Reviewer’s report

Title: Genomic Screen for Loci Associated with tobacco usage in Mission Indians

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Reviewer: Joel Gelernter

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In this article, the authors describe a 791-STR genome screen for tobacco use related loci in a sample of Mission Indians originally ascertained, apparently, for studies of alcohol dependence. Full data were available for 244 subjects (as stated on p 5; on p 6 it is stated that “genotypes were… determined for 243 subjects.”) The SSAGA was used for phenotype assessment, but the version used does not allow for categorical DSM tobacco dependence diagnosis. Two quantitative traits were defined and their heritability determined; then variance components linkage analyses were completed. Analytic methods were appropriate. No significant linkage results were identified, but there were some results that were of interest, some of which were consistent with previously published studies completed in other populations. The study is basically well-conceived and well-executed.

--Bivariate analyses, considering both tobacco use and alcohol use, were completed for chromosome 4 (p 6). Was this the only chromosome studied? More information about the bivariate analysis would be helpful, in terms of the specific phenotypes studied.

--The rates of diagnosis (58% for regular tobacco use and 30% for persistent use) were very high. What are the implications of this situation with respect to the identification of “risk” vs. “protective” loci?

--Some of the “loci of interest” had very modest statistical support, with lods scores of 1.3, for example. In the discussion too much space is devoted to weak findings with lod scores between 1 and 1.5.

--The authors note that the peak lod score observed for persistent tobacco use in the present study, coincides with that observed for drinking severity for their previous study (in this same sample). What is the degree of comorbidity between tobacco and alcohol dependence in this sample? Does this linkage observation, located in proximity to an ADH gene cluster, reflect the effects of comorbidity with alcohol-related pathology? The authors state that this cluster (as opposed to the genomic region) has been implicated in studies of tobacco use; supporting studies should be cited.

--Is there enough data in the SSAGA to get any closer to a DSM nicotine dependence diagnosis? How were the diagnosis definitions used, decided upon?

--The authors state that because the population is admixed, estimation of allele frequencies may produce biased lod scores. Given the average family size of 5.4 this could be a concern especially if there is reason to believe the levels of admixture between families are not reasonably comparable. This should be examined empirically.

There are some minor editing errors, e.g. p 3 para 1 “…North American Indians are the higher than…” Also, the authors state on the top of p 8 that their one of their aims was to identify loci associated with the two tobacco use phenotypes – they seem to mean linked.
What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I have no competing interests.