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PRIMARY HEPATOCELLULAR DAMAGE AND SUPPRESSED FAT MOBILIZATION IN HEAVY DRINKERS WITH PNPLA3 G GENOTYPE

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PNPLA3 GG genotype has been identified as important progression factor in patients with ALD and NAFLD. Since PNPLA3 function remains poorly understood, we here studied genotype distribution and various noninvasive, serum and molecular

markers of liver damage and steatosis in 521 heavy drinkers (mean alcohol consumption 191.2 g per day) prior and after alcohol withdrawal. Liver histology was obtained in 80 patients and allowed additional immunostaining for lipid droplet (LD)-associated proteins (N = 47) and expression of mRNA transcripts (N = 24). PNPLA3 GG carriers (8.2%) drunk significantly less high percentage beverages (23% vs 55%, $p < 0.001$) and showed no increased weight, BMI or diabetes. Liver stiffness (LS) was significantly elevated in G carriers (median 18 vs. 11 kPa) and correlated with histological signs of fibrosis ($r = 0.8$) and liver damage (ballooning, $r = 0.7$), but not with steatosis. In CG carrier, LS decreased significantly from 17.6 to 12.7 but less in GG carriers. Moreover, hepatic fat content as quantified by CAP did not significantly differ between the groups and decreased equally by 30 dB/m. On the molecular level, key molecules, important for lipolysis and flow of free fatty acids to the liver, were drastically reduced in G allele carriers. These included the liver-synthesized serum ApoA1, the LD-associated protein perilipin5 and the recently identified hepato-protective transcriptional cofactor transducin beta-like-related 1 (TBLR1).

Conclusion. In heavy drinkers, PNPLA3 GG primarily correlates with hepatocyte damage resulting in a reversible, inflammation-associated increase of LS and the suppression of key molecules that are important for lipolysis and hepatocellular fat mobilization.