

“The Investigation of CYP2E1 in Relation to the Level of Response to Alcohol Using a Combination of Linkage and Association Approaches”

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ABSTRACT:

A low level of response to alcohol during an individual's early experience with alcohol is associated with an increase risk for alcoholism. A family-based genome-wide linkage analysis using sibling pairs that underwent an alcohol challenge where the level of response to alcohol was measured with the Subjective High Assessment Scale (SHAS) implicated the 10q terminal region. CYP2E1, a gene known for its involvement with ethanol metabolism, maps to this region.

Variance component multipoint linkage analysis detected significant linkage to CYP2E1 which was diminished due to apparent locus heterogeneity traced to a single family with extreme phenotypes. In retrospect, circumstances recorded during testing for this family suggest that their phenotype data are likely to be unreliable. Strong allelic associations were detected for several CYP2E1 polymorphisms and the SHAS score. DNA sequencing from families that contributed the greatest evidence for linkage did not detect any changes directly affecting the primary amino acid sequence. With the removal of a single family, combined evidence from microsatellites and SNPs offer significant linkage between the level of response to alcohol and the region on the end of chromosome 10.

Combined linkage and association indicate that sequence changes in or near CYP2E1 affect the level of response to alcohol providing a predictor of risk for alcoholism. The absence of coding sequence changes indicates that regulatory sequences are responsible. Implicating CYP2E1 in the level of response to alcohol allows inferences to be made about how the brain perceives alcohol.