## Genetic variants of lipase activity in chronic pancreatitis

We read with great interest the article by Weiss *et al*[1] 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 V.2+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.

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**Table 1** We compare our association results with corresponding reports of Weiss *et al*[1]

| SNP | Genetic model | Groups compared | Cases | Cont. | p Value | OR (95% CI) | p Value reported in ref. 1 | OR reported in ref. 1 |
|---|---|---|---|---|---|---|---|---|
| *rs632111* (*FUT2*) | add. | CP vs non-alc. | 1458 | 1915 | 0.26 | 1.07 (0.95 to 1.19) | 0.003 | 1.24 (1.08 to 1.44) |
| | add. | NACP vs non-alc. | 584 | 1915 | 0.22 | 1.09 (0.95 to 1.26) | 0.017 | 1.27 (1.04 to 1.55) |
| | rec. | CP vs non-alc. | 1458 | 1915 | 0.15 | 1.07 (0.98 to 1.18)* | 0.0002 | 1.58 (1.24 to 2.02) |
| | rec. | NACP vs non-alc. | 584 | 1915 | 0.19 | 1.08 (0.96 to 1.22)* | 0.001 | 1.72 (1.25 to 2.38) |
| *rs8176693* (*ABO*) | dom. | CP vs non-alc. | 1458 | 1915 | 0.50 | 0.96 (0.87 to 1.07)*† | 0.0002 | 1.67 (1.28 to 2.18) |
| | dom. | NACP vs non-alc. | 584 | 1915 | 0.32 | 1.07 (0.94 to 1.21) | 0.030 | 1.54 (1.06 to 2.24) |
| | dom. | ACP vs non-alc. | 874 | 1915 | 0.20 | 0.92 (0.81 to 1.04)*† | 0.016 | 1.26 (1.11 to 2.37) |

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.[1]

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