EDITORIAL

The D2 Dopamine Receptor Gene and Alcoholism: A Tempest in a Wine Cup?

The purported association between the D2 dopamine receptor (DRD2) A1 allele and alcoholism (Blum et al 1990, 1991) has spawned much publicity and numerous attempts at replication. The results overall are controversial, sparking a lively debate and bringing into focus the complexities in genetic studies of behavioral disorders. Appraisals of the available data have failed to reach a consensus: Cloninger (1991) and Noble (1993) consider the relationship between DRD2 and alcoholism "confirmed", whereas Conneally (1991) and Gelernter et al (1993) advise caution.

Progress in molecular and statistical genetics has made an indelible impact on the medical sciences. Initial successes were limited to single gene disorders, but recent studies have begun to unravel more intricate disorders such as Alzheimer's disease and diabetes mellitus. Alcoholism is clinically and genetically complex. The potential utility of the new genetic tools in disorders with unclear phenotypes and complex inheritance is well recognized, as are their pitfalls and ambiguities (Baron et al 1990; Plomin 1990). Crucial to the interpretation of DRD2 studies in alcoholism are issues related to allele distribution, ascertainment (case selection), association versus linkage, and plausibility of DRD2 as a candidate gene.

Taken together, studies subsequent to Blum et al show similar DRD2 allele frequencies in alcoholics and controls (Gelernter et al 1993). Thus, considering only attempts at replication by other investigators, there is no case-control difference in the literature as a whole. Because of the significant heterogeneity among both the alcoholic and control groups, Gelernter et al (1993) reanalyzed the data after removing those samples with the highest and lowest DRD2 A1 allele frequencies. Again, the difference between alcoholics and controls was not statistically significant.

Ethnic makeup can generate dramatic population differences in DRD2 allele frequencies (Barr and Kidd 1992). This, in turn, can lead to spurious disease–allele associations. None of the ethnically matched samples (i.e., alcoholics and controls drawn from a single ethnic group using the same protocol) showed statistically significant case-control differences in allele distribution (Schwab et al 1991; Goldman et al 1992, 1993; Amadeo et al 1993).

Clinical heterogeneity has been offered as a possible explanation for the conflicting results, namely, an association limited to severe alcoholism or a modifying effect of DRD2 alleles on the severity of the disorder (Cloninger 1991; Blum et al 1991). Indeed, the original study of Blum et al was based on so-called "virulent" alcoholism. Case-control differences emerged in some subsequent studies when the analysis was restricted to "severe" alcoholism (review: Noble 1993).

This interpretation of the data is fraught with difficulties, however. First, agreed-on criteria for alcoholic subtypes have yet to be established. Measures of severity vary among studies, ranging from medical complications to withdrawal symptoms. Second, a combined analysis of the studies reported since Blum et al shows no statistically significant differences between severe and not severe alcoholics with respect to DRD2 alleles; also, the heterogeneity among studies is much greater than between the severe alcoholics and the milder alcoholics (Gelernter et al 1993). Third, there are no data on severity in the ethnically matched samples.

Association refers to population differences in case-control studies. Linkage refers to cosegregation of disease and a marker allele within families. Association studies can point to genes with relatively modest influences, whereas linkage studies are usually geared to detect genes with moderate-to-large effects. If a putative candidate gene is truly relevant to the trait under study, both methods, if properly executed, should uncover its presence.

Because families are generally less susceptible than populations to stratification or admixture due to ethnic

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variation and other social and biological variables, genetic linkage could go a long way towards resolving this issue by demonstrating an effect of DRD2. Linkage studies with DRD2 and alcoholism have yielded negative results, however (Bolos et al 1990; Parsian et al 1991). When the analysis focused on severe alcoholism only, the evidence of linkage was still negative (Parsian et al 1991). The choice of DRD2 as a candidate gene stemmed from its presumed involvement in alcohol-seeking behavior, possibly via neurotransmitter metabolism. There is no corroborating neurochemical or neuropharmacological evidence in humans, however, that would point unambiguously to dopaminergic abnormalities in alcohol-dependent individuals.

An association of pathophysiological significance between DRD2 and alcoholism could be demonstrated by biochemical or molecular means. Goldman et al (1992) reported that the DRD2 genotype does not correlate with dopamine metabolites in cerebrospinal fluid of alcoholics. Noble et al (1991) demonstrated allelic association of DRD2 with D2 receptor density. If true, this would support a physiological effect; an epiphenomenon resulting from exposure to alcohol cannot be ruled out, however. At the molecular level, copies of DRD2 were sequenced with no evidence of structural differences (Sparkar et al 1991). This makes it unlikely that DRD2 exerts a major effect on alcohol dependence consonant with the strong allelic association claimed by Blum et al. To be sure, a minor DRD2 allele effect undetectable by current techniques cannot be ruled out outright (this would be difficult to dispute). The pathophysiological significance of such an effect would be marginal at best, however.

Given the complexity of alcoholism, the prior probability that a single candidate gene, chosen on largely theoretical grounds, would fulfill its presumed promise is small indeed. A case in point would be the numerous, unsuccessful attempts to demonstrate linkage or association between other complex disorders with a presumed dopaminergic pathology (e.g., schizophrenia, manic depressive illness, and Tourette's syndrome) and various dopamine receptor genes.

The data reported to date do not uphold the claimed allelic association between DRD2 and alcoholism. Pending further study involving large samples of alcoholics and carefully matched controls, as well as alcoholic subtypes identifiable by clinical or physiological correlates, the observed case-control differences may well be artifactual, possibly due to sampling errors or ethnic variation.

Alcohol consumption is practically pandemic in the United States: so-called drinkers are a very heterogeneous population involving anybody from the occasional beer consumer to the chronic addict who might drink a fifth of whiskey a day. If physiological research is conducted, I would suggest, as a starter, that a fairly homogeneous group of chronic and severe, relatively young individuals (without comorbidity) be strictly defined and chosen, and that any interpretation of findings cautiously distinguish between causes and results of addiction. Additionally, a large population of normal young people should be tested for suspected parameters, genetic or other, and then followed to see if they have any predictive value. To yield its secrets, the complexity of alcoholism has to be matched by comparably intricate research strategies.

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