

The Genetics of Alcohol Metabolism and Alcoholism

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ABSTRACT Alcoholism is an extremely complex disease for which no generally accepted definition exists; there is a complex interaction between the socio-environmental context, the individual at risk, and the availability of alcohol. Recent human genetic studies clearly suggest that predisposition to alcohol abuse and/or to develop alcoholism is inherited. The results of family, twin, and adoption studies are compatible with the existence of genetic factors in the etiology of alcohol abuse. Pedigree analysis, linkage, and association studies have helped to detect marker loci and candidate genes that may be useful for identifying individuals at risk. The legacy of alcoholism among certain ethnic groups suggests that genetic factors can increase an individual's vulnerability for this disease. Recent molecular genetic research into the causes of alcoholism has drawn attention to the potential important role of alcohol and acetaldehyde metabolizing enzymes. Functional polymorphisms have been observed at various genes encoding these enzyme proteins that act as one of the biological determinants significantly influencing drinking behavior and the development of alcoholism and alcohol-induced organ damage.

INTRODUCTION

A necessary condition for the development of alcoholism is the availability of alcohol. Alcohol has been probably known to humans from the pre-historical times. After introduction of agriculture between 10,000 and 5,000 BC, systematic alcohol production became possible by fermentation of barley, honey, milk, and grapes by various populations. At that time, alcohol was mainly used as a food because of its vitamin and mineral content. The preserving qualities of alcoholic solutions enabled long-term storage of food, an important property in early stages of civilization. Presumably, an essential motivation for utilizing the psychotropic effects of alcohol was coping with existential fear, which certainly was omnipresent in primitive societies. This

might also have been the cause for early integration of alcohol use in religious rites. Invention of the method of distillation of alcohol around 1000 AD made the production of concentrated alcoholic beverages possible. During the thirteenth and fourteenth centuries this technique spread over Europe and paved the way for alcohol abuse and the development of alcoholism.

There is a complex interaction between the socio-environmental context, the individual at risk, and the availability of alcohol. Therefore, it is obvious that the conditions facilitating the development of the disease alcoholism and the criteria of its definition can hardly be generalized to different populations or societies. The definition proposed by National Council on Alcoholism and Drug Dependence (NACDD) and the American Society of Addiction Medicine (ASAM) reads as follows (Flavin, and Morse, 1990): Alcoholism is a primary, chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. The disease is often progressive and fatal. It is characterized by continuous or periodic impaired control over drinking, preoccupation with the drug alcohol, use of alcohol despite adverse consequences, and distortions in thinking, most notably denial.

ALCOHOL TYPOLOGY

Researchers rely on personality questionnaires to determine the category in which each alcoholic subject belongs. Five frequently used questionnaires are: the Minnesota Multiphasic Personality Inventory (MMPI), the MacAndrew Alcoholism Scale (MAC), the Eysenck Personality Questionnaire (EPQ), the Tridimensional Personality Questionnaire (TPQ), and the Connecticut Typology Questionnaire (CTQ).

Type I and Type II Alcoholism: A study of Swedish adoptees and their biological and adoptive parents resulted in the identification of two distinct alcoholism subtypes, type I and type II.

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Cloninger (1990) distinguished type I of alcoholism (low novelty seeking, high harm avoidance, high reward dependence) from type II (male-limited) alcoholism (high novelty seeking, low harm avoidance, low reward dependence). A third type of alcoholism has been proposed by Hill (1992). Like type II alcoholism, it is significantly influenced by genetic factors, but is not associated with antisocial behavior.

GENETIC EPIDEMIOLOGY

Family Studies: Because of a high degree of familial association, for many years, alcoholism was regarded as a distinct disease that may be transmitted from generation to generations (Dawson et al. 1992). A familial association could result from cultural factors tending to encourage heavy drinking in family members. Children try to model their behavior on that of their parents and doing so may also imitate their drinking habits. On the other hand, drinking may be discouraged in some families for religious, cultural or climatic grounds while in other families constraints on heavy drinking may be virtually non-existent.

Therefore, "familial" does not necessarily mean "hereditary". A critical review of studies of the familial incidence of alcoholism summarized 39 investigations published in English that comprised family data on 6,251 alcoholics and 4,083 non-alcoholics (Cotton 1979). They clearly showed that regardless of the nature of the population of non-alcoholics studied, an alcoholic is more likely to have a mother, father or a distant relative who is an alcoholic. When lifetime prevalence of alcoholism in relatives of alcoholics were compared to that in the general population, a 4-fold increased risk in first-degree relatives and a 2-fold increased risk in second-degree relatives was observed. Higher family incidence of alcohol use and abuse does not necessarily reflect a genetic determination of alcoholism. Heritable familial attributes as well as similarities in the social environment of family members also appear to play a role in familial transmission of alcoholism. Thus, family systems (family reactivity patterns, ethnic family styles, gender of the alcoholic spouse, and stages of alcoholism) are an important variable in the gen-

esis, consequences and treatment of alcoholism.

Twin Studies: The twin study paradigm is a powerful method to study complex and heterogeneous trait disorders. Differences between identical twins would presumably reflect environmental influences while differences between non-identical twins may be due to heredity, environment, or both. Therefore, if alcoholism has a hereditary basis, MZ twin pairs should tend to be more similar in their drinking behavior and alcohol-related problems than DZ twin pairs (Pickens et al. 1991).

In the Swedish study, the twins were ascertained from the persons registered by the temperance board as having a drinking problem (Kaij 1960). They were classified into 5 categories of alcohol abuse. An increasing difference in concordance rates between the monozygotic (MZ) and dizygotic (DZ) pairs with increasing degree of alcohol abuse was found. Another twin study looked at genetic influence on medical consequences of alcoholism. This study, which was based on medical histories from military service records, hospital records, and questionnaires, also gave information on alcoholism (Hrubec and Omenn 1981). The concordance rate for alcoholism, including alcoholic psychosis, was reported to be much higher in MZ twins than in DZ pairs. Reed et al. (1996) published a follow-up of this sample using medical records through 1994, and obtained similar estimates.

The British study was based on the psychiatric twin register of Maudsley Hospital (Gurling et al. 1981). In contrast to other studies, the concordance rates of MZ and DZ twins did not differ significantly, but more than one-third of the twins were below age 40 years when examined, suggesting that alcohol dependence may yet develop in a proportion of co-twins. Another large, population-based study from Finland confirmed a genetic influence on frequency, quantity, and density of drinking, but did not find such an influence for passing out (Kaprio et al. 1987). Pickens et al. (1991) reported results for same-sex twin pairs who were clinically interviewed. Twin pair similarity was high for both diagnostic definitions among males, with higher heritability estimates for alcohol abuse-dependence (AAD), and stronger evidence for family environment for AAD. A similar pattern was reported

for female twins, although the magnitude of estimates was lower than those reported for males. Koskenvuo et al. (1984) reported results from merging Finnish psychiatric records against the national twin registry to identify twins who received alcohol-related discharge diagnoses through 1979. Substantial heritability was reported for males, but due to very low prevalence in females, no concordant female cases were observed. A follow-up to this study published by Romanov et al. (1991) included information from hospital records through 1985 for male pairs, yielding more complete ascertainment and resulting in higher heritability estimates.

In a recent study, genetics has been shown to be an important determinant of vulnerability to alcoholism in females (Kendler et al. 1992). The authors have investigated 1,080 adult pairs of female twins for their alcohol-related behavior. The study revealed that at every level of alcoholism, identical twins were significantly more likely than fraternal twins to have similar history of alcoholism. These results support an earlier finding from a Swedish study of women who had been adopted out (Cloninger et al. 1981). These authors found a pattern of genetic transmission of alcoholism from mothers to daughters.

Heath et al. (1997) reported results from a telephone interview assessment of members of the Australian National Health and Medical Research Council twin registry. Participants were eligible based on prior research participation, and 86% of the eligible were interviewed. This study found strong evidence for genetic influences on the development of alcoholism for both sexes, while the evidence for common environmental effects was negligible.

Recently, a population-based sample of male twins was studied in the United States for genetic and environmental contributions to alcohol abuse and dependence (Prescott and Kendler 1999). Results based on two definitions of treatment (inpatient or outpatient alcohol treatment, and any treatment) were compared to results from the random ascertainment method originally used in the sample. Among individuals who were diagnosed as alcoholic, males were twice as likely as females to enter alcohol treatment. This difference was not accounted for by sex

differences in clinical severity or course, suggesting that there were sex-related differences in treatment entry. Among males, heritability estimates were similar across sampling methods. The treatment ascertainment methods yielded higher estimates of common environmental influences, a finding similar to the results of twin studies that employed archival and treatment-based ascertainment. Among females, heritability estimates based on the broad definition of treatment were similar to those obtained using the random ascertainment design, but estimates based on alcoholism treatment were (non-significantly) lower. These results provide partial support for the hypothesis that differences in sampling method may account for differences among studies in heritability estimates.

Adoption Studies: A systematic approach to separate “nature” from “nurture” is to study individuals separated from their biological relatives soon after birth and raised by non-related foster parents and to compare them with respect to characteristics of alcohol abuse with both their biological and adoptive parents. It is based upon the premise that the genetic trait present in the affected biological parent will still be expressed in adoptees, regardless of the genotypic status and environmental circumstances of the foster parents. In studies of intact families, the effects of genetic and common environment are not separable. Adoption studies separate these effects because adoptees receive their genetic heritage from one set of parents and their rearing environment from another set. The degree to which adoptees resemble their biological relatives is a direct measure of genetic influence, while the degree to which they resemble their adoptive relatives is a measure of the influence of family environment.

Extensive adoption studies conducted in Denmark and Sweden have provided substantial evidence that alcoholism is genetically influenced, and that there are distinct patterns of alcoholism with different genetic and environmental causes (Goodwin et al. 1974; Cloninger et al. 1981; Bohman et al. 1987). When the adopted away sons of an alcoholic parent were compared to their siblings raised by the alcoholic biological parent, a remarkably similar rate of alcoholism was noted in both groups. Subsequent

adoption studies from other countries have clearly shown that children born to alcoholic parents but adopted away during infancy were at greater risk for alcoholism than adopted-away children born to nonalcoholic parents (Sigvardsson et al. 1996).

Gender Differences in the Transmission of Alcoholism: There is consistent evidence that relatives of women treated for alcoholism have higher risk for alcoholism than relatives of treated males (Prescott et al. 1999). This suggests that women in treatment tend to have higher liability than their male counterparts (McGue and Slutske 1996). The results for untreated female alcoholics are less clear. The evidence regarding sex-specific transmission varies across studies, providing no consensus as to whether different sets of genetic factors influence the development of alcoholism in males and females (Hill 1995). Some evidence from molecular genetic studies supports the existence of sex-specific loci (Paterson and Petronis 1999), and a definitive answer to this issue will probably come from molecular rather than epidemiological studies.

Mode of Inheritance: Although adoption and twin studies have proven useful in answering the question of nature versus nurture, the mode of inheritance of alcoholism is still an unresolved matter. None of the evidence hitherto put forward suggests that susceptibility to alcoholism is inherited via a simple Mendelian dominant, recessive or sex-linked transmission. Even if the inheritance of certain biological factors involved in alcoholism is assumed to be Mendelian, the effect of these factors on the development of complex disorders may still not fit a simple genetic model. A substantial degree of etiological heterogeneity in the alcoholism phenotype results in the ultimate manifestation of the disorder dependent on poorly understood gene-environment interactions.

Characterization of High Risk and Low Risk Individuals: In the past years, a number of investigators have tried, in prospective studies, to identify possible trait markers by studying young men and women at high risk for the future development of alcoholism based on their family history of this disorder. Having an alcoholic biological father is the best single predictor of fu-

ture alcoholism in male offspring. One method of determining whether there are neuro-psychological deficits prior to the onset of alcoholism is to study children who are at risk for becoming alcoholic. In a typical prospective study young men and women at high risk for the future development of alcoholism are divided into Family History Positive (FHP) group, (who report an alcoholic parent or siblings) and Family History Negative (FHN) group (men and women who report no close alcoholic relative). The subjects are matched for demography and alcohol drinking history.

GENE IDENTIFICATION

Evidence for the familial transmission of alcoholism has stimulated researchers to look for specific genes that may confer vulnerability to alcoholism. Existence of a variable number of possible interacting genes giving a predisposition to the diseases is likely. However, the genetic dissection has been hampered by genetic complexity as well as by difficulties in defining the phenotypes. These include the choice of phenotype to be studied, whether narrow or broad, whether only mild or severe forms are included, and whether or not co-morbidity should be excluded (Hill 1998).

In searching for genes that contribute to alcoholism risk, several approaches may be utilized in order to identify the genetic loci underlying alcoholism susceptibility. Several candidate genes have been evaluated for their role in alcoholism; however, with the exception of the enzymes of alcohol metabolism, results from these studies have been inconsistent (Goldman 1995).

Candidate Genes: The number of mapped human genes now exceeds 30,000. This rapid development will facilitate gene mapping and efforts to isolate and identify the genes responsible for symptom susceptibility in many of the aetiologically unclear psychiatric diseases with complex genetic origin. Genetic mapping efforts using sib pairs, twins and individual large families have revealed preliminary or tentative evidence of susceptibility loci for alcoholism (Long et al. 1998; Reich et al. 1998). Studies in humans have reliably shown that the genes for the

principal enzymes of alcohol metabolism influence drinking behavior and alcoholism risk. Notably, the functional genetic variants of ADH that exhibit high alcohol oxidizing activity, and the genetic variant of ALDH that exhibits low acetaldehyde oxidizing activity, protect against heavy drinking and alcoholism (Chen et al. 1999; Yin and Agarwal 2001).

Polymorphic Markers: As part of the Human Genome Project, a large number of markers called microsatellites have been mapped on the human genome. These markers are short stretches of 2 to 4 nucleotides and are repeated several times. These repeats are highly polymorphic and allow to track the transmission of the microsatellites across successive generations of a family. To find chromosomal regions and genes influencing alcoholism, researchers look for certain microsatellites that are co-inherited with the disease across multiple generations.

Quantitative Trait Loci Mapping: The genetically influenced characteristics, or traits, thought to underlie responses to alcohol (sensitivity to its effects) are called quantitative traits. Many genes influence the overall characteristics, each to a certain event. Within a population a quantitative trait differs in the degree to which individuals possess it, rather than in the kind of trait they possess. Accordingly, a small section of DNA thought to contribute to a quantitative trait is called a quantitative trait loci (QTL). Quantitative traits are said to be continuously distributed in a population because individuals exhibit them to different degrees. Locating a particular quantitative trait in the genome is called QTL mapping. Once QTL analyses have identified a chromosome region containing a gene that may affect a certain phenotype (i.e. a candidate gene), tests can be performed to determine the magnitude of the gene's influence. However, the QTLs involved in human alcoholism remain to be characterized. Therefore, QTL mapping for alcohol-related traits is more commonly performed in animal models than in humans (Buck 1998). Through the development of congenic lines and transgenic and knock-out animals, candidate genes can be identified and evaluated for their role in alcohol preference. The ultimate goal of QTL mapping and cloning is to identify the genes contributing for alcoholism.

Recently, two large studies have employed a genome screen methodology to identify novel genes contributing to the risk of alcoholism (Long et al. 1998; Reich et al. 1998). This screening has resulted in the detection of suggestive linkages on human chromosomes 1, 4, and 7, but did not identify any definitive linkage.

BIOLOGICAL BASIS OF GENETIC SUSCEPTIBILITY TO DEVELOP ALCOHOLISM

On the basis of the above brief review of genetic determination of alcoholism, it becomes apparent that the development of alcoholism for some individuals depends on the presence of genetically-controlled predisposing factors interacting with environmentally-determined precipitating factors. Thus the search for potential causative genes is rather complicated; an unknown number of genes may be involved in the development of alcoholism. For many years researchers have been looking for specific genes or genetic markers for vulnerability to alcoholism.

An association with a known hereditary trait occurring in consistently higher frequency may help to identify a genetic predisposition to alcoholism. Predisposing biological markers must fulfill the following criteria: 1. the trait marker can be reliably measured in individuals and is stable over time; is genetically transmitted; the abnormal trait has a low base frequency in the general population; can identify individuals at risk with high specificity and sensitivity. 2. the abnormal trait shows high prevalence in patient population; is present during symptom remission; occurs among first-degree relatives of the probands at a higher rate than in the general population; and segregates with the illness in affected relatives of the proband. Potential markers for genetic vulnerability to alcoholism may be divided into two broad categories: biochemical markers and trait markers.

Biochemical Vulnerability Markers: Some of the well known genetically controlled biological factors that may contribute to alcoholism include: alcohol elimination rate, alcohol metabolism, polymorphisms of ADH, ALDH, and CYP2E1, alcohol's biochemical effects on the CNS, alcohol's effects on psychophysiological

performance, and alcohol's effects on electrophysiological parameters (Agarwal and Goedde 1992). A comparison among racial and ethnic groups has invariably shown that (1) a larger proportion of Orientals than Caucasians report no use of alcohol; (2) Caucasians report heavier alcohol use; and (3) a larger proportion of Orientals who drink alcohol experience facial flushing and associated sensitivity symptoms after drinking alcohol. Recent molecular genetic research into the pathophysiological causes of alcoholism has drawn attention to the potential important role of alcohol and acetaldehyde metabolizing enzymes (Agarwal 1997). Functional polymorphisms have been observed at various genes encoding these enzyme proteins which all act to alter the rate of synthesis of the toxic metabolite acetaldehyde, or decrease its further oxidation. A positive selection of such genetic polymorphisms in some populations might act as a protective factor against alcohol abuse and alcohol-related disease outcomes (Yin and Agarwal 2001).

Trait Markers of Alcoholism: Numerous studies have been performed in the past years to identify potential markers of trait abnormality in alcoholism. Electrophysiological characteristics of alcoholics and those at risk for developing alcoholism have also been identified, including the reduced amplitude of the event-related brain potential and, after ethanol ingestion, characteristic EEG alpha-wave activity. Lower platelet adenylate cyclase activity is seen in alcoholics compared to controls, presumably as a result of over-expression of an inhibitory G-protein.

Platelet Monoamine Oxidase (MAO): Monoamine oxidase (MAO), catalyzes the oxidation of monoamine neurotransmitters such as catecholamines, indolamines and other biogenic amines which possibly play an important role in the regulation of mood and behavior. Two forms - MAO A and MAO B - are known that are distributed mainly in the brain, liver and blood platelets. In human platelets only the B form is detectable. Low platelet MAO activity associated with alcohol abuse has been thought to represent a genetic vulnerability factor for alcoholism, especially the type II form (Tabakoff et al. 1990).

Adenylate Cyclase (AC): Lymphocyte and

platelet adenylate cyclase (AC) activity in alcoholic subjects was found to be less responsive to stimulation by fluoride, guanine nucleotide, or prostaglandin E (Tabakoff et al. 1990; Parisian et al. 1996). A linear discriminant analysis of the distribution of fluoride-stimulated adenylate cyclase activity in the platelets of alcoholics and controls showed that using this parameter 75% of alcoholics and 73% of controls could be classified correctly. These abnormalities in alcoholics persisted even after weeks of abstinence, suggesting that the decreased adenylate cyclase activity in blood cells is rather a trait marker than a state marker.

D2 Dopamine Receptor Gene: Recently, reports suggesting an association of the D2 dopamine receptor gene, named DRD2, and alcoholism have drawn considerable attention. Restriction of DRD2 by TaqI yields polymorphic fragment lengths identifying alleles A1 and A2 that differ in average amounts of receptor sites (Blum et al. 1993). Human cadaver studies in alcoholic group showed a significantly higher frequency of the DRD2 allele A1 than in the non-alcoholics. This finding has been replicated in a number of subsequent studies (Gelernter et al. 1991; Noble 1998).

CONCLUDING REMARKS

Complex interrelationship between functional polymorphisms of the alcohol metabolism genes suggest that alcoholism is a complex behavioral trait that is influenced by multiple genes as well as socio-economic factors. Family, twin, and adoption studies have established the importance of genetic influences in the etiology of alcoholism in males. The evidence for females is less consistent but newer studies suggest a similar degree of genetic influence. Women treated for alcoholism appear to have greater liability than treated males, but it is unclear whether this is true for untreated alcoholics. However, no simple mode of inheritance should be expected from such an endpoint. A multifactorial or multicausal system would seem most likely. Sophisticated statistical models have been applied, taking into account sex differences of psychiatric symptoms, alcoholism rates, and criminality, as well as familial transmission. A

real improvement of our understanding will ultimately depend on the integration of genetic and pathophysiological mechanisms that lead to alcoholism. In males, genetic differences are important in youth but environmental factors increasingly influence their drinking habits as they age. In females, though genetic factors determine the alcohol consumption profile, the influence of both genetic and environmental variations increase considerably with age.

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