

Genetic approaches to alcohol dependence*

DAVID BALL

Ebrii gignunt ebrios (one drunkard begets another) is an oft-quoted phrase from Robert Burton's 17th-century work *The Anatomy of Melancholy* and is attributed by Burton to the Greek historian Plutarch (Burton, 1972). Plutarch's observation, originally made in AD 110, has been used to emphasise the long-standing recognition that alcohol dependence runs in families. It has been echoed down the years and is reflected nowadays by such headlines as 'Born to the bottle' and 'Gene and tonic: science proves that alcoholics can't help it'. Indeed, such observations have been given scientific credibility by formal family studies, indicating that alcohol dependence clusters in families: rates being increased in relatives and the risks of developing this condition increasing with the number and proximity of affected relatives. However, although family studies are consistent with a genetic influence, they cannot be interpreted as proof. Additional support has been derived from adoption studies indicating that adoptees with an affected biological parent remain at a higher risk of developing alcohol dependence, a risk that is the same as that of being reared by the affected parent. Further evidence and an approximate estimate of heritability – crudely speaking how genetic a condition is – can be derived from twin studies that yield figures of 50% for males and 25% for females (Ball & Collier, 2002). These heritabilities emphasise the importance of environmental influence, especially in women.

MOLECULAR GENETIC APPROACHES

Human studies to elucidate this genetic contribution have employed two main

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approaches, namely linkage and association (Sham & McGuffin, 2002). In linkage studies alcohol dependence is tracked through pedigrees, in an attempt to identify co-inheritance of a genetic marker, a region of DNA that varies between individuals usually by sequence or size, and the condition. Two major linkage studies have been undertaken in the USA; the smaller used an ethnically homogeneous sample from a Native American population to increase the chance of identifying linkage (Long *et al.*, 1998). This study implicated regions on chromosomes 4 and 11; the former contains a gamma-aminobutyric acid (GABA) receptor subunit gene cluster, the latter the dopamine D4 receptor and tyrosine hydroxylase genes. The larger study, the Collaborative Study on the Genetics of Alcoholism, provided evidence suggesting a locus on chromosomes 1 and 7, modest evidence for a locus on chromosome 2 and evidence for a protective locus on chromosome 4, in the region of the alcohol dehydrogenase cluster of genes (Reich *et al.*, 1998). However, these regions have not been robustly confirmed in that study's replication sample, which may indicate that the effect size of the individual genes involved is approaching the limitations of the linkage approach (Hesselbrock *et al.*, 2001).

In contrast to linkage studies, association is capable of detecting genes of relatively small effect, but many thousands of markers would be required for a systematic approach that could screen the entire human genome. Association attempts to detect a difference in the distribution of a marker, between unrelated individuals with a diagnosis of alcohol dependence and a matched control sample. Because it has been applied non-systematically, association studies have usually adopted the candidate gene approach, examining genes with an *a priori* reason to support an inference of their role in alcohol dependence. Following some early biochemical

association studies, in 1990 the first reported genetic association firmly established the dopamine D2 receptor gene (*DRD2*), and thus all the dopaminergic system genes, as strong candidates (Blum *et al.*, 1990). There followed a wave of both successful and unsuccessful attempts to replicate this finding, and more robust association methods did not support the original report. So although the jury is still out regarding the veracity of this finding, most of the jurors would seem to favour an innocent verdict for *DRD2*. This highlights one of the fundamental problems with the association approach: it is highly prone to false positives, and some argue that the chances of a false-positive finding greatly outweigh that of a true-positive result (Buckland, 2001).

Wolff (1972) was the first to study whether the way the body metabolises alcohol might be an important aetiological factor in alcoholism. At that time the lower incidence of alcoholism in the ethnic groups he was studying (Japanese, Taiwanese and Koreans) was attributed to socio-environmental factors. However, his study reported differences in alcohol sensitivity, namely a high frequency of marked facial flushing, which he suggested could be related to the development of alcoholism. Indeed, the most robust and convincing association findings have been reported with those strong candidate genes, the alcohol metabolising enzymes, in these populations. Most alcohol elimination occurs through oxidation to acetaldehyde and acetate and this process is primarily catalysed by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase 2 (ALDH2).

The biological origin of this 'oriental flush reaction' has subsequently been assigned to a single base pair change in exon 12, one of the coding sequences of the *ALDH2* gene (Yin & Agarwal, 2001). A single typo, as it were, in chapter 12 of the *ALDH2* book, this disrupts the activity of the protein such that acetaldehyde accumulates, resulting in facial flushing, increased heart rate, palpitations, muscle weakness and a hot feeling in the stomach. This single base change alters one of the codons (groups of three bases that form the genetic code) from GAA, which translates to the amino acid glutamate, to AAA, coding for lysine. The V_{max} , effectively the maximum speed of the reaction, for the active enzyme tetramer is 33/min and that for the inactive enzyme is 0.94/min.

The result is a loss of ALDH2 activity in both heterozygotes and homozygotes. This is rather like having endogenous disulfiram permanently on board (disulfiram, prescribed to aid the maintenance of abstinence, acts by destroying the activity of ALDH2). Not surprisingly, therefore, this genetic difference protects against the development of alcohol dependence, with significantly lower numbers of people who are alcohol-dependent possessing the gene for the inactive enzyme. That the inactive variant does not provide absolute protection from alcohol dependence was demonstrated by the identification of a single Han Chinese individual, who satisfied DSM-III-R diagnostic criteria for alcohol dependence, yet was homozygous for the inactive variant. He achieved this by the steady sipping of alcohol, consuming less than 8 UK units (64 g) of ethanol per day (Chen *et al*, 1999).

Similarly, the alcohol dehydrogenases are strong candidate genes. They represent a complex family of at least seven genes, *ADH1–7*, clustered on the long arm of chromosome 4. Variants occur in *ADH2* and *ADH3* that affect their kinetic properties and in *ADH2* this can cause up to a 40-fold difference in V_{max} . The high-activity variants *ADH2*2* and *ADH3*1* are significantly decreased in people with alcohol dependency in east Asian populations (Yin & Agarwal, 2001). In addition there is some evidence that this is true of other populations, including Europeans. These findings related to ADH and ALDH2 support the hypothesis that protection is conferred by either faster production or slower removal of the aversive metabolite acetaldehyde.

Less robust findings have also been reported using association studies, primarily implicating genes influencing the dopaminergic, serotonergic and GABAergic systems (Dick & Foroud, 2003). The main focus of our research has tested genes of the last-named system, primarily those encoding GABA receptor subunits for an involvement in the predisposition to alcohol dependence (Loh *et al*, 1999, 2000; Sander *et al*, 1999; Loh & Ball, 2000). The GABA receptor subunit cluster on chromosome 5, containing the $\alpha 1$, $\alpha 6$, $\beta 2$ and $\gamma 2$ subunit genes, was targeted because of the recognised cross-tolerance between alcohol and benzodiazepines, evidence that the most commonly expressed receptors are formed from the subunits of this cluster and preclinical research indicating

a role in changes of alcohol sensitivity. We adopted a predominantly molecular genetic approach to this complex behaviour, in order to begin to understand the biological underpinning of alcohol dependence. However, we recognise that this will be a complex choreography of gene and environmental interactions, occurring during a process of development, such that different genes assume importance at different stages in the disease process. As such it is vital that we directly address the dash in 'nature–nurture'. The Medical Research Council's Social, Genetic and Developmental Psychiatry Centre at the Institute of Psychiatry is at the forefront of this research, exploiting longitudinal studies to examine the interaction of environmental factors, for example life events, and genes in the development of psychiatric disorders (Caspi *et al*, 2002, 2003). This approach has yet to be applied to the study of addictions.

RESEARCH AIMS

The aims of this genetic research are to enable us to understand the biological underpinning of alcohol dependence. It is anticipated that some genes will be common to addictive behaviours and others specific to substance. An appreciation of the biological associations will enable the diagnoses to be refined, enabling a more accurate prediction of prognosis. This raises the possibility of novel treatment approaches, particularly in the maintenance of abstinence, as relapse rates are very high, being approximately 80% within the first year following detoxification. It is envisaged that these treatments will be tailored to the individual and that this, in part, will be based on the individual's genetic background. Using a combination of multiple markers, it might be possible to assess an individual's risk of developing alcohol dependence, but the scope for such genetic counselling would be minimal owing to the anticipated modest effect sizes. Similarly, population screening for alcohol dependence is unlikely to be feasible (Nuffield Council on Bioethics, 1998).

In *The Training of Children*, written in AD 110 – the likely source of Robert Burton's quote – Plutarch states: 'for they usually prove wine-bibbers and drunkards, whose parents begot them when they were drunk' (Plutarch, 110). This statement actually invites an environmental interpretation,

rather than that of a hereditary influence. In exploring the genetic contribution it is often tempting to overplay its role and neglect environmental effects. It is vital to remember that the elucidation of genetic factors in this complex interaction will further illuminate the role of the environment.

FUTURE IMPACT

Psychiatric genetics has yet to deliver on its early promise and it has not yielded any major advance in the management of people who are alcohol-dependent. However, elucidation of the genetic contribution to alcohol dependence, in its developmental interplay with the environment, will have a profound effect on the approach to their problem, with important implications for the management of patients from initiation, through tolerance, dependence, physical complications and treatment response, as well as influencing attitudes to this disorder.

DECLARATION OF INTEREST

None.

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DAVID BALL, Social, Genetic and Developmental Psychiatry Centre, PO Box 82, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK

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