Research Article

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Association of diabetes and *PNPLA3* genetic variants with disease severity of patients with chronic hepatitis C virus infection

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Background & Aims: Genetic variants of patatin-like phospholipase domain-containing 3 (*PNPLA3*) and diabetes are associated with liver disease severity, in patients with chronic hepatitis C (CHC) infection. We aimed at exploring their interaction in determining hepatitis C virus (HCV)-related liver fibrosis.

Methods: The *PNPLA3* genetic polymorphism at rs738409 was verified in 1077 biopsy-proven CHC patients. Other clinical variables, including diabetes status, were analysed for factors associated with bridging fibrosis.

Results: Patients with advanced liver fibrosis had higher proportions of the GG genotype (14.5% *vs.* 10.4%, $p = 0.06$ in recessive model) and GG/GC genotype carriage (64.0% *vs.* 56.8%, $p = 0.03$ in dominant model). Stepwise logistic regression analysis revealed that factors predictive of advanced liver fibrosis included age (odds ratio [OR]: 1.02, 95% confidence intervals [CI]: 1.008–1.037, $p = 0.002$), diabetes (OR: 1.81, CI: 1.236–2.653, $p = 0.002$), α-fetoprotein (OR: 1.006, CI: 1.001–1.01, $p = 0.01$), platelet counts (OR: 1.009, CI: 1.006–1.012, $p < 0.001$), and *PNPLA3* rs738409 CG/GG genotype (OR: 1.34, CI: 1.006–1.785, $p = 0.046$). When patients were grouped according to their diabetes status, the *PNPLA3* genetic variants were associated with advanced liver fibrosis in diabetic patients only, but not in non-diabetic patients. The *PNPLA3* gene was the most important predictive factor of bridging fibrosis in diabetic patients, using the recessive model (OR: 4.53, CI: 1.356–15.106, $p = 0.014$) or the dominant model (OR: 2.20, CI: 1.026–4.734, $p = 0.04$). Compared to non-diabetic patients, patients with the diabetes/GG genotype were more likely to have advanced liver fibrosis (OR: 8.79, CI: 2.889–26.719, $p < 0.001$), followed by those with diabetes/non-GG genotype (OR: 1.55, CI: 1.048–2.286, $p = 0.03$).

Conclusions: The effect of *PNPLA3* genetic variants in HCV-related advanced liver fibrosis was enhanced in diabetic patients. The strong genetic–environmental interaction contributed to the high risk of advanced liver disease in CHC patients.

Keywords: HCV; CHC; Liver fibrosis; PNPLA3; SNP; DM.

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI, aspartate aminotransferase-to-Platelet Ratio Index; AFP, α-fetoprotein; CHC, chronic hepatitis C; DM, diabetes mellitus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; *PNPLA3*, patatin-like phospholipase domain-containing 3; SNP, single-nucleotide polymorphism.

Introduction

More than 170 million people are chronically infected with hepatitis C virus (HCV) [1], which is one of the most important causes of liver cirrhosis and liver related mortality. The magnitude of disease progression in chronic HCV (CHC) infection varies significantly among individuals. Several factors have been recognized as being associated with the progression of HCV-related liver fibrosis and with clinical outcomes, including age and time since initial HCV infection [2], hepatitis B virus (HBV) or/and human