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Quantitative risk factors as indices of alcoholism susceptibility

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Alcoholism is a complex disorder involving both genetic and environmental factors and interactions between them. Localizing and characterizing the genetic influences on susceptibility to alcohol dependence may provide new insights into pathology and new avenues for treatment and prevention. However, because of the complex nature of the disorder, the binary categorization of individuals as affected or unaffected may be a poor indicator of their underlying genetic susceptibility. Quantitative risk factors, or endophenotypes, that differentiate levels of severity among affected individuals and levels of susceptibility among unaffected individuals, provide one solution to this problem. Genetic studies of such quantitative risk factors in families of probands with alcohol dependence may help to disentangle the complex genetic architecture of this disorder.

Keywords: endophenotype; heritability; liability; linkage.

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Introduction

Alcohol dependence is a binary dichotomy of affected and unaffected (Fig 1, left). A person either meets the diagnostic criteria for alcohol dependence or does not meet them. However, as with most complex diseases, we theorize that behind this dichotomy of alcoholism lies a hidden quantitative process which we call liability, susceptibility or risk of developing alcohol dependence (Fig 1, right). When an individual meets the diagnostic criteria for alcohol dependence, we envision them as having passed a threshold on this liability distribution beyond which disease results. The liability threshold model has several conceptual advantages. Unlike the affected/unaffected dichotomy, the liability model allows for differences among affected individuals and among unaffected individuals. A mildly affected individual would have a liability value just beyond the threshold whereas a severely affected person would have a much higher liability. An unaffected individual may be at very low risk or they may be poised on the edge of affection. By allowing the position of the disease threshold to change with age and sex, we can model different prevalences of disease in males and females and increasing risk with age. Thus, we allow for the possibility that an unaffected individual who is near the liability threshold will eventually become affected.

The drawback of the quantitative model of liability is that this imaginary phenotype cannot be directly measured. Affection status allows us to infer on which side of the threshold an individual's liability value lies, but to estimate degrees of susceptibility we must look for surrogate phenotypes, measurable quantitative traits that are correlated with risk of developing alcohol dependence. In the future, such quantitative risk factors may be used to identify individuals at high risk of developing alcoholism who may benefit from early intervention. In the present, these quantitative indicators provide clues about the pathophysiology of alcohol dependence and are extremely useful for genetic studies of the inherited predisposition to alcoholism.

Alcohol dependence is obviously a complex disorder, involving the interaction of numerous genes with each other and with environmental, cultural, and social factors. As such, localizing and identifying specific genes influencing susceptibility to alcohol dependence is a formidable task. Genetic studies of alcoholism diagnosis have, so far, met with limited success, producing a number of regions with suggestive links to alcohol dependence but few definitive findings. Quantitative risk factors may provide a back door through which alcoholism susceptibility genes

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can be identified indirectly. Of the perhaps dozens of genes that affect liability to alcohol dependence, some may regulate alcohol metabolism while others influence personality, cognitive function, or neurophysiology (Fig 2). It may be easier to identify genes influencing quantitative measures in these domains that also influence susceptibility than to find genes through direct analyses of disease status. Endophenotypic measures likely represent traits that are less complex and more proximal to gene function than diagnostic category. Of the dozens of genes with small to moderate effects on susceptibility to alcohol dependence, a subset may have larger, more easily detectable effects on alcohol metabolism or neurophysiology. Thus, it may be easier to find a gene with a large effect on an endophenotype and then demonstrate that it has a smaller pleiotropic effect on susceptibility to alcoholism than to find a gene with a small to moderate effect on susceptibility.

Empirically measurable quantitative traits may also be easier to obtain and interpret than diagnostic phenotypes as they are not subject to the limitations of diagnostic uncertainties. Quantitative endophenotypes do not require decisions as to whether those who have never drunk alcohol must be considered unaffected or phenotype unknown or whether other addictive behaviors are part of the same phenotypic spectrum. Valid endophenotypic data may be obtained on individuals whose diagnostic category is uncertain, increasing the number of family members who can be included in the genetic analyses and improving the power to detect specific genetic loci.

Key messages

- **Quantitative risk factors, or endophenotypes, may be closer to gene action and genetically simpler than clinical endpoints, such as alcoholism, and thus may provide more power to localize and characterize disease susceptibility genes.**
- **Although a variety of endophenotypes related to alcoholism susceptibility have been identified – including traits related to metabolism, personality, endocrine function, drinking behavior, and electrophysiology – few of these have been the subject of genetic studies.**

What makes a good quantitative risk factor

There are several criteria to consider in selecting quantitative risk factors that will be informative for genetic studies of alcohol dependence. First and most obviously, the measure must be correlated with diagnosis and potentially with severity of disease or age at onset. However, the trait must reflect susceptibility and must not be a consequence of transient states, such as current intoxication, or due to the degenerative effects of long term drinking. To establish this, studies may compare the phenotypes not only among affected and unaffected individuals, but also in newly diagnosed affected individuals who have not yet suffered chronic effects of drinking or in patients who have maintained a period of abstinence. The correlation between affection status and quantitative trait should also be present in the newly diagnosed and abstinent groups.

To distinguish among degrees of susceptibility in as yet unaffected individuals, a quantitative endophenotype must have meaningful variation in unaffected individuals. If all or most unaffected individuals have the same trait value, the trait is uninformative in this group. For example, a quantitative scale rating the

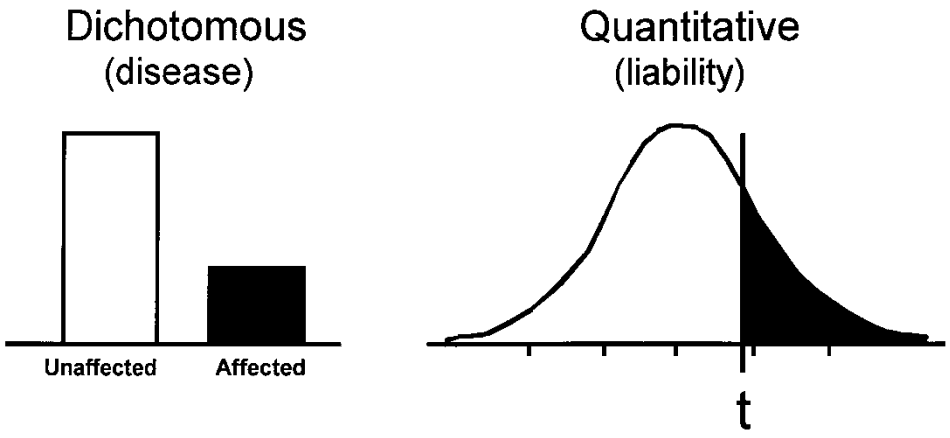

Figure 1. Dichotomous categorization of disease into affected and unaffected groups (left) and a quantitative liability distribution (right) in which individuals are modeled as becoming affected when their liability passes a certain threshold, 't'.

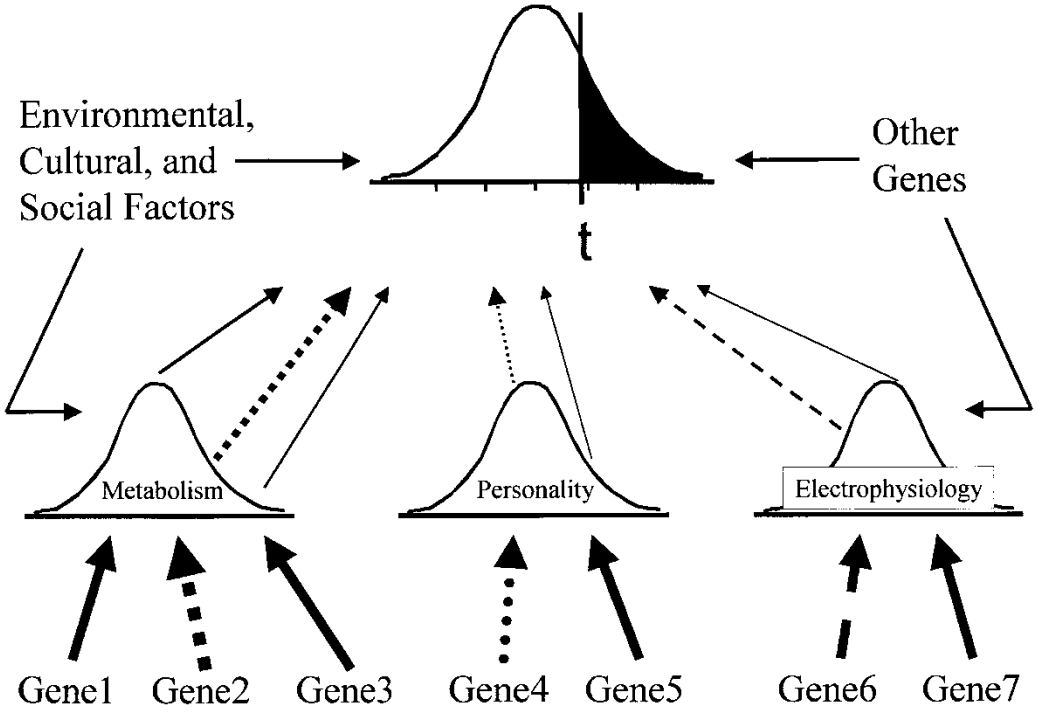

Figure 2. Quantitative risk factors or endophenotypes, such as metabolic, personality, or electrophysiological traits, are influenced by the same loci as liability to alcohol dependence and may be more proximal to gene action. Genes with small to moderate effects on liability (small arrows) may have substantial effects on the quantitative risk factors (larger arrows).

severity of alcohol craving would make a poor indicator of susceptibility if 90% of unaffected individuals reported no craving and thus had a score of zero. To establish a correlation between a quantitative trait and liability in unaffected individuals, trait levels may be compared in unaffected family members of patients and randomly selected controls under the presumption that liability is greater in the family members. Such studies may also compare alcohol-naive children of alcoholics and controls to ensure that differences in trait values are not a consequence of drinking behavior in clinically unaffected adult relatives of alcoholic probands. Prospective studies of alcohol-naive youngsters may also be done, correlating their quantitative trait values with their eventual diagnostic status or age at onset of drinking.

A wide variety of quantitative traits have been investigated as potential biomarkers of alcohol dependence. These have included phenotypes related to alcohol metabolism, endocrine measures, electrophysiology, personality, and drinking behavior. Although the studies reviewed below are limited to those involving human subjects, many of the traits explored in these projects were initially identified as potential indicators of alcoholism susceptibility through studies of animal models.

In a prospective study among twins, Whitfield et al. found that blood and breath alcohol levels in response to an alcohol challenge were higher among participants who went on to develop alcohol dependence (1). Lowered platelet monoamine oxidase (MAO) activity has been observed in alcoholics (2). However, some have seen no differences in MAO activity level between subjects with and without a family history of alcoholism (3) and it has been suggested that the association between MAO activity and alcoholism may be due indirectly to an effect of cigarette consumption on MAO activity (4). Lower platelet adenylate cyclase activity is seen in alcoholics compared to controls (3, 5, 6) and also in those with a family history of alcoholism (3, 7, 8). Catalase activity has been correlated with alcohol intake (9) and individuals with a family history of alcoholism have been shown to have higher catalase activity than those without a family history (10).

Depressed levels of beta-endorphin (11, 12) and increased levels of oxytocin and estrone were found in abstinent alcoholics as compared to controls (13). However, some studies found that levels of beta-endorphin rebounded after 5 weeks of abstinence (14). Lower levels of beta-endorphin were also found in the cerebrospinal fluid of alcoholics (15). Individuals with a family history of alcoholism showed higher baseline levels and an increase in beta-endorphin levels in response to an alcohol challenge as compared to individuals without a family history (16, 17). The amplitude of the P3 component of the evoked brain

potential (ERP) has been shown to be reduced in alcoholic individuals (18–21). Similar deficits in P3 amplitude in response to a visual target stimulus were observed in boys with a family history of alcoholism as compared to age-matched control boys (22, 23).

In a prospective study of 11 year old children, three traits related to different dimensions on a personality questionnaire (novelty-seeking, harm avoidance, and reward dependence) were found to be predictive of later alcohol abuse (24). Children who showed high novelty seeking or reward dependence or low harm avoidance had higher rates of alcohol abuse. Grillon et al. measured startle response to an auditory stimulus in children with a family history of alcoholism or anxiety disorders and in control children (25). Startle response was measured quantitatively using peak amplitude of the post-stimulus blink reflex. They found that children of alcoholic probands showed decreased habituation to the startle stimulus and less inhibition of startle response when the stimulus was preceded by a pre-pulse warning noise.

Heritability

In addition to differentiating between affected and unaffected individuals and high-risk and low-risk individuals, to be a suitable surrogate through which to localize and characterize genes influencing liability, an endophenotype must be heritable and must be measurable in large sample sizes. Heritability is measured on a scale of zero to one, with zero indicating no genetic influences on the trait and one indicating complete genetic determinism. In general, the higher the heritability the better the chance of identifying specific genes influencing the trait. However, heritability measures the strength of the overall genetic effects on a trait and does not indicate the number of genes involved or the relative contributions of those genes. The overall heritability may reflect the summed effects of many genes that will each be relatively difficult to localize or a few genes of larger effect that may be easily found. Heritability is established through family studies that compare the correlation in trait values among various classes of relatives. A good estimate of heritability may be obtained from a sample of perhaps 200 or 300 individuals (26). However, linkage studies to localize genes influencing a quantitative trait will likely require a sample size of 500 to 1000 or more, depending on the desired analytical power and the structure of the families (27). In general, for quantitative traits, larger families provide more analytical power.

The heritability of a variety of electrophysiological traits derived from EEG and ERPs has been established through family and twin studies (28, 29). Beta-endorphin levels after alcohol challenge showed significant heritability in twin studies (30). Several studies have reported heritabilities for MAO activity levels in excess of 0.7 (31, 32).

There have also been a number of studies demonstrating the heritability of quantitative traits related to drinking behavior in randomly ascertained samples. In an Australian twin sample, weekly alcohol consumption levels showed heritabilities of 0.58 in females and 0.45 in males (33). Similar results were seen in a study of Norwegian twins (34). Heath et al. found substantial heritabilities for both frequency and quantity of alcohol consumption in Australian twins (35). Similar results were seen in male twins from Finland (36). Kopun and Propping investigated the heritability of alcohol metabolism in a small sample of male twins given an oral dose of ethanol, finding heritabilities of 0.57 for rate of absorption, 0.41 for rate of degradation, and 0.46 for rate of elimination (37). Heritability of the maximum number of drinks consumed in a 24-hour period has been estimated at approximately 0.5 (38).

Genetic studies of risk factor and disease

Bivariate genetic analyses can be used to estimate to what extent the relationship between a quantitative risk factor and disease is due to pleiotropic effects of a gene or a common set of genes influencing both traits (39, 40). Like heritability estimates, this analysis is based on phenotypic correlations among family members both within and across traits. The overall phenotypic correlation is broken down into a genetic and a residual, presumably environmental, component. In this way, the phenotypic correlation between a quantitative trait and liability to disease is decomposed into genetic and environmental correlations. A genetic correlation significantly different from zero implies pleiotropy with the magnitude of the correlation indicating the extent to which the genetic effects on the two traits overlap. An additional component for non-genetic factors shared among family members, such as household, also may be included provided the pedigree structure is such that pedigrees and households are not completely synonymous.

Only a handful of studies have used bivariate analyses to specifically test for pleiotropic effects on alcoholism diagnosis and a quantitative risk factor, specifically P3 amplitude (41, 42).

Finding genes

Relatively few of these quantitative biomarkers of alcohol dependence have been the subject of genome-

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wide linkage screens in humans. Complex statistical methods may be used in these analyses, but the basic concept is that linkage analyses of quantitative traits look for patterns of DNA sharing among family members that match the patterns of phenotypic correlations (43, 44). In a chromosomal region harboring a locus influencing the trait, relatives who are phenotypically similar should share more genetic material than relatives who are dissimilar. Unlike association studies, the markers that are used for linkage studies are random and are not assumed to have any function. The alleles shared by one set of concordant relatives need not be the same as the alleles shared by another set. They serve only to mark the transmission of chromosomes through families. The advantage of this approach is that the entire genome can easily be scanned with the genotyping of a few hundred markers, meaning that a researcher need not have an *a priori* hypothesis about what genes influence the phenotype. Evidence for linkage is measured by the logarithm of odds (LOD) score. Generally, in a genome-wide screen, a LOD score over 3 is taken as significant evidence of linkage. A LOD of 3 corresponds to a point-wise *P*-value of 0.0001. This relatively conservative threshold for linkage was chosen to take into account the multiple statistical tests that are necessarily done in the course of a genome scan.

Linkage analyses of the maximum number of drinks consumed in a 24 hour period produced significant evidence of linkage near the alcohol dehydrogenase (ADH) gene cluster on chromosome 4 (38). In a study of three quantitative personality measures (Harm avoidance, Reward dependence, and Novelty seeking) from the Tridimensional Personality Questionnaire, Cloninger et al. found strong evidence for a gene on chromosome 8p influencing Harm avoidance (45). Multi-locus analyses including interactions between this chromosome 8p gene and other loci provided some support for secondary loci on chromosomes 18p, 20p, and 21q. Linkage analyses have also been conducted on quantitative traits derived from questionnaire data on drinking behavior and personality, implicating a region on chromosome 1 (46). A genome screen for loci influencing platelet MAO-B activity levels gave suggestive evidence of linkage (LOD = 2) on chromosome 6 near D6S1018 (47).

A genome scan for loci influencing P3 amplitude in response to a visual stimulus provided strong evidence of linkage on chromosomes 2q and 6q (48). Bivariate linkage analyses with alcoholism diagnosis and P3 amplitude demonstrated that the chromosome 6 locus, but not the chromosome 2 locus, has a pleiotropic effect on susceptibility to alcoholism (42). Other electrophysiological traits that have been the subject of a genome-wide linkage screen in individuals with alcoholism and their family members include ERPs in response to a semantic priming paradigm (49) and the beta frequency of the EEG (50).

Conclusion

The concept of using quantitative risk factors in genetic studies of disease is not a new idea. It has been employed for years in studies of disorders such as heart disease. For the specific case of alcohol dependence, Reich suggested a similar use of biomarkers of susceptibility in 1988 in the context of alcoholism diagnosis and treatment (51). For genetic studies of alcoholics and their family members, use of quantitative endophenotypes is an idea whose time has come. In the last few years a wide variety of potential biomarkers for alcoholism have been identified and characterized and statistical tools have been developed for finding the genes influencing these quantitative risk factors and simultaneously testing their effects on risk of alcoholism.

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