Genetic variants of lipase activity in chronic pancreatitis

We read with great interest the article by Weiss et al1 reporting genetic associations of rs632111 (fucosyltransferase 2; FUT2), rs8176693 (ABO) and rs889512 (chymotrypsinogen B2; CTRB2) with lipase levels. Weiss et al also claimed that the variants at the FUT2 and ABO loci were associated with chronic pancreatitis (CP). No association with CP was observed for the CTRB2 locus. Elevated lipase levels are a diagnostic criterion for acute pancreatitis and might mirror subclinical pancreatic injury in patients without severe complaints. Hence, variants associated with elevated serum lipase levels might also be associated with CP risk. In a recent genome-wide association study, genetic variants of CP risk were identified in PRSS1 and CLDN2-MORC4.2 A large European replication study refined these associations to alcohol-related CP.3 However, no associations were revealed at FUT2 and ABO in the former genome-wide association study.2

Given the relatively moderate association of genetic variants with CP in the paper by Weiss et al, we analysed the above-mentioned FUT2 and ABO single nucleotide polymorphism (SNPs) regarding association with CP in a German cohort of 1458 cases (non-alcohol-related CP n=584; alcohol-related CP n=874) and 5133 controls derived from the KORA study and patients with alcohol dependence (GESGA (-) consortium) according to DSM-IV criteria to replicate the finding. Controls included 1488 individuals with alcohol consumption of >60 g/day and 1915 individuals with alcohol consumption of <20 g/day.

All individuals were genotyped using Illumina SNP-chip technology. Briefly, data was filtered using Plink 1.9 at an individual- and SNP-wise call-rate >0.99 for relatedness (pi-hat <0.185), minor allele frequency >0.01 and Hardy–Weinberg disequilibrium with p value >10^-6. Imputation at 1000 Genomes reference panel (phase 1, release 3, software SHAPEIT V2+IMPUTE2.3.0) was performed with 279 188 high-quality SNPs available in all cohorts. Analyses were conducted with R applying logistic regression with the first three principal components of the SNP data included as covariates to account for possible population stratification. We analysed additive, recessive and dominant models of inheritance and subgroup and interaction analysis regarding alcohol consumption status.

Our analyses revealed no significance for rs632111 and rs8176693 in statistical models reported previously (table 1).1 For rs632111, the same (non-significant) direction of effect was observed, while for rs8176693, the effect direction was reverse. Interaction and subgroup analysis revealed significant interaction effects of rs632111 with alcohol consumption (p value 0.04, OR 0.82, 95% CI 0.68 to 0.99) and for rs8176693 for the subgroup of alcohol-dependent individuals (p value 0.04, OR 0.78, 95% CI 0.62 to 0.98); however, these associations would not withstand correction for multiple testing.

Next, we screened whether there were stronger associations in the vicinity of the reported SNPs. Here, the two regions did not reveal any convincing associations (minimum p value=0.0013, figures not shown).

In conclusion, we cannot convincingly replicate the formerly described associations in our study. Only nominal associations were found for rs632111 and rs8176693 than in other models as those reported by Weiss et al. These results indicate that further replication studies with larger sample sizes are required to clarify the role of these variants in CP risk. Furthermore, gene–environment interaction (eg, including alcohol status) needs to be considered when testing for associations with CP.
Table 1  We compare our association results with corresponding reports of Weiss et al.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genetic model</th>
<th>Groups compared</th>
<th>Cases</th>
<th>Cont.</th>
<th>p Value</th>
<th>OR (95% CI)</th>
<th>p Value reported in ref.</th>
<th>OR reported in ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs632111 (FUT2)</td>
<td>add.</td>
<td>CP vs non-alc.</td>
<td>1458</td>
<td>1915</td>
<td>0.26</td>
<td>1.07 (0.95 to 1.19)</td>
<td>0.003</td>
<td>1.24 (1.08 to 1.44)</td>
</tr>
<tr>
<td></td>
<td>add.</td>
<td>NACP vs non-alc.</td>
<td>584</td>
<td>1915</td>
<td>0.22</td>
<td>1.09 (0.95 to 1.26)</td>
<td>0.017</td>
<td>1.27 (1.04 to 1.55)</td>
</tr>
<tr>
<td></td>
<td>rec.</td>
<td>CP vs non-alc.</td>
<td>1458</td>
<td>1915</td>
<td>0.15</td>
<td>1.07 (0.98 to 1.18)*</td>
<td>0.0002</td>
<td>1.58 (1.24 to 2.02)</td>
</tr>
<tr>
<td></td>
<td>rec.</td>
<td>NACP vs non-alc.</td>
<td>584</td>
<td>1915</td>
<td>0.19</td>
<td>1.08 (0.96 to 1.22)*</td>
<td>0.001</td>
<td>1.72 (1.25 to 2.38)</td>
</tr>
<tr>
<td>rs8176693 (ABO)</td>
<td>dom.</td>
<td>CP vs non-alc.</td>
<td>1458</td>
<td>1915</td>
<td>0.50</td>
<td>0.96 (0.87 to 1.07)**</td>
<td>0.0002</td>
<td>1.67 (1.28 to 2.18)</td>
</tr>
<tr>
<td></td>
<td>dom.</td>
<td>NACP vs non-alc.</td>
<td>584</td>
<td>1915</td>
<td>0.32</td>
<td>1.07 (0.94 to 1.21)</td>
<td>0.030</td>
<td>1.54 (1.06 to 2.24)</td>
</tr>
<tr>
<td></td>
<td>dom.</td>
<td>ACP vs non-alc.</td>
<td>874</td>
<td>1915</td>
<td>0.20</td>
<td>0.92 (0.81 to 1.04)**</td>
<td>0.016</td>
<td>1.26 (1.11 to 2.37)</td>
</tr>
</tbody>
</table>

In the analysis, individuals with alcohol consumption of <20 g/day are treated as ‘non-alcoholic’. None of the associations were replicated.

*Indicates 95% CIs that do not overlap with those formerly reported by Weiss et al.
†Indicates opposite effect sizes in comparison to Weiss et al.
ACP, alcohol-related CP; add., additive; CP, chronic pancreatitis; dom., dominant; NACP, non-alcohol-related CP; rec., recessive. Encoding of models of inheritance was done using the minor allele as reported.

Collaborators  Hana Algül (II. Medizinische Klinik, Klinikum rechts der Isar of the Technical University Munich, Munich, Germany), Johannes Grothaus (Department of Medicine I, Altona General Hospital, Hamburg, Germany), Robert Grützmann (Department of General, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany), Johann Ockenga (Medical Clinic II, Internal Medicine, Gastroenterology, Endocrinology and Nutritional Medicine, Klinikum links der Weser, Klinikum Bremen Mitte, Bremen, Germany), Alexander Schneider (Department of Gastroenterology, Hepatology, Infectious Diseases, Medical Faculty of Mannheim University of Heidelberg, Mannheim, Germany), Hans-Ulrich Schulz (Department of Surgery, Otto-von-Guericke University Magdeburg, Magdeburg, Germany), Felix Stickel (Department of Visceral Surgery and Medicine, Inselhospital Bern, Bern, Switzerland), Jens Werner (Department of General Surgery, University of Heidelberg, Heidelberg, Germany), GESGA(-) (For consortium members see supplementary file).

Contributors  HK, MS, PK, HW and JS designed the project. Statistical analyses were performed by HS and MS. Samples were collected and comprehensively phenotyped by HA, JG, RG, JO, AS, H-US, FS, JW, HW, JR, and for KORA by HG, AP, KS; and for the GESGA(-) consortium by JS, MMN and MR. HS and JR wrote the manuscript with significant contribution from MS, PK and HW.

Funding  This work was supported by the Deutsche Forschungsgemeinschaft (DFG) grants (RO 3929/1-1 and RO 3939/2-1 to JR; WI 2036/2-2 and WI 2036/2-3 to HW; SFB 1052 C01; SPP 1629 TO 718/2-1), by a grant of the Colona Stiftung gGmbH to JR, the Else Kröner-Fresenius-Foundation (EKFS) to HW and by grant BMBF 01ZX1311A (e:Med program) of the German Federal Ministry of Education and Research (BMBF) to MR and MMN. MS and HK were funded by the Leipzig Interdisciplinary Research Cluster of Genetic Factors, Clinical Phenotypes and Environment (LIFE) and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC-Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ.

Competing interests  None.

Ethics approval  University of Leipzig.

Provenance and peer review  Not commissioned; internally peer reviewed.

Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2015-309521).


Received 5 March 2015
Accepted 11 March 2015
Published Online First 26 March 2015
doi:10.1136/gutjnl-2015-309521

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Genetic variants of lipase activity in chronic pancreatitis

Holger Kirsten, Markus Scholz, Peter Kovacs, Harald Grallert, Annette Peters, Konstantin Strauch, Josef Frank, Marcella Rietschel, Markus M Nöthen, Heiko Witt and Jonas Rosendahl

Gut 2016 65: 184-185 originally published online March 26, 2015
doi: 10.1136/gutjnl-2015-309521

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