No association between the ALDH2 promoter polymorphism rs886205, alcohol dependence and risky alcohol consumption in a German population

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Susceptibility to negative effects of alcohol consumption e.g. headache, nausea and flushing is associated with blood levels of toxic acetaldehyde (AcH) which is mainly eliminated by active aldehyde dehydrogenase 2 (ALDH2). A polymorphism in the coding region of the ALDH2 gene, rs671, causes loss of enzymatic activity and protection against alcohol dependence, but is predominantly present in East-Asian populations (Brennan P *et al.,* 2004). In contrast to rs671, the non-coding ALDH2 promoter polymorphism rs886205 (A>G) appears in relevant frequency in different populations, including European, as a risk marker for alcohol-related carcinoma (Hashibe M *et al*., 2006) and is known to reduce ALDH2 gene transcription and promoter activity *in vivo* and *in vitro* (Kimura Y *et al*., 2009).

In a previous longitudinal study with 82 alcohol dependent patients and 34 controls of German descent, we detected different rs886205 allele and genotype frequencies between the groups, yet not reaching significance level (allele frequency: X^2=3.18; p=0.074 and genotype frequency: x^2=2.89; p=0.089). We calculated that replication of this genetic effect in a larger cohort of at least 300 patients and controls would have sufficient power to confirm a potential impact of rs886205 on associated risk for alcohol dependence (α=0.05; 1-β=0.83).

Therefore, we genotyped marker rs886205 in 352 alcohol dependent patients according to ICD-10 (Heese P *et al.,* 2012) and two independent control cohorts consisting of 2742 (KORA S3) and 3175 (KORA S4) population-based controls. All individuals were of German descent and gave written informed consent. Genotype frequencies were in Hardy-Weinberg-equilibrium and were as follows (patients/control KORA S3/control KORA S4): A/A=66.5/68.9/68.5, A/G=31.8/28.0/28.2, G/G=1.7/3.3/3.1.

Neither genotype nor allele frequencies showed significant differences between patients and KORA S3 controls (genotype: X^2=0.82, p=0.365; allele type: X^2=0.11; p=0.745) and patients and KORA S4 controls(genotype: X^2=0.60, p=0.438; allele type: X^2=0.02; p=0.888).

In order to examine if rs886205 genotype might affect alcohol consumption (grams ethanol/day) in alcohol dependent patients and controls, we applied a logistic regression model using risky alcohol consumption as the dependent variable (male individuals >30 g/day, female individuals >20 g/d) and rs886205 genotype, age and sex as independent variables. While age and sex had a significant impact (p<0.0001), rs886205 genotype did not affect risky alcohol consumption in patients and controls (p=0.965).

So far, association between rs886205 and alcohol dependence was only investigated in East-Asian populations with contradictory outcome and biasing effects of strong linkage disequilibrium with rs671 (Harada S *et al.*, 1999). It was also suggested that the role of the ALDH2 promoter polymorphism might vary across populations due to large differences in allelic frequencies between East-Asian and European populations (Kimura M *et al*., 2006).

Our findings show for the first time that the functional ALDH2 promoter polymorphism rs886205 does not affect risk for alcohol dependence and risky alcohol consumption in German populations.

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