Linkage of an Alcoholism-Related Severity Phenotype to Chromosome 16

Tatiana Foroud, Kathleen K. Bucholz, Howard J. Edenberg, Alison Goate, Rosalind J. Neuman, Bernice Porjesz, Daniel L. Koller, John Rice, Theodore Reich, Laura J. Bierut, C. Robert Cloninger, John I. Nurnberger, Jr., T.-K. Li, P. Michael Conneally, Jay A. Tischfield, Raymond Crowe, Victor Hesselbrock, Marc Schuckit, and Henri Begleiter

There is substantial evidence for a significant genetic component to the risk for alcoholism. In searching for genes that contribute to this risk, the diagnostic criteria for alcohol dependence may not be the optimal phenotype; rather, creation of a more homogeneous phenotype will lead to a more homogeneous genetic etiology. Items from the Semi-Structured Assessment for the Genetics of Alcoholism collected from 830 individuals in 105 alcoholic families were used in a latent class analysis to identify a more homogeneous alcoholism-related phenotype. A four-class solution was chosen: class 1, unaffected group; class 2, mildly problematic group; class 3, moderately affected group; and class 4, severely affected group. Classes 3 and 4 had higher symptom endorsement probabilities than classes 1 and 2 for items reflecting severe alcohol dependence, and were combined to provide enough sibling pairs for genetic linkage analysis. A total of 291 markers distributed throughout the genome, with an average intermarker distance of 14 cM, were genotyped. Linkage analysis was performed to detect loci underlying classes 3 and 4, the moderately and severely affected alcoholics, of whom 88% met the Collaborative Study of the Genetics of Alcoholism, and >99% met ICD-10 criteria for alcohol dependence. Evidence for a locus on chromosome 16, near the marker D16S675, was found with a maximum multipoint lod score of 4.0. Analysis of additional markers on chromosome 16 yielded a lod score of 3.2, narrowed the critical region, and placed the gene between D16S475 and D16S675 in a 15 cM interval.

Key Words: Alcoholism, Linkage, Latent Class Analysis, Chromosome 16.