

# 9 Alcoholism

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*Family studies • Twin studies • Adoption studies • Genes, environment  
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Conclusions*

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There has been a long-standing acceptance by most clinicians that alcoholism sometimes shows a tendency to run in families. However, psychiatrists specialising in its treatment have only comparatively recently taken seriously the proposition that genetic factors might be important. This may in part be because of the irregular pattern of familial transmission, but probably more influential was the recognition of obvious environmental factors, particularly availability of alcohol and the assumption that family members pass on drinking habits 'by example' rather than via their genes (Kessel & Walton, 1965). A greater willingness to acknowledge that genetic factors may contribute to the familiarity of alcoholism has resulted from a series of genetic epidemiological studies carried out over the past two decades. An additional factor in influencing more recent opinion has been the advance in knowledge of the molecular pharmacology of alcohol and an increasing interest in the potential power of molecular genetic studies.

## Family studies

There have been many studies of alcoholism consistently showing an increase risk of the disorder in the relatives of alcoholics. For example, Cotton (1979) combined the data from over 30 studies to give a weighted average frequency of alcoholism of 27% in the fathers of alcoholics, and over twenty studies to give a weighted average frequency of alcoholism of 5% in alcoholics' mothers. However, studies with rigorous methods have been the exception rather than the rule (Merikangas, 1989). Only a handful have used standardised diagnostic criteria on personally interviewed relatives and have included control groups. Such studies show that, just as in the population as a whole, more male relatives are affected than females. For example, Reich & Cloninger (1990), using the Feighner criteria, report lifetime prevalences of alcoholism of between 15% in the sisters and 57% in the brothers of male probands (see Table 9.1). Interestingly, the risk of alcoholism in the first-degree relatives of female alcoholics was very similar, suggesting that the sex of the proband has

**Table 9.1** Frequency of alcoholism in spouses and first-degree relatives of 300 alcoholic probands

	Male probands			Female probands		
	<i>n</i>	% affected	Mean age	<i>n</i>	% affected	Mean age
Fathers	80	37.5	54.1	13	38.5	61.2
Mothers	125	20.8	51.2	27	3.7	59.3
Brothers	192	56.8	29.3	36	52.8	36.7
Sisters	196	14.8	31.3	49	20.4	35.3
Sons	28	32.1	23.8	20	50.0	26.3
Daughters	47	19.1	23.1	18	16.7	24.9
Spouses	100	13.0	35.9	25	56.0	41.0

Data from Reich & Cloninger (1990).

little influence on the familial distribution of the disorder. It is also noteworthy that the lifetime prevalence of alcoholism in the husbands of alcoholic women was, at 56%, similar to that in their male biological relatives. Likewise the 13% prevalence in alcoholic men's wives was comparable to the frequency in their sisters. This suggests that either there is assortative mating for alcoholism, or that people become similar to their spouses in their drinking habits, or a combination of the two.

Although some authors have suggested rates of alcoholism as much as seven times higher in relatives of alcoholics than in controls (Stone & Gottesman, 1993), the family data reported by Reich & Cloninger have to be compared with survey data from their own department which show general population lifetime prevalences of alcohol abuse of over 20% in men and 5% in women up to the age of 44. Nevertheless, this still supports the hypothesis that alcoholism is familial. However, there are two other observations on the familial aggregation of male alcoholism that make it unlikely that a purely genetic explanation will suffice. The first is that grandfather/grandson pairs may be as concordant as father/son pairs (Kaij & Dock, 1975). Secondly, in a study of half-siblings, concordances similar to those in full siblings were found (Schuckit *et al*, 1972). That is, there was as much resemblance in pairs of relatives sharing only a quarter of their genes as in those who on average share one half. Despite this, the existence of definite familial effects make genetic factors worthy of further exploration, so long as it is done with an open mind and with an awareness of the possible existence of heterogeneity (Sher, 1991).

## Twin studies

Twin studies of alcoholism and alcohol abuse or dependence are listed in Table 9.2, and some of the main findings with respect to concordance rates are summarised. The earliest study, by Kaij (1960), was based partly on interviews and supplemented by official records from a 'Temperance Board Register'. Most cases would probably now be classified as alcohol abusers rather than suffering from dependence. The study by Hrubec & Omenn (1981) was based on Veterans Hospital records and questionnaire data. None of the subjects was actually interviewed by the researchers and again, as in the study of Kaij, all were men. Both of these studies appeared to indicate a genetic contribution to alcohol abuse, but the first study to use standardised interviews, operational diagnostic criteria and to include women as well as men, showed no difference between monozygotic (MZ) and dizygotic (DZ) concordances (Gurling *et al*, 1981). Although the samples were small when divided by sex there was not even a suggestion of a genetic effect in either men or women. These results contrast with two more recent studies (Pickens *et al*, 1991; Caldwell & Gottesman, 1991) both of which, for the broad criteria of alcohol abuse and/or dependence, found higher concordance in male MZ than DZ twins. In the Caldwell & Gottesman study, ascertainment was carried out systematically via a consecutive hospital series. Recruitment in the Pickens study and the subsequent report by McGue *et al* (1992) was not systematic but precautions were taken to overcome ascertainment biases, and DSM-III criteria were used. The results suggest a moderate heritability ( $h^2$ ) in males, but a more modest effect in females, where heritability was variously estimated at 0%

**Table 9.2** Twin studies of alcohol abuse or dependence

Study	Sex	MZ		DZ	
		<i>n</i>	Concordance: %	<i>n</i>	Concordance: %
Kaij (1960)	M	32	53	142	28
Hrubec & Omen (1981)	M	271	26	442	12
Gurling <i>et al</i> (1981)	M&F	29	29	40	33
Pickens <i>et al</i> (1991)	M	50	76	64	61
	F	31	36	24	25
Caldwell & Gottesman (1991)	M	28	68	26	46
	F	17	47	3	42
McGue <i>et al</i> (1992)	M	85	77	96	54
	F	44	39	43	42
Kendler <i>et al</i> (1992)	M	81	32	79	24

(McGue *et al*, 1992), 8% (Caldwell & Gottesman, 1991) and 26% (Pickens *et al*, 1991). When the criteria were narrowed to require alcohol dependence (with or without abuse), the difference between MZ and DZ concordance rates increased. For example, Pickens *et al* found that the male concordance was 59% in MZ and 36% in DZ twins, while the female concordance was 25% for MZ and 5% for DZ subjects. These concordances correspond to heritabilities of just under 60% for alcohol dependence in men and 42% in women (Pickens *et al*, 1991). By contrast for alcohol abuse (dependence not a requirement) there was evidence of substantial shared environmental effects ( $c^2$ ), accounting for 48% of the variance in liability in men and 47% in women.

It was also of interest that when Pickens *et al* examined the particular items that contributed to the diagnosis of alcoholism, they found the greatest MZ/DZ differences (and by implication the largest genetic effects) in multiple binges, continued use of alcohol despite a worsening condition, alcohol-related job or school trouble, and morning drinking. The same pattern was not observed in women, where the only item which showed a significant difference between MZ and DZ concordance was heavy use of alcohol for a period of two weeks.

Kendler *et al* (1992) were unusual in studying only female twins in the general population, where they found higher MZ than DZ concordance for DSM-III-R alcoholism and estimated that the heritability was 56%. Also, in contrast to other recent studies, they have found no effect of shared environment.

Therefore, in summary, despite diagnostic differences, marked variation in reported concordance rates and one small study showing no evidence for genetic effect, it seems probable that there is at least a modest genetic contribution to broadly defined alcohol abuse or dependence. When consideration is restricted to alcohol dependence, the recent studies suggest moderate heritability ( $h^2$ ) in both men and women. However, in concluding this we should not overlook the fact that nearly all of the twin data suggest that the environmental contribution to alcoholism is large (McGue, 1993). Recent studies where the components of environmental variance have been estimated, most, but not all, find evidence of marked shared (i.e. familial) environment effects ( $c^2$ ) which seem to be particularly important for alcohol abuse.

### **Twin studies of 'normal' alcohol use**

An alternative approach to focusing on alcohol misuse is to study drinking patterns in normal twins. Such a study was carried out by Clifford *et al* (1984), who found that additive genetic effects (i.e.  $h^2$ ) accounted for about 40% of the variance in total weekly alcohol consumption, with shared environment ( $c^2$ ) accounting for 32%. Very similar overall results were found in men in the study of normal twins by Jardine *et al* (1984), although

here only genetic factors appeared to be an important source of resemblance in female twins. However, results from a study of Finnish twins separated before the age of 11 years (Kaprio *et al*, 1984) suggest that both genes and family environment are influential in levels of alcohol consumption. Thirty MZ and 95 DZ twin pairs were matched with twins reared together. Correlations for alcohol consumption were greater in twins reared together than those brought up apart, but in men concordance rates for heavy alcohol use were greater in all MZ than DZ pairs. More recently, Heath *et al* (1993) have suggested the need to consider alcohol use as consisting of separate underlying dimensions related to abstinence, consumption frequency and level of consumption. They have presented twin-study evidence suggesting that each of them is heritable to varying degrees.

## Adoption studies

Given the importance of shared environmental effects on drinking behaviour, adoption studies would seem to be a particularly attractive way of investigating the causes of alcoholism, since they provide the means of controlling family environment. The results for adoption studies are summarised in Table 9.3 and show the frequency of the disorder in adopted-away offspring of affected individuals as compared with that in control adoptees.

**Table 9.3** Adoption studies of alcoholism

Study	Sex	Adoptees			
		Experimental		Controls	
		<i>n</i>	% affected	<i>n</i>	% affected
Roe & Burks (1945)	M + F	27	70	27	64
Goodwin <i>et al</i> (1976)	M	55	18	70	5
Goodwin <i>et al</i> (1977)	F	49	4	48	4
Cadoret (1978)	M	6	33	78	1
Cadoret <i>et al</i> (1985)	M	127	62	28	24
	F	87	33	24	5
Bohman <i>et al</i> (1978)	M	131	36	577	13
	F	51 <sup>1</sup>	10		
	F	285 <sup>2</sup>	4		

1. Mother or both parents affected.

2. Only father affected.

The first study (Roe & Burks, 1945) found no evidence of a genetic contribution to alcoholism, but has been criticised in terms of both the small sample and the uncertain definition of the disorder. The next study, published three decades later by Goodwin *et al* (1976), was based on a national adoption register in Denmark, and its finding of an almost fourfold increase in the frequency of alcoholism in male adoptees whose biological father was alcoholic proved to be very influential in persuading sceptics about the role of genes. Nevertheless, it has been pointed out (Murray *et al*, 1983) that the apparent genetic effect in this study was crucially dependent on where the cut-off between 'problem drinking' and alcoholism was taken, since in both the experimental group and controls the frequency of problem drinking and alcoholism combined was the same. Furthermore, the same group of workers failed to find evidence of a genetic contribution to alcoholism in their study of female adoptees. Subsequent work in both the United States (Cadoret, 1978; Cadoret *et al*, 1985) and in Sweden (Bohman, 1978; Bohman *et al*, 1981) confirmed that male adoptees with an alcoholic biological parent were at increased risk of alcoholism and in addition suggested that the same was true of females. However, in the Swedish study alcoholism was increased only in the daughters of female alcoholics (Bohman, 1981).

Thus, as in the twin-study evidence, there is greater consistency in the data for men than for women, but overall and taken together with the findings from family and twin studies, the results suggest low to moderate genetic contributions to the liability to alcoholism in both sexes.

## Genes, environment and subtypes of alcoholism

One of the problems facing researchers in alcoholism is that it is frequently found in combination with other psychiatric disorders. Detailed discussion of this 'co-morbidity' problem is beyond the scope of this chapter, but its bearing on genetic studies has been reviewed cogently by Merikangas (1990). One of the most common overlaps in clinical practice is between depressive disorders and alcoholism. The overlap in families between alcoholism and depression, together with the excess of alcoholism in men and the higher rate of depression in women, has led Winokur *et al* (1975) to postulate the existence of 'depression spectrum disorder', in which alcoholism (or antisocial personality) may present as a sort of male equivalent of depression. However, data from the adoption study of Goodwin *et al* mentioned earlier argue for an environmental rather than genetic connection between depression and alcoholism. An increased risk of depression in the daughters of alcoholic fathers only occurred in those who were raised by their natural parents and not in those who were adopted away. Further genetic analyses by Reich *et al* (1975), applying the sorts of two-threshold models discussed in Chapter 2, suggest that depression and alcoholism are not merely different phenotypic manifestations

of the same genotype. This conclusion has subsequently been supported by a large-scale family study carried out by other workers (Merikangas *et al*, 1985).

Threshold analysis can also be applied to test whether different amounts of familial liability can account for the different rates of alcoholism for men and women. Under the simplest model, alcoholic women should occupy a more extreme position on the liability continuum, since they are less common than alcoholic men. Moreover, this predicts that studies of families of affected women should produce more cases than families of affected men, and as we have discussed earlier this does not happen (Reich & Cloninger, 1990). The rates of alcoholism in family members are similar whether one starts with a male or a female proband, and the data fit better with an isoproportional or 'environmental' model (Cloninger *et al*, 1981) (see also Chapter 2), where the difference between men and women can be best explained by non-familial environmental exposure to risk factors for alcoholism.

### **Subtypes of alcoholism**

The question of subtypes for alcoholism is an unresolved issue, but an influential and much discussed classification is that put forward by Cloninger *et al* (1981), based on an extension and reanalysis of the adoption data of Bohman. These data allowed a detailed cross-fostering analysis to be performed. That is, the investigators were able to compare biological offspring of alcoholics raised by normal parents and biological offspring of non-alcoholic parents raised by alcoholics. As a result of this and a sophisticated multivariate statistical treatment of the Swedish data, Cloninger *et al* proposed that the existence of type 1 or 'milieu-limited' abuse, which occurs in both men and women, is characterised by mild, adult-onset abuse and is influenced by both genetic and environmental factors. By contrast, type 2, or 'male limited', abuse is characterised by teenage onset in men. Here the history of alcohol abuse is usually severe and is associated with criminality in the biological fathers. Type 2 alcoholism is strongly influenced by genes and there is negligible influence from the postnatal environment.

Cloninger (1987) has postulated that these subtypes are associated with personality traits which in turn reflect inherited neuroadaptive mechanisms. He suggests that type 1 alcoholism is typically associated with low novelty seeking, high harm avoidance and high reward dependence. Type 2 alcoholics are in most ways opposite, showing high novelty seeking and both low harm avoidance and reward dependence. Although work elsewhere does not entirely support the hypothesis of these two positive forms of alcoholism (Schuckit & Irwin, 1989) there is much other data to suggest that a strong family history of alcoholism and a personal history of maladaptive behaviour in males is frequently associated with a type 2 profile (McGue *et al*, 1992).

# Biological basis of alcoholism

Despite methodological flaws and inconsistencies as well as freely acknowledged influences of social/cultural factors, the classical genetic studies suggest that alcoholism has a partly genetic and therefore biological basis. Broadly speaking, the ways in which this has been explored fall into three groups. These are studies of metabolic and central nervous system (CNS) response to alcohol, animal studies, and studies using molecular genetic methods. We will consider each in turn.

## **Metabolic and CNS response to alcohol**

In normal humans, genetic factors seem to exert an important influence on alcohol metabolism. Early studies of ethanol elimination rates showed moderate to high heritability, and more recently Martin *et al* (1985), in a study of normal volunteer Australian twins, estimated that the heritability for peak blood alcohol concentration after ingestion of a test dose was 62%, while the heritability of rate of elimination was 50%. This appeared to be fairly stable, in that the results on a subset of pairs who were retested suggested that only a minor proportion of the variation could be attributed to differences in drinking experience or habits. Inter-racial as well as inter-individual differences have also been described, and the molecular basis of some of these differences have been suggested by recent studies (see below).

An alternative form of investigation is to search for specific CNS responses to alcohol which may characterise alcoholics or potential alcoholics. For example, twin-study evidence suggests that the brain's response as reflected in electroencephalogram (EEG) patterns is genetically influenced (Propping, 1977, 1992). Alcoholics are said to show more alpha wave expression on the EEG, but this may be related to the effects rather than the causes of heavy drinking. However, it is of interest from the genetic viewpoint that MZ twins concordant for poor alpha wave expression are 'cured' of the EEG variant by the intake of alcohol (Propping, 1977). EEG event-related potentials (ERP) also show abnormalities in alcoholics. ERP consist of the EEG response to visual or other stimuli that have been averaged by computer. One such potential called the P300 is flattened in alcoholics, but has also been reported to show flattening in their adolescent sons (Begleiter *et al*, 1984) and has therefore been suggested as a marker of vulnerability to alcoholism.

Simpler measures of CNS response have also been investigated. For example one report suggested that ethanol-induced body sway is significantly less in a sample of healthy young men with an alcoholic first-degree relative than in a group of controls without such a family history (Schuckit *et al*, 1985).

## **Animal studies**

Selective breeding experiments on rats and mice have successfully produced strains which consistently prefer dilute alcohol to water as well as strains which differ in other ways, such as behavioural response to alcohol intake or withdrawal (reviewed by Crabb & Belknap, 1992). As well as suggesting a genetic contribution to alcohol preference and metabolism, breeding experiments suggest that individual differences among animals are best considered as quantitative traits (i.e. measured on a continuous scale rather than as a present/absent dichotomy) and that such traits are probably influenced by several genes, each of comparatively small effect. This can be inferred from breeding experiments where investigators can go on producing divergence between selected lines over many generations by continuing to select for high or low scores on a particular measure (Plomin, 1990). If strain differences were due to only one or even several genetic loci, then divergence should occur rapidly and not increase on selection continued over many subsequent generations. In current strategies DNA markers are employed to detect linkage in back-crosses (see Chapter 3) to detect quantitative trait loci (QTL) which may influence preference or alcohol metabolism (Crabb & Belknap, 1992). Another strategy, which is somewhat analogous to performing an association study in human beings, is to investigate the relationship between genetic markers and various traits in so-called recombinant inbred (RI) strains which result from repeated crossing of the offspring of two or more strains which differ with respect to a phenotype of interest (Plomin, 1990; Plomin & McClearn, 1993).

## **Molecular genetic studies in humans**

In humans, too, the advent of recombinant DNA technology has brought a shift of emphasis and a greater concentration on attempting to understand the genetics of alcoholism at a molecular level. Much attention has been directed to the alcohol metabolising enzymes alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) (reviewed by Hodgkinson *et al*, 1991). It is now known that there are three genes coding for class 1 ADH, all of which are located on the long arm of chromosome 4. Mitochondrial acetaldehyde dehydrogenase (ALDH 2), which is thought to account for most acetaldehyde oxidation, is coded for by a gene on chromosome 12. About half of all Orientals have a point mutation in the ALDH 2 gene. This results in an inactive variant of the enzyme which contributes to the characteristic 'Antabuse-like' reaction on ingestion of alcohol which occurs in many of this ethnic group. Interestingly, the inactive variant is found in only 5% of Japanese alcoholics, the rest of whom have the active type which is found in the greater majority of Caucasians (Hodgkinson *et al*, 1991).

Studies using 'random' genetic markers for linkage analysis in families multiply affected by alcoholism have also yielded positive results. For example, there has been suggestion of linkage with a classical genetic marker, the MNS blood group (Hill *et al*, 1988). Unfortunately this has not been replicated, and in the face of the evidence from family, twin and adoption studies, as well as hints from animal work, the likelihood of their being any major locus for alcoholism as opposed to several genes of small effect is low. Therefore the chances of linkage analysis succeeding must be fairly low. However, association studies, which, as we have discussed in Chapter 3, are capable of detecting genes of comparatively small effect, may hold more promise. Essentially the general assumption is that several (perhaps many) genes plus environment contribute to the liability to alcoholism, which is continuously distributed in the population, and only those individuals who at sometime exceed the threshold become affected (see Chapter 2). Thus association studies in humans are attempting to detect the QTL that contribute to liability to alcoholism.

Most recent interest has focused on a Taq-I polymorphism at the gene encoding the dopamine receptor D<sub>2</sub> (DRD2). Five different groups have reported a positive association between the less common (A1) allele and either alcoholism or alcoholism plus drug misuse (reviews by Stone & Gottesman, 1993; Uhl *et al*, 1992). However at least two other research teams were not able to replicate this finding. Given the mixed ethnic backgrounds of the inhabitants of the USA, where nearly all of the studies were conducted, it is possible that at least some of the positive results can be explained by population stratification (Chapter 3). That is, we need to be sure that this apparent association has not arisen as a result of a mixture of subpopulations coincidentally differing both in their frequency of alcoholism and of DRD2 alleles. Despite these caveats, the general strategy of looking for associations in 'candidate' genes is worth pursuing, providing we remember the possible pitfalls (see Chapter 3) and bear in mind the probability that molecular basis of susceptibility to alcoholism is likely to be heterogeneous (Devor, 1993).

## Conclusions

The findings in alcoholism and alcohol use are complex but there are strong hints of genetic components in both. The usefulness of 'classic' genetic methods, including twin and adoption studies, has not been exhausted in alcoholism, and such studies have hardly been applied at all in other forms of drug dependence, where much basic work is needed. Linkage studies where there is an attempt to search for genes of major effect in alcoholism are probably less promising than studies of 'candidate' genes which may influence patterns of normal drinking as well as the development of alcoholism. These are probably best studied at present

using association strategies. However, animal studies aiming to detect QTL are potentially promising and there is increasing evidence in breeding experiments of a genetic influence for preference or response to alcohol and other drugs of dependence. The usefulness of a search for QTL in animals and the relevance to human polygenic disorder is already apparent from studies of hypertension and diabetes in rodents. Genetic research into alcoholism is therefore likely to be one of the first areas where animal studies inform molecular genetic studies in humans.

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