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Title: Primary liver injury and delayed resolution of liver stiffness after alcohol detoxification in heavy drinkers with the PNPLA3 variant I148M

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1 What did this study explore?

Rausch et al. analyzed the influence of PNPLA3 genotype in heavy drinkers on serum markers and liver stiffness (LS) during all stages of alcoholic liver disease (steatosis, steatohepatitis and fibrosis) prior and after alcohol detoxification. Liver damage (inflammation/ballooning) with increased LS appears to be the primary event in GG carriers in response to heavy alcohol consumption, which resolves after alcohol withdrawal. Interestingly, GG carriers require a longer period of medical care in the hospital for alcohol detoxification showing advanced liver fibrosis and pointing toward more severe alcohol-related health problems.

2 How did the authors perform all experiments?

Caucasian heavy drinkers (n = 521) with a mean alcohol consumption of 192.1 g/d (median alcohol consumption: 169.0 g/d; 95%CI: 179.0-203.3) were enrolled at the Salem Medical Center, University of Heidelberg. LS was measured by transient

elastography (TE; Fibroscan, Echosens SA, Paris, France). LS and serum markers were prospectively studied in these patients with all stages of alcoholic liver disease (steatosis, steatohepatitis, fibrosis) prior and after alcohol detoxification with a mean observation interval of 6.2 ± 3.2 d. A liver biopsy with histological analysis including the Kleiner score was obtained in 80 patients.

3 How did the authors process all experimental data?

We used descriptive statistics to compute equally distributed data, including means, standard deviations and frequencies. Not normally distributed data were log transformed before statistical analysis. Comparisons of the genotype distribution of CC, GG and combined CG and GG were performed and the Spearman correlation or Chi square test for non-parametric variables (regression coefficient r, p) was used to determine the associations between laboratory findings, LS, histological scores and the genotypes. To determine whether there are significant differences between the variants (CC, CG, GG or CG combined with GG) we used a two-sample Student's *t*-test when the data were normally distributed. Binary logistic regression analysis was calculated to proof possible effects of genotype, gender, age and BMI on the outcome of AST-adapted cut-off values for fibrosis staging. Statistical calculations were performed with SPSS (version 21.0, IBM, SPSS) or SAS (version 9.4, SAS) software and two-sided *P* values < 0.05 were considered statistically significant. Statistical methods of this study were reviewed by Thomas Bruckner from Institute of Medical Biometry and Informatics, University of Heidelberg, Heidelberg, Germany.

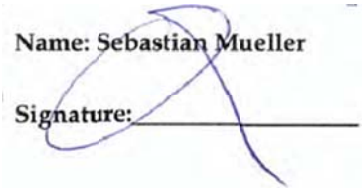
4 How did the authors deal with the pre-study hypothesis?

While the study confirmed the pre-study hypothesis in terms of PNPLA3 I148M-mediated liver damage and elevated LS, it did not reveal a pronounced role of steatosis nor was LS correlated with liver steatosis. These unexpected findings are discussed in detail in the paper.

5 What are the novel findings of this study?

This is the first study, which investigated in detail the impact of PNPLA3 I148M status, first, on detailed histological subscores in heavy drinkers, and, second, on liver stiffness and other laboratory parameters in response to alcohol withdrawal.

Sincerely,



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