The rs429358 Locus in Apolipoprotein E Is Associated With Hepatocellular Carcinoma in Patients With Cirrhosis

Info

PUBLISHED DATE
2022-01-01

JOURNAL
Hepatology Communications

LINK
https://doi.org/10.1002/hep4.1886

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Abstract

The host genetic background for hepatocellular carcinoma (HCC) is incompletely understood. We aimed to determine if four germline genetic polymorphisms, rs429358 in apolipoprotein E (APOE), rs2642438 in mitochondrial amidoxime reducing component 1 (MARC1), rs2792751 in glycerol-3-phosphate acyltransferase (GPAM), and rs187429064 in transmembrane 6 superfamily member 2 (TM6SF2), previously associated with progressive alcohol-related and nonalcoholic fatty liver disease, are also associated with HCC. Four HCC case-control data sets were constructed, including two mixed etiology data sets (UK Biobank and FinnGen); one hepatitis C virus (HCV) cohort (STOP-HCV), and one alcohol-related HCC cohort (Dresden HCC). The frequency of each variant was compared between HCC cases and cirrhosis controls (i.e., patients with cirrhosis without HCC). Population controls were also considered. Odds ratios (ORs) associations were calculated using logistic regression, adjusting for age, sex, and principal components of genetic ancestry. Fixed-effect meta-analysis was used to determine the pooled effect size across all data sets. Across four case-control data sets, 2,070 HCC cases, 4,121 cirrhosis controls, and 525,779 population controls were included. The rs429358:C allele (APOE) was significantly less frequent in HCC cases versus cirrhosis controls (OR, 0.71; 95% confidence interval [CI], 0.61-0.84; $P = 2.9 \times 10^{-5}$). Rs187429064:G (TM6SF2) was significantly more common in HCC cases versus cirrhosis controls and exhibited the strongest effect size (OR, 2.03; 95% CI, 1.45-2.86; $P = 3.1 \times 10^{-6}$). In contrast, rs2792751:T (GPAM) was not associated with HCC (OR, 1.01; 95% CI, 0.90-1.13; P = 0.89), whereas rs2642438:A (MARC1) narrowly missed statistical significance (OR, 0.91; 95% CI, 0.84-1.00; P = 0.043). Conclusion: This study associates

carriage of rs429358:C (APOE) with a reduced risk of HCC in patients with cirrhosis. Conversely, carriage of rs187429064:G in TM6SF2 is associated with an increased risk of HCC in patients with cirrhosis.