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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Authors

Stephan Buch Hamish Innes Philipp Ludwig Lutz Hans Dieter Nischalke Jens U Marquardt Janett Fischer Karl Heinz Weiss Jonas Rosendahl Astrid Marot Marcin Krawczyk Markus Casper Frank Lammert Florian Eyer Arndt Vogel Silke Marhenke Johann von Felden Rohini Sharma Stephen Rahul Atkinson Andrew McQuillin Jacob Nattermann Clemens Schafmayer Andre Franke Christian Strassburg Marcella Rietschel Heidi Altmann Stefan Sulk Veera Raghavan Thangapandi Mario Brosch Carolin Lackner Rudolf E Stauber Ali Canbay Alexander Link Thomas Reiberger Mattias Mandorfer Georg Semmler Bernhard Scheiner Christian Datz Stefano Romeo Stefano Ginanni Corradini William Lucien Irving Joanne R Morling Indra Neil Guha Eleanor Barnes M Azim Ansari Jocelyn Quistrebert Luca Valenti Sascha A Müller Marsha Yvonne Morgan Jean-François Dufour Jonel Trebicka Thomas Berg Pierre Deltenre Sebastian Mueller Jochen Hampe Felix Stickel

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.