Genetic variation in TERT modifies the risk of hepatocellular carcinoma in alcohol-related cirrhosis: results from a genome-wide case-control study

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Abstract

Objective Hepatocellular carcinoma (HCC) often develops in patients with alcohol-related cirrhosis at an annual risk of up to 2.5%. Some host genetic risk factors have been identified but do not account for the majority of the variance in occurrence. This study aimed to identify novel susceptibility loci for the development of HCC in people with alcohol related cirrhosis.

Design

Patients with alcohol-related cirrhosis and HCC (cases: n=1214) and controls without HCC (n=1866), recruited from Germany, Austria, Switzerland, Italy and the UK, were included in a two-stage genome-wide association study using a case–control design. A validation cohort of 1520 people misusing

alcohol but with no evidence of liver disease was included to control for possible association effects with alcohol misuse. Genotyping was performed using the InfiniumGlobal Screening Array (V.24v2, Illumina) and the OmniExpress Array (V.24v1-0a, Illumina).

Results

Associations with variants rs738409 in PNPLA3 and rs58542926 in TM6SF2 previously associated with an increased risk of HCC in patients with alcohol-related cirrhosis were confirmed at genome-wide significance. A novel locus rs2242652(A) in TERT (telomerase reverse transcriptase) was also associated with a decreased risk of HCC, in the combined meta-analysis, at genome-wide significance ($p=6.41\times10^{-9}$, OR=0.61 (95% CI 0.52 to 0.70). This protective association remained significant after correction for sex, age, body mass index and type 2 diabetes ($p=7.94\times10^{-5}$, OR=0.63 (95% CI 0.50 to 0.79). Carriage of rs2242652(A) in TERT was associated with an increased leucocyte telomere length ($p=2.12\times10^{-44}$).

Conclusion

This study identifies rs2242652 in TERT as a novel protective factor for HCC in patients with alcohol-related cirrhosis.