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Review

# Alcohol and gene interactions[1)]

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## Abstract

Alcohol use produces both desirable and undesirable effects, ranging from short-term euphoria and reduction in cardiovascular risk, to violence, accidents, dependence and liver disease. Outcomes are affected by the amount of alcohol used (which is itself affected by genetic variation) and also by the drinker's genes. Genetic effects have been most clearly demonstrated for alcohol dependence, and several of the genes for which variation leads to increased dependence risk have been identified. These include genes for enzymes involved in alcohol metabolism (alcohol dehydrogenase and aldehyde dehydrogenase), and genes for receptors affected by alcohol (particularly γ-aminobutyric acid receptors). Many other gene/dependence associations have been reported but not fully substantiated. Genetic effects on phenotypes other than alcohol dependence are less well understood, and need to be clarified before a full picture of gene-alcohol interactions can be achieved.

**Keywords**: alcohol drinking; alcoholism; genetic linkage; genetic polymorphism; genetic variation.

## Introduction

Alcohol use produces a variety of social, behavioural, metabolic and pathological consequences, and alcohol abuse in various forms is a leading contributor to the global burden of disease (1). The immediate results of alcohol use per se include intoxication, accidents caused by impairment of driving ability, and both public and domestic violence. Loss of control over drinking, which is a key feature of the concept of dependence, is associated with neglect of other aspects of life and damage to employment prospects and personal relationships. Alcohol also produces short- and long-term metabolic changes and cellular damage in vulnerable organs, leading in a proportion of susceptible individuals to overt disease and death. Set against these negative consequences, there is evidence that low-level alcohol consumption is associated with a reduction in cardiovascular risk compared with abstinence from alcohol (2, 3), and there are reasons to believe that the relationship is causal.

Both harmful and beneficial effects (Figure 1) are the product of interactions between alcohol itself and some characteristics of the consumer. As we shall see, the characteristics that determine the interaction with alcohol are in many cases heritable and they reflect gene-sequence differences between people. However, alcohol use is so widespread in economically developed countries (except among groups who abstain for religious reasons) that one of the components of the interaction is almost universally present among adults. The interaction therefore appears as a polygenic genetic effect, particularly because the quantity of alcohol consumed – the dose, in pharmacological terms – is itself subject to genetic influence. The fundamental gene×alcohol effect can therefore be transformed into gene×gene effects, where the genes that determine the dose of alcohol interact with the genes that determine the response. Furthermore, there are many responses, and probably separate genes affecting each type of response.

All this is consistent with the pharmacogenetic paradigm, in which a drug produces both desirable responses and undesirable adverse effects. As might be expected, these occur at different doses and, frequently, in different people. A full picture will specify the genes that affect dose (or in this case self-dosing), those that affect the pharmacokinetics of the drug, those that determine the degree of beneficial response, and those that determine susceptibility to adverse responses or side-effects. It is therefore necessary to recognise multiple phenotypes, to determine which show heritable variation, to identify the genes and polymorphisms responsible and to measure their effects. As an additional complication, the inheritance of alcohol-related problems does not follow a Mendelian dominant or recessive pattern, but results from the additive or interactive effects of multiple genes. Identifying the mostly small contributions of multiple genetic polymorphisms is a challenging task, but considerable progress has been made with the most prominent adverse effect, alcohol dependence. Because less is known about genetic influences on other aspects of alcohol and alcoholism, we consider dependence in more detail and then give some information relating to the other phenotypes. Because of space limitations, animal studies are not considered.

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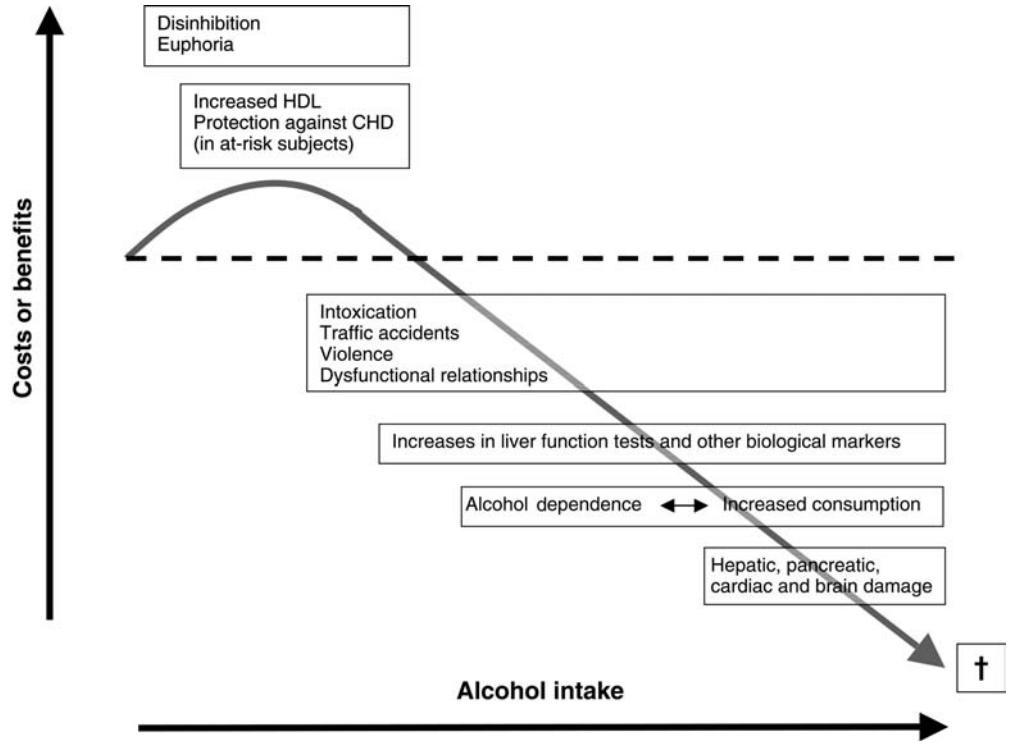


**Figure 1** Schematic relationship between alcohol intake and the positive and negative effects of alcohol. The x-axis represents increasing alcohol use, averaged over time; this is known to be affected by genetic variation between people. The y-axis represents the various costs and benefits of alcohol use; in most cases the degree of cost or benefit associated with any level of intake will vary between people, and in some cases this variation has been shown to have a genetic basis.

## Alcohol dependence

This diagnostic classification is based on behavioural and, to a lesser extent, physiological criteria (4). By these widely accepted criteria, alcohol dependence is a common condition, affecting almost 5% of US adults within the previous 12 months (5). It is not based on the amount of alcohol consumed, although dependence produces at least intermittent extremely high consumption, and high consumption increases the risk of dependence (6, 7). Most of the medical consequences of alcohol depend more directly on quantity of alcohol used than on dependence itself, but the harmful long-term consequences occur almost entirely among dependent patients because they have the highest exposure. This is why the majority of genetic studies have focused on alcohol dependence.

Firstly, we need evidence of a genetic component to susceptibility. Once it is established that genetic variation in risk of dependence exists, we need to identify the relevant genes and the sequence variations that produce the effect. There are two main approaches to this, which are in many ways complementary. Firstly, we can search the genome using linkage methods to find loci that affect alcohol dependence. Linkage analysis may be applied to selected loci, but its major strength has been the ''hypothesis-free'' application to the entire genome. The weakness, particularly for polygenic conditions in which any single locus probably makes only a minor contribution to susceptibility, is a lack of power. Many hundreds of sib-pairs are required for a study with reasonable power to detect such effects. Alternatively or additionally, we can test for association between a polymorphism and risk by directly comparing the prevalence of alcohol dependence between people of different genotypes. This has usually been done by selecting polymorphisms from ''candidate genes'' for testing.

Finally, if the results of studies are to be applied for prediction and counselling, we need to have estimates of the risk associated with each genotype and for each of the genes or polymorphisms that have shown significant effects. This is a substantial task, because precise estimates require a large amount of data and the estimates should be checked for applicability to men and women, old and young people, and across ethnic or racial groupings.

## Genetic predisposition to alcohol dependence

Familial transmission of liability to alcohol dependence has been shown in many studies, initially mainly based on clinical samples (8). Useful information about a community-based sample comes from analysis of survey data on alcohol use and alcohol dependence symptoms in the US (9). A positive family history (reported alcoholism or problem drinking among first- or second-degree relatives) was associated with increased alcohol use and more dependence symptoms among respondents. This study design does not distinguish between genetic and family-environment effects on the development of

**Table 1** Chromosomal loci reported to be associated with alcohol dependence or related endophenotypes by the COGA group.

| Phenotype | Chromosomes | Reference |
|---|---|---|
| Alcohol dependence | 1, 2, 4, 7 | (13) |
| Alcoholism severity | 16 | (17) |
| Maximum number of drinks | 4 | (18) |
| Alcoholism/depression | 1, 2, 6, 16 | (20) |
| Response to alcohol | 1, 2, 9, 21 | (21) |
| P3 evoked potential | 4, 5 | (22) |
| Platelet MAO | 2, 9, 12 | (19) |
| Factor score from data on alcohol use and alcohol-related symptoms | 1, 15 | (23) |
| Alcoholism/smoking | 2 | (24) |

Only the latest or largest study for each phenotype is cited when multiple papers with overlapping subject participation have appeared.

dependence, but other types of study point to a genetic effect.

A number of adoption studies have been conducted in which information about alcoholism or alcohol-related problems has been collected for the biological parents of adoptees. Since the children were raised in an environment free from the effects of their parents' behaviour, any increased risk to the children of alcoholics can be interpreted as evidence for genetic transmission. Of five studies of this kind, four found a significant increase in risk in adopted-away children of alcoholics compared with that for children of unaffected birth parents, and synthesis of the data from all five studies suggests a doubling of risk associated with having an affected parent, at least for men.

Twin studies, in which the concordance of monozygotic and dizygotic twin pairs is compared, also support the hypothesis of genetic transmission of liability to alcohol dependence. Results of adoption and twin studies up to 1995 were reviewed by Heath and colleagues (10, 11). Since then, results of a large study on Australian twins have appeared (12) and it is of interest to note that the risk associated with having a dizygotic twin sibling with alcohol dependence was approximately two-fold, similar to that associated with an affected parent. The risk associated with having an affected monozygotic co-twin affected was higher, approximately four-fold, and it was estimated that almost two-thirds of the variation in liability to alcohol dependence is due to genetic variation. This was true for both men and women.

## Linkage studies of alcohol dependence

Linkage-based approaches to identification of genes causing disease require the recruitment and study of pairs of relatives or of extended families, rather than individual subjects, and this requires substantial investment. So far, information has been published on three types of subjects. These are alcoholism-dense families recruited from clinical sources by the Consortium on Genetics of Alcoholism (COGA) (13); families from Native American groups with a high prevalence of alcohol dependence (14, 15); and participants in the Framingham Heart Study (16). The fullest information has come from the COGA group, who made use of a number of quantitative traits associated with alcohol dependence, as well as the simple division of participants into affected/non-affected groups. These linkage studies are summarised in Table 1. In principle, measurement of quantitative variables known or suspected to be genetically associated with alcohol dependence (endophenotypes) improves the power to detect linkage and allows the definition of loci that affect particular aspects of the alcoholic phenotype. The endophenotypes used as supplements to the diagnostic category of alcohol dependence include dependence severity (17), the maximum number of drinks in a single day (18), electroencephalographic evoked potentials, alcohol tolerance (discussed below) and platelet monoamine oxidase (19). However, identification of a chromosomal region showing linkage to one of these endophenotypes does not immediately provide a new candidate gene for more detailed testing. Most of the papers cited in Table 1 did not suggest candidates; two that did could only point to multiple genes of unknown relevance, and two others led to the known candidate alcohol dehydrogenase (ADH) on chromosome 4.

## Association studies of alcohol dependence

The alternative approach of allelic association studies has much greater statistical power, but it has so far required selection of candidate genes or regions. These candidates may be chosen on the basis of relevant physiological or pathological roles for gene products, or because linkage analysis has shown that more detailed investigation of some chromosomal region is justified. Associations may be sought between phenotypes and functional polymorphisms, which alter the amino acid sequence of a protein or are expected to affect gene expression; or with genetic markers (usually single nucleotide polymorphisms, SNPs); or with haplotypes comprising several SNPs in linkage disequilibrium. In the near future, SNP association studies covering the entire genome are likely to become economic and will supplement current linkage and association methods.

Despite a large number of association studies on alcohol dependence, only a few genes have shown

repeatable positive results. The first was the mitochondrial form of aldehyde dehydrogenase (ALDH) responsible for the conversion of ethanol-derived acetaldehyde to acetate. Among the polymorphisms associated with alcohol dependence, that of *ALDH2* comes closest to the classical type of inborn error of metabolism, with *ALDH2**2 resulting in an inactive enzyme and accumulation of the compound that it usually metabolises, acetaldehyde (25). The increased tissue and circulating acetaldehyde produces effects such as skin flushing, headache and nausea, which make alcohol consumption unpleasant and reduce the probability of alcohol dependence. This enzyme deficiency is confined to people of Chinese, Japanese or Korean descent, and there is some evidence that its impact has decreased as people in Japan, at least, come under greater social pressure to drink alcohol (26). Discovery of the genetic basis and the mechanism of the alcohol flush reaction, coupled with its effect on alcohol dependence risk, gave a considerable boost to the view that biological factors are important in substance use disorders.

Polymorphisms in ADH also affect alcohol dependence risk. There are many ADHs, of which at least the Class 1 enzymes encoded by *ADH1A*, *ADH1B* and *ADH1C* convert ethanol to acetaldehyde at concentrations found in vivo after alcohol consumption. Variants of *ADH1B* (*ADH1B**1, *ADH1B**2 and *ADH1B**3), which differ in their sequence and kinetic properties, have been recognised for many years and there is strong evidence, initially from Asian populations in which the *ADH1B**2 allele is common and now from European populations also (27, 28), that people who are homozygous for *ADH1B**1 are more likely to be alcohol-dependent than heterozygotes, or homozygotes for the *ADH1B**2 allele. The mechanism of this effect is surprisingly uncertain; the usual explanation is that the ADH1B*2 enzyme, which has a higher in vitro $V_{max}$ than ADH1B*1, results in faster conversion of ethanol to acetaldehyde and therefore higher steady-state acetaldehyde concentrations after alcohol consumption. This would produce an aversion to alcohol use in a similar manner to ALDH2 deficiency, but probably to a lesser degree. However there is little evidence that *ADH1B**2 is associated with faster ethanol metabolism in vivo, and none that acetaldehyde concentrations are increased. Nor has it been shown that people with one or two *ADH1B**2 alleles find alcohol consumption unpleasant.

Meta-analysis of studies on ADH1B variation and alcohol dependence risk, with the aim of determining the relative risk for people of different genotypes, has shown two unexpected features (29). As mentioned above, initial studies were done on Asian populations. Data have now accumulated on many European subjects also, but the estimates of relative risk for the *ADH1B**11 and *ADH1B**12 genotypes show significant heterogeneity between populations. The data are summarised in Figure 2, which shows the cumulative estimates of odds ratios for European, Japanese and Han Chinese populations. For reasons that are not yet clear, *ADH1B**2 has more effect on dependence risk in Asians than in Europeans. The explanation may lie in gene-environment interactions, if social habits in European societies reduce the influence of this genotype. Alternatively, there may be another polymorphism very close to *ADH1B**2 in Asians, but not in Europeans, which affects alcohol use and dependence. Detailed analysis of SNPs and haplotypes in the *ADH* region of chromosome 4 should throw light on this question.

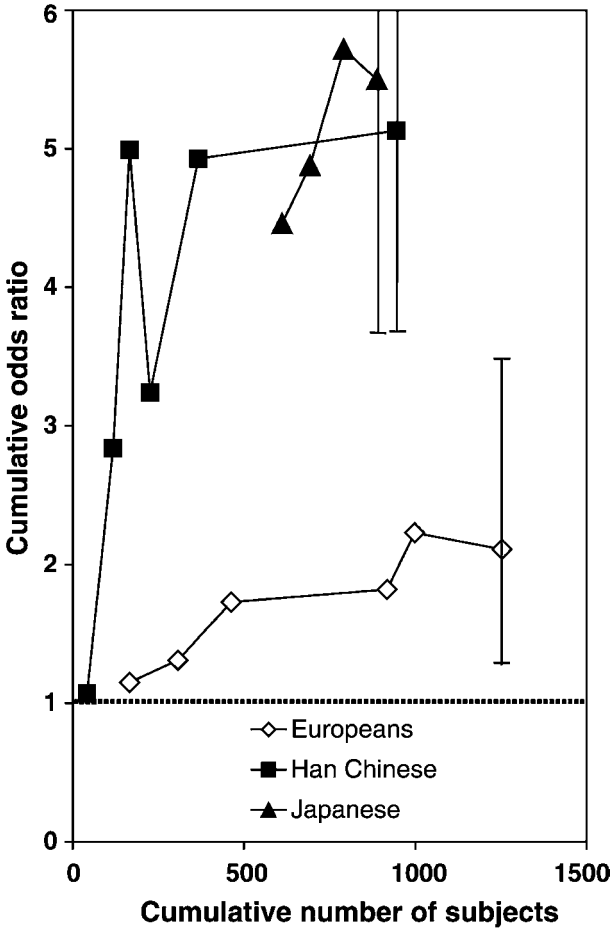


**Figure 2** Odds ratios for alcohol dependence in people with *ADH1B**11 compared to *ADH1B**12 genotype, by geographic or ethnic group. The x-axis shows the cumulative number of patients and controls included in published studies, while the y-axis shows the estimated odds ratios. Error bars show the 95% confidence intervals for each group. Data from reference (29).

The second finding from this meta-analysis was that the effects of *ADH1B**2 alleles are not simply additive, but neither do they follow a simple Mendelian pattern of recessive or dominant. Among the Chinese and Japanese subjects who had a sufficiently high *ADH1B**2 allele frequency to allow inferences about homozygotes, the relative risk for people with the *ADH1B**11 genotype was five-fold greater than for those with the *ADH1B**12 genotype, but the risk associated with *ADH1B**12 was only 1.5-fold that for *ADH1B**22.

There are of course other variants of *ADH* genes. Evidence on the effects of *ADH1B**3 (found originally in people of African descent, but also present among Native Americans) is sparse, but there are indications that it may confer protection against alcohol depend-

ence by metabolic mechanisms similar to those proposed for *ADH1B**2 (30–33). The *ADH1C* polymorphism, which is common in Europeans, does not seem to exert any independent influence on dependence risk. Nevertheless, linkage analysis has shown in at least three studies (14, 15, 18) that the *ADH* region of chromosome 4 affects dependence risk and it is difficult to see how the comparatively uncommon *ADH1B**2 allele could account for this effect in Europeans or Native Americans. Other *ADH* genes, particularly *ADH4* and *ADH7*, may have variants that are significant.

Moving away from genes affecting ethanol metabolism, many association studies have examined genes relevant to neurotransmitters, their metabolism and receptors. There have been reports on genes related to serotonin, dopamine and endorphins, with a mix of positive, negative or contradictory results. Studies on γ-amino butyric acid (GABA) receptors have been more productive.

GABA receptors are good candidates for association studies on alcohol-related phenotypes, both because of biological plausibility and because linkage studies have shown suggestive results near GABA gene clusters. Recent studies have produced two positive results for *GABRA2* on chromosome 4 (34, 35); one positive and one negative result for *GABRA6* on chromosome 5 (36, 37); and one positive result for *GABRG3* on chromosome 15 (38). Each of these studies has been based on typing multiple SNPs over a substantial region and testing for association between an alcohol dependence-related phenotype and individual SNP genotypes or haplotypes. This has identified the relevant gene within each GABA receptor cluster, but the haplotypes each extend over a large region and the causative polymorphisms have not been characterised.

## Other alcohol-related phenotypes

### Alcohol consumption

The level and pattern of alcohol consumption is important in itself, because of the physical and social consequences of intoxication, and also because of the interaction between high intake and a high risk of dependence. High alcohol intake is associated with a number of metabolic changes, discussed below, and abstinence or very low intake is associated with higher rates of cardiovascular disease.

There is a positive relationship between usual alcohol intake, as reported in surveys or questionnaires, and the probability of having experienced alcohol dependence. This has been shown in population samples from the United States (6, 39), and more recently in the Australian twin studies. The nature of this association was examined (7) and found to be almost entirely due to genetic, rather than environmental, influences common to both intake and dependence. However, the two phenotypes of heavy drinking and alcohol dependence did not show a complete overlap of the genetic influences, and it was possible to conclude that some genes affect both intake and liability to dependence, while others affect only the liability to dependence. Linkage and association studies should be able to identify which genes affect each of these phenotypes.

As mentioned above, most linkage studies have concentrated on alcohol dependence or on endophenotypes closely associated with dependence. Linkage data on habitual alcohol consumption have been published for participants in the Framingham Heart Study (40). The phenotype analysed was heavy alcohol consumption, but the unaffected group was abstainers. People who drank, but did not meet the criteria for heavy drinking, were excluded. However, a number of suggestive linkage results were found; these were in some cases close to linkage peaks reported by others for dependence, and in other cases were close to candidate genes. In particular, weakly positive results were reported near the *ALDH2* and *ADH* loci. Further linkage analyses for quantitative measures of usual alcohol intake are needed, and may be feasible using studies in which the primary focus was on other phenotypes.

Published studies on associations between gene polymorphisms and habitual alcohol intake are mainly about alcohol-metabolising enzymes. Among Chinese people, *ALDH2* variation affected both alcohol use and alcohol dependence, but although *ADH1B* variation affected the risk of alcohol dependence, it was not shown to affect drinking patterns in non-alcoholic subjects (41). One study of Japanese people (42) gave very similar results, but another (43) found that *ADH1B* genotype did affect the level of intake. Results from Australia (44) showed that *ADH1B* variation affected alcohol intake as well as dependence, but only in men.

At present, little is known about the genes that affect alcohol use (rather than alcohol dependence), but this is a topic worth further study because variation in alcohol use among people who are not alcohol-dependent can affect both the potentially beneficial and potentially harmful metabolic effects of drinking.

### Co-morbidity

There is a large body of clinical and survey-based evidence that alcohol dependence is associated with increased probability of other substance dependence (including nicotine dependence), depression, and antisocial personality or conduct disorder. This is true not only for the affected individual, but also for their relatives (45), consistent with possible genetic variants that increase the risk of two or more of these conditions. This type of evidence has led to several linkage and association studies on putative subtypes of alcoholism defined by comorbidity. Given the polygenic nature of alcoholism and of the comorbid conditions, it is unlikely that there will be clear separation between one subtype of alcoholism with associated comorbidities and another without, but there are prospects of identifying gene variants with multiple effects.

Some of the COGA linkage studies listed in Table 1 have addressed this question in relation to alcoholism

and depression, and alcoholism and smoking. Interpretation of the results is complex, but the authors suggested that a locus on chromosome 1 might predispose some people to alcoholism and others to depression, and there was suggestive evidence that a locus on chromosome 4 affects liability to comorbid alcoholism with depression.

The COGA group have also reported a joint association analysis of the two phenotypes of alcohol dependence and depression (46). SNPs and haplotypes in the muscarinic acetylcholine receptor M2 (*CHRM2*) gene showed associations with each phenotype and also with the presence of both. However, there were interesting differences, because one haplotype was associated with protection against both alcohol dependence and depression, another was associated with increased risk of alcohol dependence, and a third with increased risk of depression. Although no causative polymorphisms have been identified, it seems that different variants within the one gene can lead to different, although associated, conditions.

### Intoxication

Resistance to intoxication is believed to be a risk factor for alcohol dependence. A low level of subjective and objective responses to a test dose of alcohol has been reported as more common in sons of alcoholics than controls, and to be predictive of alcohol dependence. The reasoning is that people who are resistant to alcohol's effects will tend to drink more, and have a higher risk of becoming dependent. Consequently, at least two linkage studies on this broad phenotype have been performed (21, 47), although the assessment was based on self-report in one case and measurements taken after alcohol challenge in the other. These yielded ten and nine loci, respectively, with LOD scores greater than 2.0, despite a comparatively small number of subjects in the second study.

Several association studies based on laboratory studies of susceptibility to intoxication have appeared. A small study based on the original San Diego cohort implicated variation in the serotonin transporter gene and the GABA $\alpha$6 receptor (48), and significant effects of the serotonin transporter gene polymorphism have been confirmed in a recent extension of this study (49). An effect of a variant in the serotonin transporter gene on intoxication was also found in monkeys (50). Another small study of the $\mu$-opioid receptor gene (51) found an effect of a polymorphism that alters receptor affinity for $\beta$-endorphin on subjective measures of response to alcohol. However, in this case the genotype associated with greater response to alcohol was also associated with a positive family history for alcoholism, which is contrary to the original hypothesis. Clearly, there are still issues to be resolved in this area.

### Metabolic effects

High alcohol intake produces multiple biochemical consequences, including increases in liver function tests ($\gamma$-glutamyl transferase, alanine aminotransferase), lipids (triglyceride), urate, asialo- and disialotransferrin isoforms, measures of iron status (ferritin), and blood lead. There is also indirect or experimental animal evidence for increases in cellular metabolites that are harder to measure in humans, such as acetaldehyde adducts and lipid oxidation products. Many of these changes are associated either with alcohol-related liver disease or with cardiovascular or diabetes risk, but it is notable that these metabolic consequences of alcohol use do not occur in all at-risk subjects. Little is known at present about the factors that enhance or suppress them, but this is an area for collaboration between clinical chemistry and genetic epidemiology in the future.

Alcohol use also brings about increases in high-density lipoprotein (HDL)-cholesterol and apolipoproteins A1 and A2, which may account for much of the cardiovascular protective effect of drinking. Again, it is possible that the response of HDL-cholesterol to alcohol use varies between people and it has been reported that this response depends on *ADH* genotype (52). The results suggested that *ADH1C* genotype affects HDL-cholesterol responses to alcohol use and cardiovascular mortality through an effect on alcohol metabolism. However, another study that classified drinkers by *ADH1B* type (53) reported no significant difference in HDL-cholesterol by genotype, and the in vitro properties of *ADH1B* enzymes suggest that any effect should be greater than for *ADH1C*. A later study (54) of the effects of both *ADH1B* and *ADH1C* variation on HDL-cholesterol and apolipoproteins A1 and A2 found no evidence of differences in the response to alcohol intake by genotype. Therefore, the interesting initial report has not been replicated by further work, although no other study has yet been able to assess *ADH*$\times$alcohol interaction effects on cardiovascular morbidity or mortality.

## Conclusions

The search for a gene or genes ''for alcoholism'' has widened into a series of investigations of genetic effects on aspects of alcohol-related disease. This reflects the probable diversity of the phenotype and its causes, adds power to statistical analysis, and should ultimately give a more detailed picture of interactions between the contributing factors. There has been substantial progress in relation to alcohol dependence, with several genes known to be important, but there remains a need to establish their mechanisms of action and to define relative risk by genotype across sex, age and ethnic groups.

Genetic effects on alcohol-induced organ damage remain to be defined. There is difficulty in conducting linkage studies on clinical endpoints such as cirrhosis or hepatoma because of the need to collect affected relatives. Study of alcohol-related disease may need endophenotypes, a candidate gene approach, or a genome-wide association design.

The implications of these genetic findings for prevention and clinical practice are not yet clear. We are close to being able to assess alcohol dependence risk

from haplotypes made up of SNP markers, but this is not likely to be clinically useful in patients who have developed dependence. Nor is there any evidence, so far, that prediction and prevention are effective in people who are at high genetic risk. Evidence of the value of prediction or early diagnosis, and the availability of effective treatment, are (as usual) necessary before testing can move from a research activity to the clinical laboratory.

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## References

1. Rehm J, Room R, Monteiro M, Gmel G, Graham K, Rehn N, et al. Alcohol as a risk factor for global burden of disease. Eur Addict Res 2003;9:157–64.
2. Thun MJ, Peto R, Lopez AD, Monaco JH, Henley SJ, Heath CW Jr, et al. Alcohol consumption and mortality among middle-aged and elderly US adults. N Engl J Med 1997;337:1705–14.
3. White IR. The level of alcohol consumption at which all-cause mortality is least. J Clin Epidemiol 1999;52:967–75.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994.
5. Grant BF. Prevalence and correlates of alcohol use and DSM-IV alcohol dependence in the United States: results of the National Longitudinal Alcohol Epidemiologic Survey. J Stud Alcohol 1997;58:464–73.
6. Dawson DA. Consumption indicators of alcohol dependence. Addiction 1994;89:345–50.
7. Whitfield JB, Zhu G, Madden PA, Neale MC, Heath AC, Martin NG. The genetics of alcohol intake and of alcohol dependence. Alcohol Clin Exp Res 2004;28:1153–60.
8. Cotton NS. The familial incidence of alcoholism: a review. J Stud Alcohol 1979;40:89–116.
9. Harford TC, Parker DA, Grant BF. Family history, alcohol use and dependence symptoms among young adults in the United States. Alcohol Clin Exp Res 1992;16:1042–6.
10. Heath AC. Genetic influences on alcoholism risk. Alcohol Health Res World 1995;19:166–71.
11. Heath AC, Slutske WS, Madden PA. Gender differences in the genetic contribution to alcoholism risk and to alcohol consumption patterns. In: Wilnack RW, Wilsnack SC, editors. Gender and alcohol. Rutgers, NJ: Rutgers University Press, 1997:114–49.
12. Heath AC, Bucholz KK, Madden PA, Dinwiddie SH, Slutske WS, Bierut LJ, et al. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. Psychol Med 1997;27:1381–96.
13. Reich T, Edenberg HJ, Goate A, Williams JT, Rice JP, Van Eerdewegh P, et al. Genome-wide search for genes affecting the risk for alcohol dependence. Am J Med Genet 1998;81:207–15.
14. Long JC, Knowler WC, Hanson RL, Robin RW, Urbanek M, Moore E, et al. Evidence for genetic linkage to alcohol dependence on chromosomes 4 and 11 from an autosome-wide scan in an American Indian population. Am J Med Genet 1998;81:216–21.
15. Ehlers CL, Gilder DA, Wall TL, Phillips E, Feiler H, Wilhelmsen KC. Genomic screen for loci associated with alcohol dependence in Mission Indians. Am J Med Genet 2004;129B:110–15.
16. Bergen AW, Yang XR, Bai Y, Beerman MB, Goldstein AM, Goldin LR. Genomic regions linked to alcohol consumption in the Framingham Heart Study. BMC Genet 2003;4(Suppl 1):S101.
17. Foroud T, Bucholz KK, Edenberg HJ, Goate A, Neuman RJ, Porjesz B, et al. Linkage of an alcoholism-related severity phenotype to chromosome 16. Alcohol Clin Exp Res 1998;22:2035–42.
18. Saccone NL, Kwon JM, Corbett J, Goate A, Rochberg N, Edenberg HJ, et al. A genome screen of maximum number of drinks as an alcoholism phenotype. Am J Med Genet 2000;96:632–7.
19. Saccone NL, Rice JP, Rochberg N, Williams JT, Goate A, Reich T, et al. Linkage for platelet monoamine oxidase (MAO) activity: results from a replication sample. Alcohol Clin Exp Res 2002;26:603–9.
20. Nurnberger JI Jr, Foroud T, Flury L, Su J, Meyer ET, Hu K, et al. Evidence for a locus on chromosome 1 that influences vulnerability to alcoholism and affective disorder. Am J Psychiatry 2001;158:718–24.
21. Schuckit MA, Edenberg HJ, Kalmijn J, Flury L, Smith TL, Reich T, et al. A genome-wide search for genes that relate to a low level of response to alcohol. Alcohol Clin Exp Res 2001;25:323–9.
22. Almasy L, Porjesz B, Blangero J, Goate A, Edenberg HJ, Chorlian DB, et al. Genetics of event-related brain potentials in response to a semantic priming paradigm in families with a history of alcoholism. Am J Hum Genet 2001;68:128–35.
23. Dick DM, Nurnberger J, Jr., Edenberg HJ, Goate A, Crowe R, Rice J, et al. Suggestive linkage on chromosome 1 for a quantitative alcohol-related phenotype. Alcohol Clin Exp Res 2002;26:1453–60.
24. Bierut LJ, Rice JP, Goate A, Hinrichs AL, Saccone NL, Foroud T, et al. A genomic scan for habitual smoking in families of alcoholics: common and specific genetic factors in substance dependence. Am J Med Genet A 2004;124:19–27.
25. Crabb DW, Edenberg HJ, Bosron WF, Li TK. Genotypes for aldehyde dehydrogenase deficiency and alcohol sensitivity. The inactive ALDH2(2) allele is dominant. J Clin Invest 1989;83:314–6.
26. Higuchi S, Matsushita S, Imazeki H, Kinoshita T, Takagi S, Kono H. Aldehyde dehydrogenase genotypes in Japanese alcoholics. Lancet 1994;343:741–2.
27. Whitfield JB, Nightingale BN, Bucholz KK, Madden PA, Heath AC, Martin NG. ADH genotypes and alcohol use and dependence in Europeans. Alcohol Clin Exp Res 1998;22:1463–9.
28. Borras E, Coutelle C, Rosell A, Fernandez-Muixi F, Broch M, Crosas B, et al. Genetic polymorphism of alcohol dehydrogenase in Europeans: the ADH2*2 allele decreases the risk for alcoholism and is associated with ADH3*1. Hepatology 2000;31:984–9.
29. Whitfield JB. Alcohol dehydrogenase and alcohol dependence: variation in genotype-associated risk between populations. Am J Hum Genet 2002;71: 1247–50.
30. Thomasson HR, Beard JD, Li TK. ADH2 gene polymorphisms are determinants of alcohol pharmacokinetics. Alcohol Clin Exp Res 1995;19:1494–9.
31. Wall TL, Carr LG, Ehlers CL. Protective association of genetic variation in alcohol dehydrogenase with alcohol dependence in Native American Mission Indians. Am J Psychiatry 2003;160:41–6.

32. Ehlers CL, Gilder DA, Harris L, Carr L. Association of the ADH2*3 allele with a negative family history of alcoholism in African American young adults. Alcohol Clin Exp Res 2001;25:1773–7.
33. Ehlers CL, Carr L, Betancourt M, Montane-Jaime K. Association of the ADH2*3 allele with greater alcohol expectancies in African-American young adults. J Stud Alcohol 2003;64:176–81.
34. Edenberg HJ, Dick DM, Xuei X, Tian H, Almasy L, Bauer LO, et al. Variations in GABRA2, encoding the alpha 2 subunit of the GABAA receptor, are associated with alcohol dependence and with brain oscillations. Am J Hum Genet 2004;74:705–14.
35. Covault J, Gelernter J, Hesselbrock V, Nellissery M, Kranzler HR. Allelic and haplotypic association of GABRA2 with alcohol dependence. Am J Med Genet 2004;129B:104–9.
36. Radel M, Vallejo RL, Iwata N, Aragon R, Long JC, Virkkunen M, et al. Haplotype-based localization of an alcohol dependence gene to the 5q34 γ-aminobutyric acid type A gene cluster. Arch Gen Psychiatry 2005;62:47–55.
37. Dick DM, Edenberg HJ, Xuei X, Goate A, Hesselbrock V, Schuckit M, et al. No association of the GABA(A) receptor genes on chromosome 5 with alcoholism in the collaborative study on the genetics of alcoholism sample. Am J Med Genet B Neuropsychiatr Genet 2004; 132B:24–8.
38. Dick DM, Edenberg HJ, Xuei X, Goate A, Kuperman S, Schuckit M, et al. Association of GABRG3 with alcohol dependence. Alcohol Clin Exp Res 2004;28:4–9.
39. Grant BF. The relationship between ethanol intake and DSM-III-R alcohol dependence: results of a national survey. J Subst Abuse 1993;5:257–67.
40. Wyszynski DF, Panhuysen CI, Ma Q, Yip AG, Wilcox M, Erlich P, et al. Genome-wide screen for heavy alcohol consumption. BMC Genet 2003;4(Suppl 1):S106.
41. Muramatsu T, Wang ZC, Fang YR, Hu KB, Yan H, Yamada K, et al. Alcohol and aldehyde dehydrogenase genotypes and drinking behavior of Chinese living in Shanghai. Hum Genet 1995;96:151–4.
42. Higuchi S, Matsushita S, Muramatsu T, Murayama M, Hayashida M. Alcohol and aldehyde dehydrogenase genotypes and drinking behavior in Japanese. Alcohol Clin Exp Res 1996;20:493–7.
43. Tanaka F, Shiratori Y, Yokosuka O, Imazeki F, Tsukada Y, Omata M. Polymorphism of alcohol-metabolizing genes affects drinking behavior and alcoholic liver disease in Japanese men. Alcohol Clin Exp Res 1997;21:596–601.
44. Whitfield JB, Nightingale BN, Bucholz KK, Madden PA, Heath AC, Martin NG. ADH genotypes and alcohol use and dependence in Europeans. Alcohol Clin Exp Res 1998;22:1463–9.
45. Nurnberger JI Jr, Wiegand R, Bucholz K, O'Connor S, Meyer ET, Reich T, et al. A family study of alcohol dependence: coaggregation of multiple disorders in relatives of alcohol-dependent probands. Arch Gen Psychiatry 2004;61:1246–56.
46. Wang JC, Hinrichs AL, Stock H, Budde J, Allen R, Bertelsen S, et al. Evidence of common and specific genetic effects: association of the muscarinic acetylcholine receptor M2 (CHRM2) gene with alcohol dependence and major depressive syndrome. Hum Mol Genet 2004;13:1903–11.
47. Wilhelmsen KC, Schuckit M, Smith TL, Lee JV, Segall SK, Feiler HS, et al. The search for genes related to a low-level response to alcohol determined by alcohol challenges. Alcohol Clin Exp Res 2003;27:1041–7.
48. Schuckit MA, Mazzanti C, Smith TL, Ahmed U, Radel M, Iwata N, et al. Selective genotyping for the role of 5-HT2A, 5-HT2C, and GABA alpha 6 receptors and the serotonin transporter in the level of response to alcohol: a pilot study. Biol Psychiatry 1999;45:647–51.
49. Hu X, Oroszi G, Chun J, Smith TL, Goldman D, Schuckit MA. An expanded evaluation of the relationship of four alleles to the level of response to alcohol and the alcoholism risk. Alcohol Clin Exp Res 2005;29:8–16.
50. Barr CS, Newman TK, Becker ML, Champoux M, Lesch KP, Suomi SJ, et al. Serotonin transporter gene variation is associated with alcohol sensitivity in rhesus macaques exposed to early-life stress. Alcohol Clin Exp Res 2003;27:812–7.
51. Ray LA, Hutchison KE. A polymorphism of the mu-opioid receptor gene (OPRM1) and sensitivity to the effects of alcohol in humans. Alcohol Clin Exp Res 2004;28: 1789–95.
52. Hines LM, Stampfer MJ, Ma J, Gaziano JM, Ridker PM, Hankinson SE, et al. Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. N Engl J Med 2001;344:549–55.
53. Hashimoto Y, Nakayama T, Futamura A, Omura M, Nakarai H, Nakahara K. Relationship between genetic polymorphisms of alcohol-metabolizing enzymes and changes in risk factors for coronary heart disease associated with alcohol consumption. Clin Chem 2002; 48:1043–8.
54. Whitfield JB, O'Brien ME, Nightingale BN, Zhu G, Heath AC, Martin NG. ADH genotype does not modify the effects of alcohol on high-density lipoprotein. Alcohol Clin Exp Res 2003;27:509–14.

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