43', composed in 1801. One could speculate that during the last months of his life, the composer might have suffered from acute-on-chronic liver failure (ACLF) caused by the HBV infection on top of his alcohol-induced progressive liver damage. This additional insult precipitated the lethal deterioration of liver function (Figure 1). ACLF is a new disease entity,<sup>3</sup> defined as acute liver failure in patients with chronic liver diseases. Bajaj et al.<sup>4</sup> described ACLF 'as a potentially reversible condition in patients with chronic liver disease with or without cirrhosis that is associated with the potential for multiple organ failure and mortality within 3 months in the absence of treatment of the underlying liver disease, liver support, or liver transplantation'. The data available in Begg's paper<sup>1</sup> are not sufficient to determine if Beethoven suffered from multiple organ failure or only liver failure. Of note, acute viral infections have been identified as precipitating events of ACLF.<sup>5,6</sup> In terms of hepatitis B, acute infection is rare but can result in rapid dysfunction of pre-injured liver, and flares of chronic HBV infection have been described as triggers of ACLF.<sup>7</sup> Patients with HBV-ACLF have been reported to suffer from high short-term mortality,<sup>8</sup> in line with the data from the metagenomic analyses revealing the viral infection, and Beethoven's rapid demise.

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**FIGURE 1** showing the hypothetical sequential impact of *PNPLA3* and *HFE* risk genotype, chronic alcohol abuse and HBV infection on LvB's liver, based on a figure by Jalan et al.<sup>11</sup> Despite a vicious combination of *PNPLA3* risk genotype and chronic alcohol consumption, the organ proves its proverbial regenerative capacity and resilience to maintain sufficient function over 30+ years of abuse.

Begg's study<sup>1</sup> is a major success of molecular genetic analyses. However, we reckon the observation that Beethoven suffered from HBV infection and that ACLF can be triggered by acute viral infections deserves more prominence. This finding might be used as a motivational lever to promote wider acceptance for vaccination against viral infections. Indeed, as highlighted by the pandemic and reviewed recently by Jeng et al.,<sup>9</sup> vaccinations represent an effective means to prevent severe viral infections. Regardless of how long Beethoven suffered from HBV infection, one can imagine that prior vaccination against HBV, if it had been available at the time, might have prevented the acute deterioration of his vulnerable liver, which was challenged by the "devil's triangle" of gene variants, environmental toxins, and virus. This represents an important positive message, which is urgently needed in view of the persisting vaccine hesitancy following COVID-19.<sup>10</sup>

#### ACKNOWLEDGEMENTS

Portrait of Beethoven by Stieler was reproduced in Figure 1 with kind permission of Beethoven Haus Bonn. Open Access funding enabled and organized by Projekt DEAL.

#### CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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**How to cite this article:** Liebe R, Lammert F, Krawczyk M. A vaccine for Beethoven's vulnerable liver. *Eur J Clin Invest*. 2023;53:e14035. doi:[10.1111/eci.14035](https://doi.org/10.1111/eci.14035)