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LETTER TO THE EDITORS

T. Geijer · E. Jönsson · J. Neiman

Comment to "Dopamine D2 receptor gene polymorphisms in Scandinavian chronic alcoholics: a reappraisal"

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Our previous article (Geijer et al. 1994) reported no association of alcoholism to a dopamine D2 receptor polymorphism. Data from this article have been reevaluated and criticized by K. Blum et al. (Blum et al. present issue).

Blum et al. claim that recalculation of a selection of our data yields statistical significance supporting an association between prevalence of the DRD2 A1 allele and some of our alcoholic patient groups. This view seems to derive from a misunderstanding of our control and patient groups.

The total number of control subjects we investigated was 90. Of these, 6 were found to have a lifetime diagnosis of DSM-III-R alcohol dependence. One of these individuals had a concurrent diagnosis of cannabis dependence and bipolar disorder NOS. This was the only control subject in the study with any DSM-III-R substance abuse or dependence except for alcohol or nicotine. Three subjects had previous alcohol abuse according to DSM-III-R criteria. The 9 persons with alcohol diagnosis were excluded. The remaining 81 were used as the first control group (C1). In this group 14 subjects were found to have the following DSM-III-R diagnoses: major depression (single episode, mild), bipolar disorder NOS, psychotic disorder NOS, anxiety disorder NOS, panic disorder (with agoraphobia), social and simple phobia, obsessive – compulsive disorder, hypochondriasis, unspecified nonpsychotic mental disorder ($n = 2$), bulimia nervosa, functional enuresis, adjustment disorder NOS and depressive disorder NOS.

When these 14 subjects were removed from the 81 subjects the second control group (C2; $n = 67$) emerged. From this group 15 subjects with first-degree relatives with alcohol problems were removed, which yielded the third control group (C3). This group ($n = 52$) was in turn reduced by 12 subjects with second- but not first-degree relatives with alcohol diagnoses. The remaining 40 constituted the fourth control group (C4). Thus, C4 is a subsample of C3, which makes it inappropriate to combine the two groups for statistical analysis.

Among the alcoholic subjects, P1, P2, P3, and P4 overlap each other, and P5 includes P6. Furthermore, different criteria have been employed to define the two main alcoholic groups, P1 and P5. Thus, these alcoholic groups or subgroups of our article are not distinctly separate from each other.

As the objective of our study was to evaluate the DRD2 A1 allele frequency/prevalence among alcohol-dependent subjects, all controls with alcohol diagnosis were removed in all calculations, although this reduced the sample size as well as the power of analysis. If the controls with alcohol diagnosis had been included in the C1 group, this would not have changed the results. The A1 prevalence and frequency did not differ (Yates $\chi^2 = 0.03$; $df = 1$; $P = 0.86$) between controls with alcohol diagnosis (33 and 22%, respectively) and the C1 sample (36 and 21%, respectively). This observation suggests that exclusion of controls with alcohol diagnosis does not alter the A1 allele frequency or prevalence among an otherwise unscreened population. As the relation between DRD2 TaqI polymorphisms and the other diagnostic entities found among the controls is not clear, and does not necessarily imply a deviant DRD2 A1 frequency, we found it meaningful also to include them in the initial control group (C1). We reasoned in the same way concerning the presence of familial alcoholism, but successively reduced the sample into the "pure" C4 group.

The interviews performed gave no indication for any case in the controls with Tourette's syndrome, attention deficit/hyperactivity disorder, or pathological gambling. One control was obviously obese. In the present study we did not control for height or weight. However, during previous investigations (Sedvall et al. 1980; Wiesel et al. 1982; Oxenstierna et al. 1986), a physical examination including height and weight measurements was performed, and all subjects were found to be physically healthy. No structured schedule concerning smoking habits was given; therefore, we were not able to assess the subjects for nicotine dependence.

T. Geijer (✉) · E. Jönsson · J. Neiman
Department of Clinical Neuroscience, Karolinska Hospital, 171 76 Stockholm, Sweden

Parts of the criticism concern the criteria used to select patients with severe alcoholism. Different clinical patient materials certainly include various degrees of severe alcoholics, depending on the patient population and the method of selection. We feel that this makes the comparisons and results of various statistical calculations difficult to interpret. Using DSM-III-R criteria, as was done in our study, might be a weaker way than others to define severe alcoholism. However, this was clearly stated in the article, and there is no general agreement or convention concerning what constitutes a severe alcoholic. Furthermore, among the studies in which the severity of alcoholism have been investigated, various criteria based on different instruments have been employed: the Severity of Alcohol Dependence Questionnaire (SADQ), the Alcohol Use History Questionnaire and the Medical Alcohol checklist (Blum et al. 1991), SADQ and Structured Clinical Interview for DSM-III-R (Cook et al. 1992), pathological anatomical complications of alcohol (Parsian et al. 1991; Geijer et al. 1994), alcohol consumption 60 days prior to the study using the time-line follow-back method (Gelernter et al. 1991) and the Major Criteria for the Diagnosis of Alcoholism, and the National Council of Alcoholism (Arinami et al. 1993). The different criteria used in these studies have resulted in an average increase in the DRD2 A1-allele prevalence of 11%, (range 2–19%) and an average decrease of 46% (range 25–69) in the number of alcoholic subjects. In our study (Geijer et al. 1994) the increase in A1 allele prevalence in the patient group (P1) was 5%, and the decrease in alcoholic subjects was 24% when moderate alcoholics were excluded. Hypothetical χ^2 analysis of our alcoholic patient sample (P1), assuming that another instrument for selecting severe alcoholics had given an A1-allele prevalence increase of 11% and a sample reduction of 46%, does not yield a significant difference compared with our controls (C1, C2, C3, and C4).

Since the data cannot be treated in the way Blum et al. suggest (for reasons stated herein), no significant association between the DRD2 polymorphisms and alcoholism can be detected in our data. A vague tendency of increased A1-allele frequency exists in some of our alcoholic subsamples, but this has been accounted for in our previous article (Geijer et al. 1994).

We see no reason to modify our former conclusion that our data do not support an association between the DRD2 TaqI A1 allele and alcoholism.

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