Reviewer's report

Title: Genome wide association for substance dependence: convergent results from epidemiologic and research volunteer samples

Version: 1 Date: 2 September 2008

Reviewer: Herbert Lachman

Reviewer's report:

This report by Johnson et al is a genome wide association analysis carried out for addiction vulnerability to assess the possibility of ascertainment bias in research volunteers. The author’s rationale for the study is the notion that research volunteers have a higher frequency of certain heritable personality traits, such as neuroticism, that may bias results of case control genetic association studies in addiction. The study addresses this potential confounder by analyzing a large cohort from the so-called Epidemiological Catchment Area (ECA) in which subjects were ascertained as a “probability sample of individuals in dwelling units within census tracts near the Johns Hopkins Medical Institutions.” Within this cohort the investigators identified 80 subjects with substance dependence and matched them to non-addicted controls. DNA was genotyped by pooling and compared with more classically derived case control addiction cohorts. One hundred and seventy two addiction-associated genes were identified that overlapped in the two groups. Moreover, there was overlap in the ECA cohort genetic findings with other addiction studies. Although the sample size is quite small, the results appear to be convincing. (The small sample size is mentioned by the authors as a limitation of the study.) Thus, by showing that methods used to ascertain cases and controls in addiction studies are reliable, the paper is an important addition to the addiction genetics field (and perhaps psychiatric genetics as a whole). With case control studies in psychiatric genetics becoming ever-larger to satisfy stringent statistical criteria for significance caused by testing large numbers of SNPs (in the face of small effect sizes), this is a welcome addition to the literature. The paper has a few minor issues. Many of the overlapping genes shown in the supplementary table do not show statistically significant differences between cases and controls. Their presence on the table is not clear. Also, how do these findings relate to the group’s previously published results? A quick view shows that many, if not most, do not overlap. This reviewer realizes that the small sample size may affect results and that the primary aim was to show overlap in the different cohorts. However, genetic data is being presented and it would be of interest to other investigators to explore the findings with a little more depth. Finally, it is not clear what method was used to show that the overwhelming majority of targeted genes were expressed in the brain (primarily hippocampus). Was it determined experimentally by the investigators? Was it the result of a UCSC search or a perusal of the Allen Brain Atlas?
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.