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NEWS AND COMMENTARY

Alcoholism

Study boosts evidence on linkage regions associated with alcoholism

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Multiple studies are reporting linkage to regions on chromosomes 2 and 4 for alcoholism phenotypes. The linkage appears to be robust to both sample ascertainment and phenotype measurement. In a recent paper, Wilhelmsen *et al*[1] reported linkage to regions on chromosomes 2 and 4 for quantitative phenotypes related to alcoholism. Using families from a sample selected for heavy smoking, linkage analyses were conducted for the total score on a commonly used screening instrument for alcoholism (the CAGE questionnaire) as well as measures of the quantity and frequency of drinking. Three different measures all resulted in peaks on chromosome 2 at 43 cM, with the LOD scores ranging between 2.0 and 3.4. This region on chromosome 2 has been linked with alcohol dependence in a report by the Collaborative Study on the Genetics of Alcoholism (COGA) group[2] and is near a linkage peak reported in an analysis of heavy drinkers from the Framingham Heart Study.[3]

Two additional regions were reported on chromosome 4, one with a peak at 10 cM and another at 103 cM, both with LOD scores >2.7. The linkage region centered at 103 cM on chromosome 4 was for the measure of consuming more than six alcoholic drinks and this region has been linked in three separate analyses from the COGA group,[2,4,5] analyses of the Framingham study,[6] and a Native American sample.[7] This region is of interest because a cluster of alcohol dehydrogenase genes is near 100 cM on chromosome 4. Alcohol dehydrogenase polymorphisms have been demonstrated to affect alcohol consumption in Asian populations, and recently in other ethnic groups.[8] Also nearby are the genes of the GABA receptor cluster at 68 cM on chromosome 4. Edenberg *et al*[9] demonstrated that GABRA2 gene, which codes for a subunit of the $GABA_A$ receptor, was associated with alcohol dependence in the COGA sample.

The Wilhelmsen *et al*[1] sample was selected not for having high-density alcohol consumption, but for high-density smoking. Owing to a high correlation between alcohol consumption and smoking, enough heavy drinkers were available to conduct a linkage analysis of alcoholism related phenotypes. Both human twin studies and animal models have demonstrated that this shared vulnerability for smoking and drinking is in part genetically mediated.

The work by Wilhelmsen *et al*[1] adds another sample to the growing literature on linkage regions for alcoholism. The success in the search for genes conferring increased vulnerability for alcoholism has been mixed, although now with an increasing number of studies being published, there appears to be increasing support for specific chromosomal regions. Initially, the search for these alcoholism linkage regions was marked by results that were difficult to interpret. For example, the COGA group published several genome scans of members of high-density alcoholic families, using somewhat different definitions of the disorder. One sample revealed loci on chromosomes 1, 2, and 7 with lod scores of 2.0–3.0. A scan in a separate sample failed to confirm the sites on chromosomes 2 and 7, and supported the chromosome 1 site only if the phenotype was changed. The second scan also suggested a new site (lod 3.4) on chromosome 3.[2] In combination, COGA's two samples yielded sites on chromosomes 1, 3, and 7 with lod scores of 2.4–2.9. After further changing the definition COGA then found evidence of linkage (lod 4.0) on chromosome 16.[10] A still-different phenotype uncovered a site on chromosome 4 (lod 3.5).[4]

However, now, as additional groups publish on independent samples, the convergence of results on the same chromosome, and in the same region, adds support to the notion that genes in these regions will be found that are associated with alcoholism. These results are furthermore robust to differences in sample ascertainment and phenotypic measurement ■

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