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

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Susceptibility to the negative effects of alcohol consumption, for example, headache, nausea, and flushing is associated with blood levels of toxic acetaldehyde, 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 *et al.*, 2004). In contrast to rs671, the noncoding *ALDH2* promoter polymorphism rs886205 (A > G) appears in relevant frequency in different populations, including European, as a risk marker for alcohol-related carcinoma (Hashibe *et al.*, 2006), and is known to reduce *ALDH2* gene transcription and promoter activity *in vivo* and *in vitro* (Kimura *et al.*, 2009).

In a previous longitudinal study with 82 alcohol-dependent patients and 34 controls of German descent, we detected different rs886205 alleles and genotype frequencies between the groups, but not reaching significance (allele frequency: $\chi^2 = 3.18$; $P = 0.074$ and genotype frequency: $\chi^2 = 2.89$; $P = 0.089$). 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 the associated risk for alcohol dependence ($\alpha = 0.05$; $1 - \beta = 0.83$).

Therefore, we genotyped marker rs886205 in 352 alcohol-dependent patients according to ICD-10 (Heese *et al.*, 2012) and two independent control cohorts that included 2742 (KORA S3) and 3175 (KORA S4) population-based controls. All individuals were of German descent and provided 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: $\chi^2 = 0.82$, $P = 0.365$; allele type: $\chi^2 = 0.11$; $P = 0.745$) and patients and KORA S4 controls (genotype: $\chi^2 = 0.60$, $P = 0.438$; allele type: $\chi^2 = 0.02$; $P = 0.888$).

To examine whether the rs886205 genotype might affect alcohol consumption (grams of ethanol per 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/day) and rs886205 genotype, age, and sex as independent variables. Although age and sex had a significant impact ($P < 0.0001$), the rs886205 genotype did not affect risky alcohol consumption in patients and controls ($P = 0.965$).

So far, an 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 *et al.*, 1999). It was also suggested that the role of the *ALDH2* promoter polymorphism might vary across populations because of large differences in allelic frequencies between East-Asian and European populations (Kimura *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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Conflicts of interest

There are no conflicts of interest.

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