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Genetic Studies of Alcoholism and Substance Dependence

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During the past year, there has been a surge in genetic studies of alcohol and substance dependence. This increased interest is the result both of high repeated-heritability estimates of the addictive disorders and related phenotypes (typically ~50%–60%) and of the appreciation that methods for detecting, mapping, and characterizing oligogenic susceptibility genes are rapidly improving. Thus, the full promise of genetics may become available to increase prevention and to improve the treatment of these extremely destructive common disorders. This article is primarily a review of recent human linkage and candidate-gene studies of alcoholism and related phenotypes, although we include other forms of substance dependence that show substantial comorbidity with alcoholism and with each other. We do not consider the large body of research that uses animal models to approach these questions.

Diagnosing Alcohol Dependence

Several sets of diagnostic criteria for alcohol dependence have been used in genetic studies. Older diagnostic criteria (i.e., Diagnostic and Statistical Manual [DSM] IIIR [American Psychiatric Association 1987] and Feighner [Feighner et al. 1972] criteria) prominently featured social and psychological problems as well as biomedical symptoms of dependence (i.e., tolerance, craving, loss of control, and withdrawal). Recently implemented criteria (DSM IV [American Psychiatric Association 1994 and International Classification of Disease [ICD] 10 [World Health Organization 1993]) are more narrowly defined, require more symptoms for diagnosis, and feature biomedical symptoms of dependence. The criteria sets classify individuals in overlapping, nested, reliable categories that have been validated by their predictive value. The symptoms and criteria for a diagnosis of dependence are similar across substances, including nicotine.

As part of the alcohol-dependence syndrome, tolerance of the intoxicating effects of alcohol usually occurs. Thus, increasing amounts are necessary to maintain the same effect. Debilitating withdrawal symptoms, including tremors and confusion, may occur when consumption ceases or is abruptly reduced, symptoms that are rapidly abolished if sufficient alcohol is consumed. Physical, psychological, and social impairment often is progressive or proceeds intermittently, resulting in trouble at work, deteriorating health, and destruction of family relationships. Symptoms tend to cluster at the onset, and rapid deterioration may follow an apparent period of social or controlled drinking.

Alcohol dependence (alcoholism) is a common familial disorder that is a leading cause of morbidity and premature death (Caces et al. 1995). The heritability of risk for alcohol dependence has been estimated by studies of the adopted-away offspring of affected and unaffected parents (~39% [Cloninger et al. 1981]) and by twin studies (~60% [Heath et al. 1997]).

Alcoholics in the community are at increased risk for affective and anxiety disorders, behavioral (externalizing) disorders of childhood, antisocial personality disorder, and drug dependence, including nicotine dependence (Kessler et al. 1997). Nonalcoholic relatives in alcoholic families are also at increased risk. Family and twin studies that test the independence of alcohol dependence and its comorbid disorders support the existence of both common genetic liabilities and disease-specific genetic factors (Bierut et al. 1998; Tsuang et al. 1998). For example, the genetic correlations between alcoholism and affective disorders and alcoholism and nicotine dependence has been reported to be .50 and .68, respectively (Kendler et al. 1993; True et al. 1999). Several heritable quantitative traits that may be closely related to the susceptibility to develop alcoholism, including electroencephalographic patterns and measures of personality, have also been measured in alcoholics and their families. Studies that use these features may be more successful in identifying susceptibility genes than those that rely on a diagnosis of overt alcoholism.

Event-related brain potentials (ERPs) are voltage mea-

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sures of electroencephalographic activity following visual or auditory stimuli. The P3 potential represents a positive deflection 300–500 ms after a stimulus and is elicited when a stimulus is perceived and attentional resources are allocated toward its processing. The amplitude of the P3 potential of abstinent, as well as active, alcoholics is reduced, suggesting that it may be a trait marker for the disorder. Begleiter (1984) reported, in a controlled study, that the amplitude of the P3 potential was significantly reduced in the preadolescent sons of alcoholic fathers, although the sons had never consumed alcohol or illicit drugs. Subsequent research has confirmed and extended these findings to the daughters of alcoholics. Furthermore, reduction of the P3 potential in abstinent alcoholics and in high-risk nonalcoholic offspring has been significantly related to the number of alcoholic relatives rather than to individual alcohol intake (Pfefferbaum et al. 1987). Almasy et al. (1998) reported that the heritability of the P3 amplitude varied between .49 and .60. Taken together, these studies suggest that the amplitude of the P3 ERP is well suited to linkage and association studies for the detection of alcoholism-susceptibility genes.

Cloninger (1993) developed a psychobiological model of personality structure after a classical adoption study of alcoholism in Sweden. In this formulation of personality traits, four stable, quantitative dimensions of personality (harm avoidance, novelty seeking, reward dependence, and persistence) are measured by means of the Tridimensional Personality Questionnaire (TPQ). According to twin studies, each of the four dimensions is moderately heritable (40%–60%) and is influenced by different sets of genes. Their utility in genetic studies of alcoholism is suggested by the observation that childhood personality traits predict alcohol abuse in young adults. Furthermore, alcoholics have been reported to score higher for "harm avoidance" and "novelty seeking" and lower in "reward dependence" than do nonalcoholics.

COGA and Other Genetic-Linkage Studies of Alcohol-Dependence Phenotypes

The Collaborative Study of the Genetics of Alcoholism (COGA) is a multicenter study whose goal is the detection and characterization of genes that influence susceptibility to alcohol dependence and related phenotypes. COGA systematically ascertained ~1,200 families to assess the familial distribution of alcohol dependence and related disorders. Informative, cooperative families were accepted for more-detailed genetic study if $\geqslant 3$ interviewed first-degree relatives, including the proband, were affected. Pedigrees were then extended into second- and third-degree branches, depending on the availability of affected relatives. Adult lifetime psychiatric status was assessed by direct interview of all family members, and a detailed family history was obtained. Personality traits were assessed with the TPQ. Standardized electroencephalographic and ERP studies were conducted in neurophysiology labs that had been carefully calibrated to minimize center effects. Blood was drawn for DNA preparation and lymphoblastoid cell lines were developed and cryopreserved.

COGA was designed as a two-stage genetic study with an initial sample and a larger replication sample. To date, a complete-genome survey of the initial sample of 105 families (987 individuals) densely affected with alcohol dependence has been completed. A genomewide survey of the replication sample (152 families with 1,219 individuals) is in analysis (351 markers). Phenotypic data and DNA from the initial sample are to be made available to the scientific community, as of September 1999. For linkage analyses, diagnosis of alcohol dependence required affected individuals to meet DSM IIIR and Feighner (1972) criteria (termed "COGA" criteria). In a random community sample of control families, the expected lifetime prevalence of this phenotype is ~17.5% in males and 4% in females, with a risk ratio for sibs of 2.8–7.8, depending on the sexes of probands and of sibs. Age at onset averaged ~22 years. The genomewide screen examined 291 markers at an average intermarker distance of 13.8 cM, using a set of 382 affected sibling pairs.

Numerous studies have already used the data from COGA to probe linkage of specific alcoholism-related phenotypes (table 1). Evidence for linkage with susceptibility to developing alcohol dependence was reported (Reich et al. 1998; ASPEX 1999) on chromosomes 1, 2, and 7. The most significant finding was a LOD score of 3.5 on chromosome 7. On chromosome 1, two peaks separated by 60 cM were observed, with LOD scores of 2.9 and 1.6. When more-stringent diagnostic criteria were used (ICD 10 criteria), the linkage finding on chromosome 1 was still significant, and a region on chromosome 16 now gave evidence for linkage. Moreover, linkage analysis of an "unaffected but exposed" phenotype (individuals who drank but had few, if any, symptoms of alcohol dependence) suggested that a protective locus exists on chromosome 4 near the loci for alcohol dehydrogenases (ADH). "Protective" ADH alleles that reduce alcohol consumption have been found in Asian populations, so this finding in a largely African American and non-Hispanic white sample is intriguing.

Long et al. (1998) reported a genomewide scan for genetic linkage to alcohol dependence (DSM III-R criteria) in a Southwestern American Indian tribe. Clinical evaluations and genotypes were available for 152 subjects from extended pedigrees forming 172 sib pairs.

Table 1

Evidence for Genetic Linkage from Genomewide Surveys for Alcohol Dependence And Related Phenotypes

Method of Analysis and Phenotype	Maximum LOD Score	Chromosome (Distance from pter [cM])
Extended pedigree variance components (SOLAR)		
ERPs (P3 amplitude)[a]		
O2 lead[b]	3.28	2 (218)
Cz lead[b]	3.41	6 (213)
	1.82	5 (73)
T8 lead[b]	2.10	5 (76)
	2.07	13 (45)
Harm avoidance[c]	3.2[d]	8 (17)
Multipoint affected sib pairs (SIBPHASE [ASPEX])		
Alcohol dependence (COGA diagnosis)[e]	2.93	1 (169)
	3.49	7 (94)
	1.80	2 (92)
"Unaffected" by alcohol dependence[f]	2.50	4 (87)
Severe alcohol dependence[g]	4.0	16 (14)
Multipoint QTL (SIBPAL [SAGE]) Haseman-Elston regression		
Alcohol dependence[h](DSM III-R)	3.1	11 (0)
	2.8	4 (68)

[a] Begleiter et al. (1998).

[b] Leads on the scalp: O2 = right occipital, Cz = median central, T8 = right temporal (American Electroencephalographic Society 1991).

[c] Cloninger et al. (1998). Also referred to as anxiety proneness.

[d] This locus also displayed evidence for epistatic interaction with other loci: chr18, 20 cM, joint two-locus LOD 4.5; chr20, 0 cM, joint two-locus LOD 4.6; chr21, 26 cM, joint two-locus LOD 5.1.

[e] Reich et al. (1998). DSM III-R (American Psychiatric Association 1987) plus Feighner (Feighner et al. 1972) criteria.

[f] Reich et al. (1998).

[g] Foroud et al. (1998). Defined by a multivariate latent class analysis of alcoholism symptoms.

[h] Long et al. (1998). Native American population.

Multipoint analysis of sib pairs provided highly suggestive evidence for linkage on chromosomes 4 and 11 (LOD scores of 2.8 and 3.1, respectively). Both regions harbored neurogenetic candidate genes. The region on chromosome 4 is near the gene for the $\beta 1$ GABA receptor, and the region on chromosome 11 is near genes for tyrosine hydroxylase and dopamine D4 receptor. The region on chromosome 4 that contains the ADH loci was also implicated in this study, supporting the findings from the COGA dataset.

Foroud et al. (1998) used latent class analysis, a statistical method for finding subtypes of related cases from multivariate categorical data, to derive a narrow phenotype of severe dependence. These authors built on the symptoms of alcohol dependence and nondiagnostic severity items in COGA, and their goal was to increase the power of linkage analysis by reducing genetic heterogeneity. Multipoint affected sib-pair linkage analysis with the derived phenotype yielded a LOD score of ~4 on chromosome 16, in the same region where linkage had been suggested according to the ICD 10 criteria for alcohol dependence.

Begleiter et al. (1998) reported heritability estimates and genetic correlations for visual P3-amplitude ERPs recorded at 19 electrodes (grouped in 5 clusters) across the scalp in the COGA study. Individual heritabilities ranged 0.30–0.50. The genetic correlations between electrode measurements within clusters suggested that 81% of the genetic variation in P3 amplitude is shared in common. Begleiter et al. (1998) used a variance-components multipoint approach to search the genome for QTLs that influence P3 amplitude, making use of 607 individuals from 103 families, including 758 sib pairs. They reported evidence for genetic linkage on chromosomes 2, 6, 5, and 13, with maximum LOD scores of 3.28, 3.41, 2.10, and 2.07, respectively. Even when the large number of tests of linkage are taken into account, empirical estimates show these results to be highly significant.

Cloninger et al. (1998) carried out a genomewide scan of personality traits measured by the TPQ in 758 sib pairs from the COGA sample, using the program SOLAR (Blangero and Almasy 1996) to test for quantitative trait loci. This work showed that harm avoidance, a measure of proneness to anxiety, was significantly linked to a locus on chromosome 8 that explained 38% of the

variance in this trait. There was also significant evidence for epistatic interaction between this locus and others on chromosomes 18, 20, and 21. Taken together, these loci explained most of the heritable variance for this trait.

These genomewide screens suggest that multiple genes of small effect increase or decrease susceptibility to developing alcohol dependence. However, of the loci implicated so far, only a region on chromosome 4 is supported by evidence from two independent studies. Furthermore, closely related traits appear to be linked to distinct genomic regions; even traits that are genetically correlated do not share evidence for linkage at common loci when the phenotypes are analyzed independently.

The Genetic Analysis Workshop in September 1998 (GAW 11) featured phenotypic and genotypic data from COGA (Almasy and Borecki, in press). Investigators analyzed clinical diagnoses, detailed symptom profiles, platelet monoamine oxidase (see Shih and Thompson 1999 [in this issue]) activity measures, personality trait measures (TPQ), multiple ERP measures of visual P3 amplitude, and tobacco consumption in 987 individuals (from 105 kindreds). Genotypes from a genomewide screen were also provided. Workshop proceedings include 68 papers with many new approaches to quantitative and qualitative linkage and linkage/disequilibrium. Of particular interest was the emergence of linkage and disequilibrium analyses of multiple loci using measures from several domains. Analyses at multiple loci may lead to detection of epistatic interactions, revealing much larger genetic effects than do individual analyses of oligogenic loci. A note of caution is in order, however. Although some robust findings were reported—for example, the evidence of a susceptibility locus on chromosome 1—results from both qualitative and quantitative traits were sensitive to changes in phenotype definition.

Candidate-Gene Studies of Susceptibility to Alcoholism

Candidate-gene studies of alcohol dependence are reported regularly. The dopamine receptor gene *DRD2*, which maps to chromosome 11 in humans, has received much attention, as the dopamine system has been correlated with novelty seeking and the CNS reward mechanism (Edenberg et al. 1998*a*). A case-control study reported that a *Taq*I-A1 polymorphism in this gene is associated with alcoholism (especially with "severe" alcoholism; Blum et al. 1990); since then, many studies have disputed this result. However, this sequence variant is not a functional polymorphism and is >10 kb from the coding region of the *DRD2* gene, which makes a tight association unlikely. Many studies have shown that the frequency of the A1 allele is not increased in alcoholic populations. In particular, a study of several different ethnic groups reported that the frequency of the *Taq*I A1 allele varied from .18–.20 in whites to .80 in Cheyennes, suggesting that the earlier finding may have been spurious population association (Goldman et al. 1993). An analysis of the COGA data set was undertaken with the transmission/disequilibrium test (TDT) and the affected-family–based association test (AFBAC) to avoid false positives caused by population stratification. This study found no evidence of linkage or association between the *DRD2* locus and alcohol dependence (Edenberg et al. 1998*a*).

ADH and aldehyde dehydrogenases (ALDH) have been well studied as protective factors. These enzymes are responsible for the oxidative metabolism of ethanol. Functional polymorphisms of the *ADH2, ADH3,* and *ALDH2* genes have received particular scrutiny. The mutant allele *ALDH2*2* acts dominantly over the normal *ALDH2*1* allele and eliminates detectable ALDH2 activity in the liver, causing facial flushing, light-headedness, palpitations, and nausea when alcohol is consumed (Thomasson et al. 1991). A role for *ALDH2* in the development of alcoholism has been firmly established in several Asian populations. In particular, multiple studies of Chinese (especially the Han subpopulation), Japanese, and Korean populations show increased frequency of *ALDH2*1* homozygotes in alcoholics over controls. It thus appears that the *ALDH2*2* allele protects individuals from the development of alcoholism. However, this allele is rare in non-Asians (Neumark et al. 1998).

Recently, several studies of ADH in Asian and non-Asian populations have been reported. A study of ADH and ALDH in Chinese men showed that the frequency of *ALDH2*2* was significantly lower in alcoholics than in controls (Thomasson et al. 1991). The *ADH2*2* and *ADH3*1* alleles (which are associated with high rates of acetaldehyde production) were shown to have significantly lower frequency in alcoholics than in controls, even after subpopulations homozygous for *ALDH2*1* were extracted. A study of 377 male and female subjects of European descent found that the *ADH2* genotype influences alcohol dependence, consumption, and problems in men, although no influence was seen in women of the same background (Whitfield et al. 1998). Another study compared treatment-enrolled heroin-dependent Jewish men in Israel to a Jewish control group living in the same city. All individuals studied were homozygous for the *ALDH2*1* allele. Neumark et al. (1998) showed that mean peak weekly alcohol-consumption levels were significantly lower among carriers of the *ADH2*1* allele. As several authors have suggested, the effects of the *ADH* genes could result from the avoidance of adverse effects of acetaldehyde by individuals with especially rapid production of this metabolite, so that carriers of

these alleles are less likely to become alcoholics (Thomasson et al. 1991; Neumark et al. 1998).

The serotonergic system has also been studied as a risk factor for addictive behavior. In particular, the 5-HT serotonin transporter gene (*5-HTT*) and the *5-HT1B* receptor gene have been considered as candidate genes. A functional polymorphism in the *5-HTT* promoter (see Catalano 1999 [in this issue]) was shown to affect 5-HT uptake in lymphoblastoid cells (Edenberg et al. 1998*b*). A study of 319 Germans showed that the frequency of the "short" allele in the severely affected alcoholics was significantly higher than that in the controls (Sander et al. 1997). A family-based analysis using the COGA data, however, found no evidence of linkage or association between this polymorphism and alcohol dependence (Edenberg et al. 1998*b*).

Opioidergic neurotransmission has also been studied in connection with alcoholism. One study examined the association of a polymorphic (CA)n repeat at the OPRM1 locus, which encodes the μ-opioid receptor, with alcohol dependence in 320 white and 108 African American substance-dependent or control subjects (Kranzler et al. 1998). Modest association was seen in the white population, but not in the African American population. Furthermore, a study of this receptor gene in 667 Germans found no significant association in allele frequency between alcoholics and controls (Sander et al. 1998).

Finally, a recent cladistic analysis tested an association between the Y-chromosome haplotype variation and alcohol dependence and related personality traits (Kittles et al. 1999). Haplotypes were constructed for 359 Finnish males by use of alleles at eight loci, allowing the authors to derive a cladogram that linked the 102 observed haplotype configurations. Using a series of contingency tables nested according to cladogram hierarchy, Kittles et al. (1999) identified a significant association with alcohol dependence at three of the Y-haplotype clades, although no association with personality variables was evident.

The Genetics of Tobacco Use

Cigarette smoking is both comorbid with and genetically correlated with alcoholism, as well as being a major risk factor for lung cancer and cardiovascular disease. Twin studies have estimated the heritability of smoking initiation and nicotine dependence to be >50%, with estimates as high as 84% (Kendler and Gardner 1998; True et al. 1999). Multiple aspects of smoking behavior have been studied. Thresholds on lifetime use (e.g., 100 cigarettes) and combined intensity and duration of use (e.g., $\geq$1 pack/day for $\geq$6 mo) are used to define smoking initiation and help define such subphenotypes as current smokers, heavy smokers, and nicotine-dependent individuals.

Thus far, there is only one published genomewide scan for linkage to nicotine dependence (Straub et al. 1999). The study consisted of 308 affected subjects from New Zealand and a follow-up of 211 affected subjects from the United States. The strongest findings were on chromosomes 2 and 10. The chromosome-2 peak (parametric LOD score 2.63 at 150 cM) was repeated in the replication sample, although the chromosome-10 peak (parametric LOD score 2.20 at 127 cM) failed to replicate. Smaller signals were detected on chromosomes 4, 16, 17, and 18. Although this study was modest, its results suggest that further studies will be productive. Studies have examined a variety of candidate genes, most notably the dopamine receptor genes *DRD2* and *DRD4* and the nicotine-metabolizing gene *CYP2A6*. Although there have been some positive findings for each of these, each candidate has failed to replicate in subsequent studies. Two candidates, tyrosine hydroxylase and the serotonin transporter gene, have yielded purely negative results.

Candidate-Gene Studies of Substance Dependence

As with alcohol dependence, there have been profound secular trends in rates of marijuana and cocaine dependence in the United States and other countries, related to differences in availability, acceptability, and other societal changes. Despite these secular trends, there is growing evidence of specific genetic vulnerabilities to substance dependence. The study of the genetics of alcohol and other substance dependence is complicated by the frequent comorbidity of these disorders. Several recent studies have begun to unravel the relationship of alcohol dependence and other substance dependence and have implicated specific genetic factors in the development of these disorders (Bierut et al. 1998; Merikangas et al. 1998; Tsuang et al. 1998). Studies have examined marijuana-, cocaine-, and heroin-dependent samples to test candidate genes such as dopamine and opiate receptors, but these results are preliminary. The most studied candidate genes are the dopamine and opiate receptors.

Studies of the *OPRM1* gene have demonstrated a weak association with substance dependence, defined as alcohol, cocaine, or opioid dependence (Kranzler et al. 1998). No significant association was found with a specific drug, but the subdivided sample reduced the power to detect association. Similarly, Mayer et al. (1997) reported a weak association between a δ-opioid receptor-gene polymorphism and opiate dependence. In addition, several associations have been reported between substance dependence and the dopamine receptor genes (Duaux et al. 1998; Uhl et al. 1998; Vanyukov et al.

1998). These studies are confounded by both the frequent comorbidity of alcohol dependence with other substance dependence and the combining of different substance-dependence diagnoses (marijuana, cocaine, and opiate) into a single category of "substance dependence." These results require further study to fully understand the role these genes may play in substance dependence.

Future Directions

During the past year, several new large-scale state and federal (NIH) initiatives have begun to study the genetics of alcohol and substance dependence. Large databases that are suitable for candidate-gene and linkage studies will therefore become widely available over the next few years. Genetic studies of alcohol dependence have been in place for more than a decade, so this disorder will receive the most attention in the short term; however, studies of dependence on other substances will soon follow. Candidate genes and chromosomal regions will be drawn from linkage analysis, from studies of animal models, and from rapid progress in neuroscience. Since all of the addictive disorders manifest phenotypes in multiple correlated domains, susceptibility genes ought to express their phenotype in more than one domain as well. Accordingly, successful replication studies in these disorders will require a genetic finding to occur in several independent samples and in multiple domains. Technical and statistical advances in molecular analysis will greatly facilitate the search for susceptibility alleles, and it seems likely that specific and nonspecific genetic mechanisms that increase and reduce susceptibility to development of alcohol and substance dependence will be identified (Collins 1999).

Electronic-Database Information

URLs for data in this article are as follows:

ASPEX (affected sib pairs exclusion [1999]), ftp://lahmed.stanford.edu/pub/aspex/index.html
COGA Web site, http://zork.wustl.edu/niaaa/

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