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Committed to improving medical understanding of alcohol-related problems

FROM THE EDITOR



Dr GE Ratcliffe

Liver Disease in England

A recent review of liver disease epidemiology by Professor Eileen Kaner and her colleagues in Newcastle confirms a significant increase in all liver disease in England, particularly in alcoholic liver disease.¹ Perhaps more disturbingly the review does not identify a central database of clinical activity on liver disease, and describes data codes that do not clearly distinguish between all the different types and causes of liver disease. I do not believe that, as a specialty, hepatology is alone in these deficiencies. Without accurate statistics, however, it is not possible to properly plan definitive clinical services to care for this liver disease epidemic. Recommendations to correct these deficiencies are included in this very thorough and wide-ranging report.

A few random jottings

A clue in a recent *Daily Telegraph* cryptic crossword read 'The alcohol of life'. The answer, of course, was 'aqua vitae' (4,5). It is curious how the literal translation, 'water of life', developed into a guise of well-known alcoholic beverages dependent on their country of origin. I daresay that a company attempting to market a new alcoholic beverage of that name today would meet resistance from some quarters. However, as such beverages already exist it has to be accepted as one of those odd quirks of life.

I read somewhere that Noah is considered

to be the first reported alcoholic. The story is related in Genesis 9 that the Good Lord instructed Noah to replenish the earth. Noah started to farm and planted a vineyard, on the fruits of which he became drunk. His sons found him stuporose and naked and it was the latter which concerned them more, sufficient for them to cover his nakedness. Noah recovered: but to label him as alcohol dependent after one binge is an exaggeration. To be noted the first recorded case of alcohol intoxication possibly, but no more. Interestingly an associated story concerns Noah's relationship with Satan. The latter conveyed the qualities of wine to Noah:

*A man drinks one glass and he is
as meek as a lamb*

*Two glasses and he is boastful and feels
as strong as a lion*

Three or four he behaves like a monkey

*If he becomes intoxicated, he resembles the pig.
(Midrash Tanhuma 58)*

Not much has changed over the succeeding millennia.

This issue

Identification of genes possibly associated with alcohol dependency is a subject of great interest. The identification of the human genome some years ago was greeted with great excitement, not least by many researchers from fields keen to identify any responsible genetic variation. The two articles below illustrate many of the issues associated with genetic research, not least that definitive answers are not necessarily conclusive.

Future issues of *Alcoholis* will include a review of the affects of alcohol on the nervous system written by Professor Dai Thomas.

Reference

- 1 Kaner E, Newbury-Birch D, Avery L *et al.* *A rapid review of liver disease epidemiology, treatment effectiveness and service provision in England.* London: National Institute for Health Research, 2008. Grant 078/0001.

Meta-analysis of the association of the *Taq1A* polymorphism with the risk of alcohol dependency: a HuGE Gene-Disease Association review

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This article summarises a recent study and paper published by the authors in the *American Journal of Epidemiology* as part of the Human Genome Epidemiology Network (HuGENet) initiative.¹

Introduction

Alcohol is known to increase dopaminergic function in the mesolimbic system, a brain reward system thought to be crucial in drug-mediated reinforcement behaviour, and therefore may be involved in the pathogenesis of alcohol dependence. The human dopamine 2 receptor gene (DRD2) *Taq1A* allele has been implicated as a vulnerability factor for alcohol dependence in a number of studies and reviews. It is suggested that the *Taq1A* polymorphism may be in linkage disequilibrium with an upstream regulatory element or another functional gene that confers susceptibility to alcoholism.

Blum et al were the first to report a significantly higher frequency of the A1 allele of the *Taq1A* polymorphism near the DRD2 gene in alcoholics compared with nonalcoholic controls.² This finding suggests an increased susceptibility to alcohol dependence in people with a particular variant of the DRD2 gene. Some later studies supported this initial finding although other studies, reviews, and meta-analyses have generally been less positive about the evidence for an association between DRD2 and alcohol dependence.³ It has been suggested that the nature of the control group may determine whether

significant population-based associations are found. Therefore, the association of the DRD2 *Taq1A* allele with alcohol dependence remains unclear and controversial.

To determine whether this allele is associated with alcoholism, the authors conducted a Human Genome Epidemiology (HuGE) review and meta-analysis, with the aim of systematically reviewing all available evidence from observational studies regarding the association of the DRD2 *Taq1A* allele with alcohol dependence. This HuGE review was undertaken under the auspices of the HuGE Network, coordinated from the US Center for Disease Control (CDC; see www.cdc.gov/genomics/hugenet/). The HuGE Network is a global collaboration of individuals and organisations committed to the assessment of the impact of human genome variation on population health and how genetic information can be used to improve health and prevent disease. A 2007 publication outlines the approach and methods of HuGE reviews.⁴

Method

Eligible studies were identified by searching Medline, Embase and BIOSIS from their inception to August 2006. Two investigators independently extracted data by using a structured form. Discrepancies were resolved by discussion and consultation with a third reviewer. The following information was sought from each report: selection and diagnostic criteria of the alcohol-dependent group; selection and classification criteria of the control group; demographic information including ethnicity, age, and sex; all alleles investigated; method of ascertainment of genotype; blinding of personnel performing

genotyping to clinical status of the study participants; methods used to create balanced groups (matching procedures or statistical adjustment methods); genotype and allelic frequencies; and statement of Hardy-Weinberg equilibrium. Unadjusted odds ratios were estimated for published genotype frequencies. Pooled odds ratios were calculated by using a random-effects model stratified by geographic region/ethnicity.

Results

Out of 1,056 titles and abstracts 116 full-text papers were obtained. Of these, 44 met the eligibility criteria and 44 studies with a total of 9,382 participants were included. Forty-two were case-control studies, and two were cross-sectional surveys. Forty-three studies, including a total of 5,273 cases and 3,995 controls, reported genotype frequencies for the *Taq1A* polymorphism and alcohol dependency.

For all studies combined, when the dominant model of gene action (A1A1 + A1A2 v A2A2) was assumed, a small but significant association of alcohol dependency with being homozygote or heterozygote for the A1 allele was detected. The odds ratio was 1.38 (95% confidence interval (CI): 1.20, 1.58) when random effects were used, although substantial statistical heterogeneity was detected between studies ($I^2=50.5%$, $p=0.0001$). Stratifying the studies into subgroups by ethnic group produced similar results, with significant associations detected in the two largest subgroups: white (odds ratio (OR) = 1.57, 95% CI: 1.29, 1.91) with substantial heterogeneity ($I^2=57.0%$, $p=0.0001$) and Chinese (OR=1.35, 95% CI: 1.04, 1.75) with no heterogeneity ($I^2=0%$, $p=0.71$).

Pooling the results of the same studies, but assuming the recessive model of gene action (A1A1 v A1A2 + A2A2), also showed a small but significant positive association of alcohol dependency with being homozygote for the A1 allele. The combined odds ratio was 1.22 (95% CI: 1.05, 1.43) using random effects this time, with no statistical heterogeneity detected between studies ($I^2=0\%$, $p=0.92$). Again, subgroup analyses showed no notable differences between different populations, with a significant association detected in the white subgroup (OR=1.40, 95% CI: 1.03, 1.91) with no heterogeneity ($I^2=0\%$, $p=0.92$) and in the Chinese subgroup (OR=1.41, 95% CI: 1.00, 2.00) with no heterogeneity ($I^2=0\%$, $p=0.52$).

In sensitivity analyses, exclusion of three studies with significant departures from Hardy-Weinberg equilibrium did not change the pooled results or explain the heterogeneity. In analyses restricted to studies reporting use of ethnic matched controls, associations remained significant with markedly reduced heterogeneity (Table 1). Furthermore, similar patterns of association were found in analyses restricted to studies with blinding (Table 1) and adequate screening of control group (Table 1) with little impact on heterogeneity.

For the dominant model, a cumulative meta-analysis showed that, with each additional study, although being significantly greater than one since 1990, the magnitude of the effect decreased over time; the odds ratio came closer to one and remained relatively stable beginning in 2000. For A1 homozygotes versus both other genotypes (recessive model), the odds ratio became greater than one after 1991 and has remained so since then, reaching significance in 2001. The pooled odds ratio has changed very little since 2001.

Discussion and conclusion

This large meta-analysis of mainly case-control studies found a small but significant association of the *Taq1A* polymorphism with alcohol dependency in both a dominant and a recessive model of gene action. Given the modest effect size found by the meta-analysis, many of the individual

Table 1. Association in studies with a control group matched for ethnicity.

	Studies (N)	OR (95% CI) dominant [†]	I^2 % [§]	Studies (N)	OR (95% CI) recessive [‡]	I^2 % [§]
Overall	26	1.18 (1.04, 1.34)	22.3	26	1.18 (1.01, 1.39)	0
Association in studies which reported blinding						
Overall	13	1.54 (1.12, .12)	57.9	13	1.05 (0.77, .43)	0
Association in studies with screening for alcohol dependency in the control group						
Overall	38	1.33 (1.15, 1.55)	51.5	39	1.20 (1.02, 1.41)	0

N=Number of studies; [†]A1A1+A1A2 versus A2A2; [‡]A1A1+A1A2 versus A2A2; [§]variability between studies due to heterogeneity rather than by chance. Reproduced with permission of the American Journal of Epidemiology.

studies were obviously underpowered. There were substantial variations between studies, however, particularly in the white subgroup. The observed heterogeneity could be due to differences in how the samples were selected and screened or to methods of genotyping or interaction with other risk factors.

Although the modest strength of association found in this study is of a similar magnitude to odds ratios reported for meta-analyses of other candidate genes and mental health disorders because of the numerous potential sources of bias in the primary studies, overestimation of the association cannot be ruled out.⁵ While there is convincing evidence for a genetic contribution to alcohol dependence derived from family, twin, and adoption studies, it cannot be explained by a single gene operating under Mendelian laws of inheritance. Therefore, a single gene predisposing to alcoholism is not anticipated, and the likelihood is that many, of relatively modest influence, interact with environmental factors and operate during a process of development. As such, the relatively small effect identified by this study regarding the contribution of the *A1* allele or another genetic variant linked to it is much more in keeping with the current understanding of the genetic contribution to such complex disorders and behaviours.

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MCA MCQs

1 Children of problem drinkers may experience – True or False

- A Anxiety and depression
- B Low self-esteem
- C Poor school performance
- D Accidental injury
- E Physical and sexual abuse

Source: Edwards G, Marshall EJ, Cook CCH. The treatment of drinking problems. A guide for the helping professionals. 4th edn. Cambridge: Cambridge University Press, 2003.

2 In delirium tremens – True or False

- A Disturbance may fluctuate
- B Classically includes clouding of consciousness and confusion, vivid hallucination and marked tremor
- C Symptoms of delirium peak after 96 hours
- D The withdrawal precipitating the episode may occur following a self-determined effort to give up drinking
- E Recurrent attacks are rare

Source: Edwards G, Marshall EJ, Cook CCH. The treatment of drinking problems. A guide for the helping professionals. 4th edn. Cambridge: Cambridge University Press, 2003.

3 In Wernicke's encephalopathy – True or False

- A The classic triad of confusion, ataxia and eye signs occurs in the majority of patients
- B Early diagnosis depends on clinical judgement and experience
- C When alcohol misuse is involved thiamine must be given parenterally because of associated thiamine malabsorption
- D Recurrent episodes may occur, some of which might be subclinical
- E Autopsy studies have shown up to 60% of cases not being diagnosed in life

Source: Thomson AD, Cook CC, Guerrini I et al. Wernicke's encephalopathy: plus ça change, plus c'est la même chose. Alcohol Alcohol 2008;43:180–6.

4 Alcohol and the liver – True or False

- A Alcohol is responsible for 70% of cirrhosis deaths in the UK
- B The mortality rate from alcohol-related cirrhosis rose from 1 to 8 per 100,000 deaths between 1975 and 2000
- C The highest rates of cirrhosis and alcohol-related deaths in the UK occur in Scotland
- D The lowest alcohol-related death rate from liver disease in the UK occur in south east England
- E Up to two thirds of a sample of patients with alcoholic liver disease were not admitted to hospital with an alcohol-related condition prior to being diagnosed with liver disease

Source: Kaner E, Newbury-Birch D, Avery L et al. A rapid review of liver disease epidemiology, treatment effectiveness and service provision in England. London: National Institute for Health Research, 2008.

[Answers on back page](#)

Genes and alcohol problems

David Ball, Senior Lecturer and Consultant Psychiatrist, Institute of Psychiatry, London

In a section entitled 'Parents a cause by propagation' of his literary and psychiatric classic *The anatomy of melancholy* Robert Burton provides the quote 'Ebrii gignunt ebrios, one drunkard begets another' from Plutarch the Greek historian (c. AD 46–113). As such, the familial nature of alcohol problems has long been recognised, but how much of this can be attributed to genes?

Classical genetic studies have provided formal evidence that genes are involved in this 'familiality'. Thus family studies demonstrate that alcohol problems cluster in families with approximately double the rates in relatives of an affected individual. While this is compatible with the involvement of genes, it does not prove that they are involved, as this clustering may also be due to the family environment. This can in part be dissected out by using adoption studies, in which the rate of alcoholism in individuals adopted away from their biological parent, who is thus afflicted, is compared with that in other adoptees. Rates for such individuals are increased fourfold and indeed there does not seem to be any protection from being adopted away from the family environment of that biological parent. The other main approach employed is that of twin studies in which the rate of alcohol dependence in co-twins who are monozygotic, is compared with those who are dizygotic. Monozygotic twins are essentially genetic clones of each other whereas dizygotic twins have approximately half of their DNA in common. By comparing the rates in both, not only is it possible to obtain evidence that genes are involved, but this also provides an approximate

estimation of how genetic or heritable the condition is. For alcohol dependence heritability estimates are typically 50% for males and 25% for females.

Linkage and association

Having established that there is reasonable evidence for a genetic underpinning in alcohol dependence, the advent of molecular genetics heralded the possibility that the specific genes involved could be identified. Two main approaches have been adopted; namely linkage and association.

Linkage is a family-based approach usually employing multiply affected pedigrees. Essentially the method tracks alcohol dependence through these pedigrees and attempts to identify a co-inheritance between the condition and a genetic marker (variations in the DNA often of sequence or size). If such a co-inheritance is identified this suggests that there is a gene involved in alcohol dependence in the region around the marker. Linkage studies are systematic in that it is possible to examine the whole of the human DNA (the genome) for such a co-inheritance using 300 to 400 markers. The major disadvantage of linkage, however, is that it is only effective in identifying genes that have a large effect in the condition under study and this may not be the case in alcohol dependence. As such there have been several major linkage studies reported, primarily from the US, with a disappointing lack of consistency and replication.

Association compares unrelated affected individuals, for example those with a diagnosis of alcohol dependence, with controls. Genetic markers are examined in both groups and the distribution of their variants compared. A statistically significant difference in the distribution indicates that a gene involved in alcohol dependence is very close to the marker concerned. Association studies have the advantage that they can identify genes of relatively small effect size. Until recently, however, these have not been applied systematically as this would require the use of thousands of markers. As a consequence, a candidate gene approach has been

adopted in which the genes studied are those for which there is an a priori reason to select them; for example they are implicated in alcohol metabolism or the neuropharmacology of alcohol action. Consequently, those genes that have been examined, and therefore appear to be associated with alcohol dependence, are the usual suspects including those involved in alcohol metabolism and those of the dopamine, gamma-aminobutyric acid and serotonin systems. However, the major draw back with association studies is that they are prone to false positive reports. Paradoxically, it has been estimated that a positive association in alcohol dependence with a significance value of 0.05, has a 99.5% likelihood of having occurred by chance. With recent advances in molecular genetics it is now possible to undertake systematic scans of the human genome for association with alcohol dependence, using DNA microarrays that can examine up to a million markers in one reaction. The false positive rate, however, will continue to hamper the analysis. Ironically another possible confounder in these molecular genetic studies is the very fact of an interaction between the genes and environmental factors. Such interactions may actually obscure the genetic contributions and only recently has a study addressed this issue, with a preliminary report that maltreatment during childhood may result in earlier alcohol use, in those with a predisposing genetic variant at the serotonin transporter.

Aldehyde dehydrogenase 2 gene

Thus linkage, as an approach may not be sufficiently sensitive to identify the genes implicated in the predisposition to alcohol dependence, while association may be hampered by false positives. Despite this, one of the most robust findings in psychiatric genetics has been reported in alcohol dependence and this is the protective effect conferred by a genetic variation in the metabolic pathway of alcohol, specifically in the aldehyde dehydrogenase 2 gene (ALDH2). In contrast to the systematic search for genes that subsequently identifies the biological processes involved, this finding was identified through the

traditional method of first characterising the biochemical lesion and subsequently tracking back to the gene implicated. Wolff was studying drinking behaviour in several oriental populations (Japanese, Taiwanese and Koreans) at a time when the difference in rates of alcoholism were attributed to socioenvironmental factors. He reported differences in the reaction to alcohol; namely a high frequency of marked facial flushing and suggested in his 1972 paper that this may be related to the risk of developing alcoholism. This reaction occurs in some 20–40% of oriental subjects and has been called the 'oriental flush reaction'. The genetic origin of this flushing response to alcohol has been tracked back to a single base change in the ALDH2 gene that destroys the activity of the enzyme; a single typo as it were in one volume of the gene. Thus when alcohol is consumed, most of it is metabolised in the liver by a group of enzymes, called alcohol dehydrogenase, to acetaldehyde, this toxic product would normally be rapidly broken down by ALDH2. Because of the genetic lesion above, however, those affected individuals accumulate acetaldehyde resulting in the flushing response which is just part of a wider aversive experience in response to alcohol. Indeed ALDH2 is the site of action for disulfiram, one of the few medications used to help individuals maintain abstinence. This drug acts as a suicidal inhibitor of the enzyme by destroying its activity. Unsurprisingly individuals with the inactive variant of ALDH2 are less likely to develop alcohol dependence however this does not afford an absolute protection. Other studies also suggest that genetic variation in the ADH genes that alter the speed of the reaction can also affect an individual's risk of developing alcohol problems.

Bad v good DNA

The bold hope of this 'new genetics' is that the unravelling of the biological foundation of alcohol problems will provide a framework on which to develop novel treatments and orientate existing approaches. Alcohol dependence may prove to be a collection of related disorders, with

Continued overleaf

distinct treatment response profiles and outcomes. It may therefore be possible to target and tailor treatment packages based upon the genetic background of an individual, possibly identified by genetic testing. The development of alcohol dependence and other alcohol problems is envisaged as a complex choreography, with multiple genes interacting with environmental factors throughout a process of development. As such there will be little scope for genetic screening and limited opportunity for this information to be misapplied for eugenic ends. Indeed we all carry 'bad' DNA in our fluid genomes; the evidence from the increased rate of miscarriage in unions between first cousins suggests that on average each of us is carrying 1.4 deleterious segments of DNA, termed lethal equivalents, which if they were not balanced by 'good' DNA would be incompatible with life. Using information from multiple genetic tests combined into one reaction it may be possible to alter an individual's risk of developing alcohol-related problems. While this may be useful information, there is also the concern that those assigned a low genetic vulnerability may ignore any residual risk of alcohol-related harm while those rated as high risk may adopt a nihilistic approach to any prospective treatment.

Classical genetics indicates that genes are important in the predisposition to alcohol problems. Furthermore a genetic variant of ALDH2, associated with low enzymatic activity, can dramatically reduce drinking behaviour and subsequently

protect against the risk of developing alcohol dependence. The new techniques of molecular genetics promise to identify genes, characterise their function and ultimately elucidate their contribution to the biological underpinning of alcohol problems. Currently, however, these approaches are limited by issues of sensitivity or specificity and they have yet to deliver upon that initial promise.

Summary

Plutarch recognised that alcohol problems run in families and it is very tempting to attribute this to genes. However, the likely source of Burton's quotation is from Plutarch's *The training of children* in which he states 'for they usually prove wine-bibbers and drunkards, whose parents begot them when they were drunk'. As such this is an environmental interpretation and is a timely reminder that the development of alcohol problems is a complex interaction of genes and environment during a process of development.

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MCA MCQ answers

1. A True, B True, C True, D True, E True
2. A True, B True, C False (72–96 hrs), D True, E False
3. A False (15–20%), B True, C True, D True, E False (up to 80%)
4. A True, B True, C True, D True, E True



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