Reviewer’s report

Title: Association between single nucleotide polymorphisms in the Mu Opioid receptor gene (OPRM1) and self-reported responses to alcohol in Southwest California Indians

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Reviewer: Ulrich W. Preuss

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The manuscript is on an association study between OPRM haplotypes with subjective responses to 2-3 drinks of alcohol in a subgroup of a larger family-based sample of Southwest California Indians. 14 single nucleotide polymorphism of OPRM were genotyped in 251 individuals. Subjective response expectations were assessed using the subjective high assessment scale (SHAS-E). The results indicate that subjective response was significantly associated with at least one minor allele for at least one of 7 SNPs (p<0.01) in the OPRM1 receptor gene. The most commonly genotyped OPRM1 polymorphism in the literature, Asn40Asp (A118G) G allele was associated with reporting a less intense response to alcohol.

The question posed in the manuscript is, in general, interesting since OPRM1 is the site of action of alcohol relapse preventing compounds, like naltrexone. Genetic variations of the gene therefore influence several alcoholism-related phenotypes like subjective response to alcohol. The article is well written, the discussion and conclusions lend adequate support to the data.

A few issues should be clarified before publication:

1. The authors genotyped 251 individuals from a family study. Was a power analysis conducted to estimate appropriate sample size for the statistical associations?

2. Please report on psychometric properties of SHAS-E (e.g. in Schuckit and Smith, 2000, J Stud Alcohol). The psychometric properties of this instrument are of importance because reliability and validity of this measure have significant influence on the results reported. A more direct assessment of subjective alcohol effects are body sway measures. Were they used in this study? if not, please mention this in the limitations of the study.

3. Heritability of level of response to alcohol has been reported to range between 0.4 to 0.5 in twins (Martin, 1988). Other studies used the SRE (Self-Rating of the Effects of Alcohol, Schuckit et al 1997) to assess alcohol effects and reported correlation between related individuals of 0.16 to 0.22 (Schuckit et al 2001). How does the heritability results of the current investigation compare to those of the previous studies?
Minor:
1. in the methods part, the authors should give more details on family descent of study participants or refer to a more elaborate version of the study methods in a previous publication.
2. OPRM1 receptor is located on chromosome 6 (6q24-q25). Previous linkage analyses on level of response do not indicate a relationship to this chromosomal region. A previous linkage study (Schuckit et al 2005) reported that this chromosomal region was not related to SHAS measures. Please discuss.
3. One OPRM1 SNP was found to be in Hardy-Weinberg Equilibrium. Was this SNP excluded from subsequent analysis?
4. Were the significant results in table 2 corrected for multiple testing? If a correction was employed which of the associations remained significant?
5. Please provide a linkage disequilibrium matrix (using D\# or R2) for the 14 OPRM1 SNPs analyzed to compare with future studies.