

LETTER TO THE EDITOR

Lack of Association Between Genetic Polymorphisms of *ARRB2* and Alcohol Dependence in a Caucasian Population

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Beta-arrestin 2 (*ARRB2*) is expressed in the brain and it is involved in μ -opiate and dopamine D2 receptor signaling (Lefkowitz and Shenoy, 2005). It has recently been shown that the *ARRB2* genotype may contribute to the inter-individual variability in the response to methadone maintenance treatment (Oneda *et al.*, 2010). In addition, *ARRB2* modulates the acute response to ethanol and mediates its rewarding effects in mice (Bjork *et al.*, 2008). To investigate the significance of this finding in human, genomic DNA was collected from 45 males and 28 females of Caucasian origin, 18 years old or older, who met the criteria for the diagnosis of alcohol dependence (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV, American Psychiatric Association, 1994). Potential study subjects were excluded if they had a history of psychotic or bipolar disorders. The DNA from 103 males and 108 females of Caucasian origin without any lifetime history of psychotic or mood disorders, alcohol or heroin dependence [assessed using the semi-structured Diagnostic Interview for Genetic studies (Nurnberger *et al.*, 1994) or the Schedules for Assessment in Neuropsychiatry (Wing *et al.*, 1990)] was used as non-alcoholic control group. The ethics committees of the corresponding centers (Lausanne, Geneva) approved the study and written informed consent was obtained from all participants.

Four Single Nucleotide Polymorphisms (SNPs) (*rs34230287* in the promoter, *rs3786047* in intron 1, *rs1045280* in exon 11 and *rs2036657* in the 3'UTR) were selected on the basis of high heterozygosity and uniform coverage of the gene. Genotyping was performed using commercially available TaqMan probe (Applied Biosystems, Rotkreuz, Switzerland) with ABI PRISM 7000 Sequence Detection System as previously described (Oneda *et al.*, 2010). χ^2 test was used to compare allele and genotype frequencies across the alcoholic and non-alcoholic subjects. Logistic regression was used for the analysis adjusted for sex and age. Haplotype block structure was determined using the Haploview program.

Linkage disequilibrium among the four SNPs was high ($D' > 0.94$). All the SNPs were in Hardy–Weinberg equilibrium ($P > 0.2$). In the alcoholic group, the observed allele frequencies were 32% (95% CI = 24.1–39.7%) for *rs1045280*, *rs3786047*, *rs2036657* and 27% (95% CI = 20.4–35.4%) for *rs34230287*. In the control group, the observed allele frequencies were 30% (95% CI = 26.4–35.5%) for *rs2036657*, *rs3786047*, *rs34230287* and 22% (95%

CI = 17.7–25.8%) for *rs34230287*, respectively. For all the SNPs analyzed, the allele and genotype frequencies were not significantly different between the alcoholic patients and the control group, nor in the multivariate analysis following adjustment for sex and age ($P > 4$). Finally, the four marker haplotypes were not significantly associated with alcohol dependence ($P > 0.1$) either.

On the basis of results obtained in animals (Bjork *et al.*, 2008), *ARRB2* gene appeared to be a potential candidate for association studies with alcoholism. No association could be demonstrated in the present study, which is, to our knowledge, the first report on this matter in human. Our data are in line with previously published results using the Indian ethanol preferring and non-preferring rats (Saba *et al.*, 2006). In addition, the *ARRB2* gene does not reside in any of the quantitative trait loci for ethanol preference that have been identified in rodents so far (Saba *et al.*, 2006). In a recent study with 272 opioid-dependent patients and 217 control subjects without any lifetime history of psychotic or mood disorders, alcohol or heroin dependence, *ARRB2* was not found to be a vulnerability gene for opioid dependence either (Oneda *et al.*, 2010). Further studies are needed to confirm the lack of association between *ARRB2* and alcoholism dependence in other cohorts but based on the present study, a strong association appears unlikely.

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