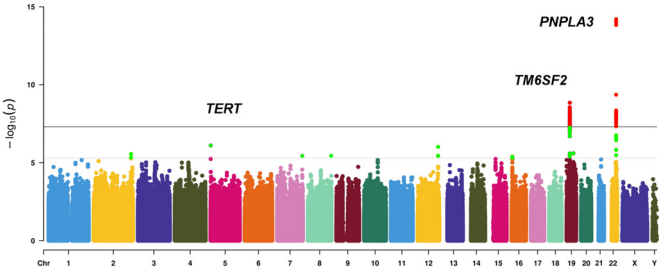
LB002

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

Stephan Buch[1], Hamish Innes[2], Philipp Lutz[3], Hans Dieter Nischalke[4], Jacob Nattermann[4], Jens U. Marquardt[5], Janett Fischer[6], Karl Heinz Weiss[7], Jonas Rosendahl[8], Astrid Marot[9], Marcin Krawczyk[10], Markus Casper[10], Frank Lammert[10], Florian Eyer[11], Arndt Vogel[12], Silke Marhenke[12], Johann von Felden[13], Rohini Sharma[14], Stephen Atkinson[15], Andrew McQuillin[15], Clemens Schafmayer[16], Christian Strassburg[17], Heidi Altmann[1], Stefan Sulk[1], Veera Raghavan Thangapandi[1], Mario Brosch[1], Carolin Lackner[18], Rudolf E. Stauber[18], Ali Canbay[19], Alexander Link[20], Thomas Reiberger[21], Mattias Mandorfer[21], Georg Semmler[21], Bernhard Scheiner[21], Christian Datz[22], Stefano Romeo[23], Stefano Ginanni Corradini[24], Luca Valenti[25], Sascha Müller[26], Marsha Morgan[15,27], Jean-Francois Dufour[28], Jonel Trebicka[29], Thomas Berg[30], Pierre Deltenre[31], Sebastian Mueller[32], Jochen Hampe[1], Felix Stickel[33]. *[1]University Hospital Dresden, TU Dresden, Medical Department 1, Dresden, Germany; [2]Glasgow Caledonian University, School of Health and Life Sciences, Glasgow, United Kingdom; [3]University of Bonn, Department of Internal Medicine I, Bonn, Germany; [4]University of Bonn, Department of Internal Medicine I, Bonn, Germany; [5]University of Luebeck, Department of Medicine, Lübeck, Germany; [6]Leipzig University Medical Center, Division of Hepatology, Department of Medicine II, Leipzig, Germany; [7]Salem Medical Center Heidelberg, Department of Internal Medicine, Heidelberg, Germany; [8]University Hospital Halle/Saale, Department of Gastroenterology, Halle/Saale, Germany; [9]Université Catholique de Louvain, Department of Gastroenterology and Hepatology, CHU UCL Namur, Belgium; [10]Saarland University, Department of Medicine II, Saarland University Medical Center, Homburg, Germany; [11]Technical University of Munich, Department of Clinical Toxicology, Klinikum Rechts der Isar, München, Germany; [12]Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; [13]University Medical Center Hamburg-Eppendorf, First Department of Medicine, Hamburg, Germany; [14]Imperial College London, London, United Kingdom; [15]University College London, UCL Institute for Liver and Digestive Health, Division of Medicine, London, United Kingdom; [16]Rostock University Medical Center, Department of General, Visceral, Vascular and Transplant Surgery, Rostock, Germany; [17]Universitätsklinikum Bonn, Medical Department 1, Bonn, Germany; [18]Medical University of Graz, Institute of Pathology, Graz, Austria; [19]University Hospital, Ruhr University Bochum, Department of Medicine, Bochum, Germany; [20]Otto-von-Guericke University, Department of Gastroenterology, Hepatology and Infectious Diseases, Magdeburg, Germany; [21]Medical University of Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Vienna, Austria; [22]Teaching Hospital of the Paracelsus Medical University Salzburg, Department of Internal Medicine, General Hospital Oberndorf, Oberndorf, Austria; [23]University of Gothenburg, Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, Wallenberg Laboratory, Gothenburg, Sweden; [24]Sapienza University of Rome, Division of Gastroenterology, Department of Translational and Precision Medicine, Gastroenterology Unit, Rome, Italy; [25]Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Internal Medicine and Metabolic Diseases, Milan, Italy; [26]Clinic Beau-Site, Department of Surgery, Berne, Switzerland; [27]UCL Institute for Liver and Digestive Health, Department of Medicine, Royal Free Campus, London, United Kingdom; [28]University of Bern, Hepatology, Department of Biomedical Research, Bern, Switzerland; [29]Goethe University Frankfurt, Department of Internal Medicine I, Frankfurt, Germany; [30]Leipzig University Medical Center, Division of Hepatology, Leipzig, Germany; [31]Centre Hospitalier Universitaire Vaudois, Division of Gastroenterology and Hepatology, Switzerland; [32]Salem Medical Center, Center for Alcohol Research, University of Heidelberg and Medical Department, Heidelberg, Germany; [33]University Hospital of Zurich, Department of Gastroenterology and Hepatology, Zurich, Switzerland*
Email: stephan.buch@uniklinikum-dresden.de

Background and aims: Hepatocellular carcinoma (HCC) often develops in patients with alcohol-related cirrhosis (ArC) at an annual risk of up to 2.9%. 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 risk factors for the development of HCC in people with alcohol related cirrhosis.
Method: Patients with alcohol-related cirrhosis with HCC (cases: n = 1, 214) and without HCC (controls: n = 1, 866), recruited from Germany, Austria, Switzerland, Italy and the UK, were included in a two-stage GWAS utilizing a case-control design. A validation cohort of 1, 520 people misusing alcohol but with no evidence of liver disease was included to control for possible association effects of alcohol misuse *per se*. Genotyping was performed using the Infinium®Global Screening Array (GSA) (version 24v2, Illumina) and the OmniExpress Array (version 24v1-0a, Illumina).
Results: Associations with variants rs738409 in *PNPLA3* and rs58542926 in *TM6SF2* previously associated with HCC in patients with alcohol-related cirrhosis were confirmed at genome-wide significance. In addition, a novel locus rs2242652 in *TERT* (telomerase reverse transcriptase) attained genome-wide significant association in the combined meta-analysis with alcohol-related HCC at ($p = 6.41 \times 10^{-9}$, odds ratio (OR) = 0.61 (95%CI, 0.52–0.72). This protective association remained significant after correction for sex, age, BMI, type 2 diabetes, and ancestry. The minor alleles of variants rs2242652 ($p = 2.12 \times 10^{-44}$) and rs10069690 ($p = 4.08 \times 10^{-84}$) in *TERT* were associated with increased leukocyte telomere length.



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

LB003

Reprogramming necroptosis limits immune responses and prevents liver cancer development

Mihael Vucur[1], Ahmed Ghallab[2], Anne Schneider[1], Jakob Kather[3], Olivier Govaere[4], Augusto Villanueva[5], Achim Weber[6], Thomas Longerich[7], Frank Tacke[8], Christoph Roderburg[1], Johannes Bode[1], Fabian Geisler[9], Ulf Neumann[10], Jan G. Hengstler[2], Mathias Heikenwälder[11], Tom Lüdde[1]. *[1]University Hospital Duesseldorf, Department of Gastroenterology, Hepatology and Infectious Disease, Germany; [2]Leibniz Research Centre for Working Environment and Human Factors (IfADo) at the Technical University Dortmund, Germany; [3]Department of Medicine III, University Hospital RWTH Aachen, Germany;, Germany; [4]Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University; [5]Division of Liver Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, United States; [6]Department of Pathology and Molecular Pathology, University Hospital Zurich, Switzerland; [7]Institute of Pathology, University Hospital Heidelberg, Germany; [8]Department of Hepatology and Gastroenterology, Charité-Universitätsmedizin, Berlin, Germany; [9]Second Department of Internal Medicine, Klinikum rechts der Isar, Technische Universität München, Germany; [10]Visceral and*