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Linkage Findings on Chromosome 2 Suggest a Gene Predisposing To Multiple Behavioral Undercontrol Phenotypes

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ABSTRACT

Evidence from independent studies is converging to suggest that a region on chromosome 2p contains a gene (or genes) that predispose to multiple behavioral phenotypes related to behavioral undercontrol. Here we present data from the Collaborative Study of the Genetics of Alcoholism (COGA) and the Nicotine Addiction Genetics Project (NAG) demonstrating linkage to chromosome 2 with multiple, related phenotypes.

INTRODUCTION

Considerable overlap is observed between many psychiatric disorders. Twin studies have suggested that some of this overlap may be due to common genes that influence multiple phenotypes (also called pleiotropy). In particular, several studies have demonstrated that disorders characterized by behavioral undercontrol may be related through share genetic vulnerabilities. Alcohol use and smoking (Hopfer et al., 2001), conduct disorder, and other drug use (Kendler et al., 2003) have all been demonstrated to have shared genetic liability.

SAMPLES

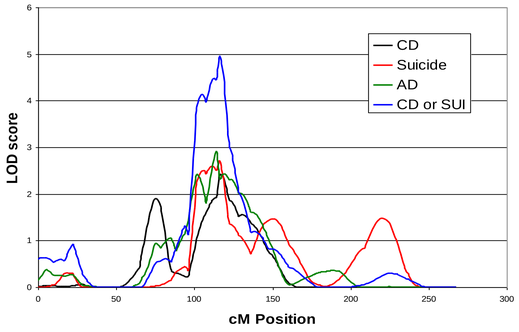
COGA. The Collaborative Study on the Genetics of Alcoholism (COGA, PI Henri Begleiter, MD) is a multi-site collaborative project designed to identify genes that contribute to the development of alcoholism and related disorders. Densely affected alcoholic families were ascertained from inpatient and outpatient treatment centers at several sites across the United States. Genome-wide linkage analyses have been conducted on a sample of 2273 individuals from 262 alcoholic families. All COGA subjects were interviewed using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA).

NAG. The Nicotine Addition Genetics Project (NAG, PI Pam Madden, PhD) was initiated with the goal of identifying genes involved in nicotine addiction and related phenotypes. Nuclear families containing at least one pair of heavy smoking siblings have been ascertained from Australia and Finland. Only data from Australian families are presented here. Linkage analyses on chromosome 2 are based on a sample of 1501 individuals from 289 families. NAG participants were interviewed using a semi-structured polydiagnostic interview developed from the SSAGA.

ANALYTIC METHODS

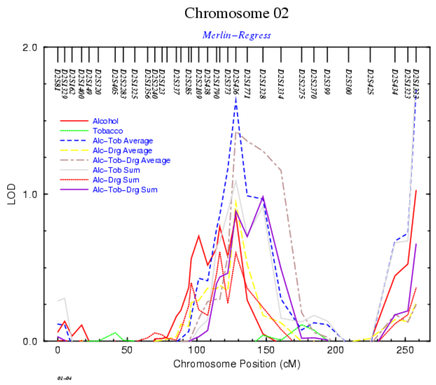
Linkage analyses were carried out on the binary COGA phenotypes using the program ASPEX. All possible pairs were analyzed using the SIB_IBD routine, which uses ibd sharing estimates from pairs with genotyped parents. Binary phenotypes in the NAG project were analyzed using the program Merlin. Quantitative and semi-quantitative traits in both studies were analyzed using the Merlin-regress routine.

In the COGA sample, the phenotypes alcohol dependence (measured using DSMIII-R and Feighner Definite criteria), conduct disorder (CD), and suicide attempts (SUI) all show linkage to chromosome 2p. A maximum lod score of 5.0 is observed in the region with the phenotype CD or SUI.

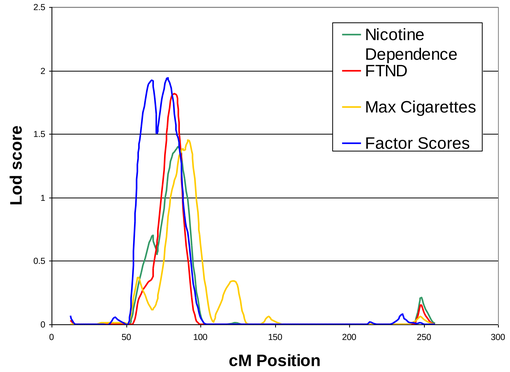


Phenotype	# Pairs	Maxlod	Position	Allele-sharing
CD	113	2.4	117cM	64%
Suicide	58	2.7	117cM	68%
Alcoholism	797	2.9	114cM	55%
CD or SUI	239	5.0	117cM	63%
CD, SUI, or Alcoholism	988	3.7	114cM	56%

In the COGA sample, a series of quantitative phenotypes were constructed from the substance classes: alcohol, tobacco, opioids, sedatives, stimulants, cocaine and marijuana. Phenotypes for each class were defined based on the number of DSMIII-R dependency criteria. The eight phenotypes we analyzed were alcohol, tobacco, average of alcohol and tobacco, average of alcohol and drugs, average of alcohol, tobacco and drugs, sum of alcohol and tobacco, sum of alcohol and drugs, sum of alcohol, tobacco and drugs (Dunn et al., in preparation). Results from linkage analyses of these phenotypes on chromosome 2 are shown below.



In the NAG sample, several primary smoking phenotypes show linkage to chromosome 2p. These include Nicotine Dependence Scores, Fagerstrom Test for Nicotine Dependence (FTND) Scores, the Maximum Number of Cigarettes Smoked, and quantitative factor scores derived from DSM and FTND nicotine dependence items. Each of these phenotypes was log-transformed and age, age^2, and sex were regressed out. The analyses were conditioned on ever smoking. The results from linkage analyses of these phenotypes on chromosome 2 are shown in the graph below.



DISCUSSION

Multiple phenotypes related to behavioral undercontrol evidence linkage to chromosome 2p, across independent datasets. In the COGA project, we find linkage with the phenotypes alcohol dependence, conduct disorder, suicide attempts, and quantitative indices of multiple substance use. In the NAG project, we find linkage with several smoking-related phenotypes to a similar region on chromosome 2. The marker yielding the maximum lod score in the NAG project is approximately 10cM from the marker yielding the maximal lod score in the COGA sample. These peaks are sufficiently close as to be beyond the resolution of linkage analyses (Roberts et al., 1999), and provide converging evidence of a gene in the region that influences multiple substance use phenotypes and related behavioral problems. Several candidate genes are located in the region, including G-protein coupled receptors and zinc finger proteins. Next, we plan to initiate association studies of candidate genes in the region.

ACKNOWLEDGMENTS

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In memory of Theodore Reich, M.D., Co-Principal Investigator of COGA since its inception and one of the founders of modern psychiatric genetics, we acknowledge his immeasurable and fundamental scientific contributions to COGA and the field.

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