Chapter 22

Alcoholism

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Background

Alcohol use disorders (AUDs) are very common around the world, and cause a tremendous burden of disability and death [1]. AUDs can be defined as "maladaptive patterns of [alcohol] use leading to clinically significant impairment or stress" [2]. Current diagnostic criteria, both from the *Diagnostic and Statistical Manual on Mental Disorders* (DSM-IV) [3], used in the United States, and from the *International Classification of Diseases* (ICD-10) [4], used elsewhere, divide AUDs into alcohol dependence and abuse/harmful use. Criteria for alcohol dependence (alcoholism) are very similar in the two diagnostic systems, based on a syndromic definition [5]. The criteria include withdrawal, tolerance, loss of control of drinking, impaired work or social activities, and continued use despite known problems. A diagnosis of alcohol dependence requires that an individual endorse at least three out of seven DSM-IV criteria (Table 22.1) or three out of six comparable ICD-10 criteria. Fewer individuals meet ICD-10 criteria than meet DSM-IV criteria [6, 7]. In spite of the heterogeneity in this syndromic definition, the diagnosis of alcohol dependence is one of the most reliable in the DSM-IV [6, 8, 9]. The reliability of an abuse diagnosis is much lower [6, 9, 10].

This article will focus on alcohol dependence (alcoholism), because the diagnosis is more reliable and because most of the genetic data focus on dependence. US data from the 2001–2002 National Epidemiological Survey on Alcohol and Related Conditions (NESARC) showed a 12-month prevalence of 3.8% for alcohol dependence defined by DSM-IV: 5.4% in men and 2.3% in women [11]. Lifetime prevalence of alcohol dependence is 12.5% in the United States.

Table 22.1 DSM-IV diagnostic criteria for alcohol dependence requires meeting 3 or more of the following criteria during a 12-month period.

1. Tolerance
2. Withdrawal signs or symptoms
3. Drinking more than intended
4. Unsuccessful attempts to cut down on use
5. Excessive time related to alcohol (obtaining it, hangover)
6. Impaired social or work activities due to alcohol
7. Use despite physical or psychological consequences

Alcoholism is a genetic disease with a necessary environmental component

Alcoholism is a complex genetic disease, with convincing evidence that variations in both genes and environment contribute to differences among individuals in risk. Multiple lines of evidence converge to support the idea of a genetic contribution to the risk. These include adoption studies that demonstrate the adoptees more closely resemble their biological parents than their adoptive parents in risk [12–15]. They also include twin studies, showing greater concordance in alcoholism between monozygotic twins (MZ) (who share all of their genes) than between dizigotic twins (DZ) (who share only half of their genes) [14, 16–18]. The fact that MZ co-twins of alcoholics are not all alcoholics is a clear demonstration that the disease is not determined only by genes. A third line of evidence is that aspects of alcoholism, including strong preference for alcohol over water, willingness to work for alcohol, sensitivity to the hypnotic or activating effects of alcohol and to withdrawal, and demonstrations that

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alcohol is rewarding even in the presence of food and water, can be modeled in selectively bred rodent lines [19–23]. A fourth line of evidence comes from early genetic studies in humans that demonstrated genetic variations in alcohol metabolism affect risk for alcoholism [24–27] (and see below). Although there might be caveats to any one line of evidence, the convergence of data provides overwhelming evidence that genetic variations contribute to individual variations in the risk for alcoholism. The lack of a simple pattern of inheritance indicates that the genetic risk results from the combined contributions of many genes, and probably in part from gene × gene and gene × environment interactions.

There is a necessary environmental component to the disease: consumption of alcohol. Absent that, underlying genetic vulnerabilities may surface in other problems or diseases, but not in alcoholism. Unlike other psychoactive drugs, ethanol is ingested in large amounts; legal intoxication in the United States is defined as a blood alcohol concentration of 0.08%. Drinking that allows blood alcohol to reach 0.08% or above has been defined as binge drinking [28]. Although there is significant variation among individuals, a typical 170 pound man would generally reach this level after drinking about 5 standard drinks within 2 hours and an average women would reach this level after ingesting about 4 drinks, due to differences in weight and body composition. (A standard drink in the United States contains 14 g of pure ethanol, and is approximately equivalent to 12 ounces of beer, 5 ounces of table wine, or 1.5 ounces of 80-proof spirits.) Alcohol consumption must generally be in the binge range and frequently repeated to develop the problems that result in diagnosis of alcohol dependence. The risk of meeting criteria for alcohol dependence rises nearly linearly with the frequency of binge drinking [29]. Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) indicate that the number of criteria for abuse and dependence that are met rise with the frequency of binge drinking [2, 29].

This necessary environmental factor, alcohol, interacts with the underlying genetics to result in the disease of alcoholism. Variations in the environment related to alcohol accessibility, price, and social norms, therefore, can affect the prevalence of alcoholism.

There are three main approaches to identification of variations in specific genes that affect alcohol dependence: candidate gene studies, linkage studies (followed up with association studies of variants within the linked regions), and genome-wide association studies. This chapter cannot discuss all of the rapidly growing literature in the area; illustrative examples are chosen, often from the work of the Collaborative Study on the Genetics of Alcoholism (COGA).

Candidate gene studies

The earliest genetic association studies in alcoholism were candidate gene studies targeting coding variations in the genes that metabolize alcohol. Most ingested alcohol is metabolized in the liver, primarily in a two step reaction: oxidation to acetaldehyde, which is further oxidized to acetate. The first step, oxidation to acetaldehyde, can be catalyzed by alcohol dehydrogenases, cytochrome P450s, and catalase. The great majority of the alcohol is oxidized by the alcohol dehydrogenases (ADH), with the accompanying reduction of NAD^+ to NADH (Figure 22.1). The second step, oxidation of acetaldehyde to acetate, is catalyzed primarily by aldehyde dehydrogenases (ALDH), with reduction of another molecule of NAD^+ to NADH. Humans have seven ADHs and two ALDHs that catalyze most of the ethanol metabolism. Variations in the genes encoding enzymes of alcohol metabolism have long been known to affect the risk for alcoholism [24–27, 30].

A variation in *ALDH2* has dramatic effects on alcohol metabolism. The *ALDH2*2* allele encodes a nearly inactive subunit of the mitochondrial aldehyde dehydrogenase 2 that is responsible for much of the oxidation of ethanol. Presence of a single *ALDH2*2* allele renders the ALDH2 catalytic activity (measured *in vitro*) below the usual limit of detection [31]. In individuals with a single copy of the inactive *ALDH2*2* allele consumption of even small amounts of alcohol causes a dramatic rise in acetaldehyde in blood, which triggers a highly aversive reaction similar to that caused when a patient taking disulfiram (Antabuse®) drinks alcohol; the reaction includes flushing, tachycardia,

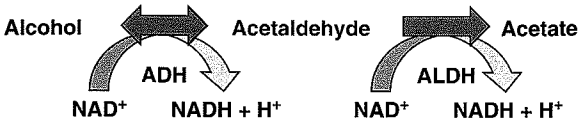

Figure 22.1 The primary pathway of alcohol metabolism in the liver is oxidation by alcohol dehydrogenases (ADH) and aldehyde dehydrogenases (ALDH) enzymes, with acetaldehyde as the intermediate.

Figure 22.2 Genomic arrangement of human *ADH* genes on chromosome 4q.

and nausea. This aversive reaction greatly reduces their propensity to drink, the amount consumed per occasion, and their risk for alcoholism [24, 26, 27, 31–35]. It is not totally protective: some individuals continue to drink despite the high acetaldehyde levels. But for someone with a single *ALDH2*2* allele, the relative risk of alcoholism range from about 0.13 to 0.40 in different Asian populations [35, 36]. *In vivo*, having two copies of the *ALDH2*2* allele leads to an even more severe reaction and is nearly totally protective against alcoholism; among thousands of cases reported in the literature, there are only three alcoholics homozygous for *ALDH2*2* [35, 36].

Variations in ADHs that catalyze the first step in ethanol metabolism also strongly affect the risk for alcoholism. Humans have seven *ADHs* that arose from repeated gene duplications; the genes encoding them are clustered in a small region of chromosome 4 (Figure 22.2). The kinetic properties of these enzymes suggest that at low levels of alcohol, enzymes encoded by *ADH1A*, *ADH1B*, and *ADH1C* play the major role in metabolism; ADH1B is the ADH present at highest levels in the adult liver and presumably contributes most. When ethanol is present at higher levels (intoxicating) the enzyme encoded by *ADH4* makes an increasing contribution. ADH7, located in the esophagus and stomach lining, can contribute to "first pass" metabolism of ethanol because ethanol is at very high concentrations in stomach during drinking. Variants in *ADH1B* and *ADH1C* that increase the rates at which the enzymes they encode oxidize ethanol reduce the risk for alcoholism [24, 26, 27, 35–40]. The strongest effects are due to variants in *ADH1B* that are relatively common in Asians (*ADH1B*2*, in which arginine 48 is replaced with histidine) and in people of African ancestry (*ADH1B*3*, in which arginine 370 is replaced with cysteine). Blood acetaldehyde levels do not dramatically rise in individuals with these variants, and there is no severe flushing reaction comparable to that in individuals with the *ALDH2*2* allele. Nevertheless, the protection against alcoholism provided by the *ADH1B*2* allele is very strong, with relative risks approximately 0.18–0.26 for 1 allele and 0.10–0.14 for 2 (in Asian subjects homozygous for *ALDH2*1*) [35, 36, 40, 41]. Neither of these alleles are common among individuals of European ancestry, although *ADH1B*2* is found at moderate frequency in people of Jewish ancestry [42, 43]. The low allele frequency makes studies more difficult, but *ADH1B*2* also appears protective in individuals of European descent (with relative risk about 0.5) [38, 40, 44]. A recent large-scale study has conclusively demonstrated protective effects in Europeans [45]. Recent genetic studies have shown that variations in *ADH4* play a significant role in affecting risk for alcoholism, as do noncoding variations in *ADH1A* and *ADH1B* [37]. Other variations in the *ADH* region were also shown to affect alcohol metabolism [46], including variations in and near *ADH7* [47] *ADH1A*, *ADH1B*, *ADH1C*, and *ADH4* [48]. Clearly there is more to be learned about the contributions of the *ADH* genes to both alcohol metabolism and alcoholism.

Despite the fact that blood acetaldehyde levels do not rise substantially in individuals with the *ADH1B*2* or *ADH1B*3* alleles, it is generally thought that both the more rapid generation of acetaldehyde by these ADHs and the reduction in the rate of elimination of acetaldehyde by the inactive ALDH affect the risk for alcoholism by at least transiently increasing acetaldehyde levels in the liver, triggering aversive reactions that reduce excessive drinking. A combination of the strongly protective alleles at both *ADH1B* and *ALDH2* loci is synergistic, and drops relative risk of alcoholism in Asians to about 1–10% [35, 36]. Thus variations in the *ADH* and *ALDH* genes play strong roles in affecting the risk for alcoholism. These are among the strongest and best replicated findings in the genetics of complex diseases. Despite their strong impact on some populations, the coding variations in *ADH* and *ALDH* genes do not explain a large fraction of the differences in risk in populations of European ancestry in which the alleles with the strongest effects are rare.

There have been many other candidate gene studies, some with markedly mixed results. A full description of these is beyond the scope of this article, but several will be discussed as illustrative of the field. Perhaps the most famous is the association of the TaqIA allele of the dopamine D2 receptor gene (DRD2-TaqIA; rs1800497) with alcoholism, first reported in a small study in 1990 [49]. There have been numerous attempts to replicate this, and although most have been negative, e.g. [50–52], one recent meta-analysis suggests a small but significant

effect that might be due in part to publication bias [53]. The "DRD2-Taq1A" polymorphism actually lies within an adjacent gene, *ANKK1* (ankyrin repeat and kinase domain containing 1) [54]. A recent family study showed that although rs1800497 was not significant, a different allele at *DRD2* (rs6277, a synonymous single nucleotide polymorphisms [SNPs]) was [55]. Another family-based analysis showed that the association in this region with alcohol dependence is strongest in the region of *ANKK1* that is not in linkage disequilibrium (LD) with *DRD2* [50], and another family and case-control study suggested the evidence for association with alcoholism in this region is in the *NCAM1*, *TTC12*, and *ANKK1* genes [56, 57]. There remains much complexity in interpreting these data.

The opioid system has been implicated in addictions, not only for opiates but also for alcohol [58, 59]. There are three main opioid receptors and three main genes encoding endogenous ligands. *OPRM1* encodes the mu receptor (MOR), and *POMC* encodes its primary ligands; *OPRK1* encodes the kappa receptor (KOR) and *PDYN* its primary ligands; *OPRD1* encodes the delta receptor (DOR) and *PENK* its primary ligands. The mu receptor has been most widely studied, particularly a coding variation (Asn40Asp); a recent meta-analysis of those studies concluded that there was no significant evidence for association [60]. COGA examined all six genes from this system, and found that variations in the kappa system were associated with alcoholism [61], but variations in the mu or delta system were not [62], nor were variations in the related nociceptin system [63]. It was particularly intriguing that variations in the genes encoding both the receptor *(OPRK1)* and its ligand *(PDYN)* were associated. Follow-up molecular studies demonstrated that one associated polymorphism affected the level of expression of *OPRK1* [64].

NPY is a candidate gene based upon studies of a rat model of alcohol preference [65–67], knockout mice [68], and some but not all human studies, e.g. [69–71]. *NPY* itself is on human chromosome 7 and was not significantly associated with alcoholism in the COGA sample [72]. Three NPY-receptor genes on chromosome 4 were also evaluated, and two of these gave evidence of association: *NPY2R* was associated with alcohol dependence and alcohol withdrawal symptoms, and *NPY5R* was associated with alcohol withdrawal characterized by seizures [72].

There are many other potential candidate genes, including genes in nearly all neuronal receptor/ligand systems. When variations in one gene is found to affect the risk for alcoholism, it is reasonable to examine other genes in the system(s) to which it belongs; this has been useful, for example, in following up initial findings with *GABRA2* [73] in other GABA-receptor genes [74, 75]. There are, however, advantages to taking an unbiased approach toward identifying genes that affect risk, such as genetic linkage or whole genome association studies.

Genetic linkage studies

Genetic linkage studies provide an unbiased approach toward identifying genetic variations that affect the risk for a complex genetic disease such as alcoholism. Linkage studies follow the inheritance of particular regions of the genome within families. The regions are tagged by some readily assayable marker; microsatellite markers were the most widely used when the studies on alcoholism began, but SNPs are now easier to assay. Linkage studies test for significantly excess (or reduced) transmission of particular regions of the genome to affected family members. Because nearby sites along a chromosome are usually transmitted together, a relatively small number of markers can report on the genome. This is a technical advantage for linkage studies, but the drawback is that linkage studies generally identify relatively large regions, usually between 20 and 50 million base pairs, that contain many genes. Because linkage studies look within individual families, they can identify a region in which different rare alleles affect the risk in different families.

The earliest whole genome linkage studies on alcoholism were reported in 1998 [76, 77]. The Collaborative Study on the Genetics of Alcoholism (COGA) recruited families of individuals in treatment for alcoholism at six sites across the United States, and did genetic studies on those families in which at least three first-degree relatives met criteria for alcohol dependence [77]. The initial linkage study encompassed 987 individuals from 105 families, and reported suggestive evidence for linkage with alcoholism on chromosomes 1 and 7, weaker evidence on chromosome 2, and linkage with a protective phenotype on chromosome 4q [77]. Long et al. [76] studied 172 sibling pairs from a southwest Native American population, and reported evidence for linkage on chromosome 11p, 4p and for several markers in the *ADH* region of 4q. A follow-up study of an additional 157 families from the COGA project supported their original findings on chromosomes 1 and 7 and also revealed

some evidence for linkage on chromosome 3 [78]. A smaller study provided support for the linkage on chromosome 1 [79]. Analysis combining the diagnostic phenotype with an electrophysiological variable (amplitude of the P300 component of the event-related potential) gave the strongest evidence of linkage in a broad region of chromosome 4q that encompassed the ADH genes [80]. A quantitative trait, maximum drinks in a 24 hour period, also showed linkage on chromosome 4q [81]. Results from the Irish Affected Sib Pair Study of Alcohol Dependence again showed linkage to a broad region of chromosome 4q, and weaker, suggestive evidence on chromosomes 1q, 13q, and 22q for alcohol dependence, on 2q, 9q, and 18p for symptom count [82], on chromosome 9 for age at onset, on chromosomes 1 and 11 for initial response to alcohol, 1, 6, and 22 for tolerance, on chromosomes 12 and 18 for maximum drinks, and on chromosome 2 for withdrawal symptoms [83]. A more recent linkage study of alcohol dependence in a set of African-American families originally ascertained for cocaine or opioid dependence showed evidence for linkage to chromosome 10q [84]. As noted above, these linkage studies point to chromosomal regions, rather than specific genes.

Follow-up of linkage studies

A productive approach to identifying genes that affect the risk for alcoholism is to follow-up linkage studies with association studies of variants within the linked regions. One can either analyze variations spanning the entire linkage region in a systematic manner, based upon LD, or target candidate genes within the region. The systematic approach generally requires more genotyping and correction for more multiple testing, but has the advantage of being relatively unbiased. A disadvantage is that the location of the peak of linkage is not necessarily centered on the key gene(s) contributing to the linkage, so it is possible to miss the gene contributing to the linkage signal if too narrow a region is analyzed. The candidate gene approach leverages prior data and biological understanding to reduce the number of genes that are tested, but might miss potentially important genes for which there is no prior evidence or hypothesized role in alcoholism.

These issues will be illustrated by discussing some results from COGA. There was some evidence from the initial COGA analysis for linkage to markers on chromosome 4p around a GABA receptor gene [77], and results from a linkage study in Southwest Native Americans showed the strongest linkage there [76]. Our interest in the region was greatly enhanced by a very strong linkage of an electrophysiological phenotype believed to be related to susceptibility to alcoholism, the amplitude of the β-EEG [85]. A cluster of 4 $GABA_A$ receptor genes was located in the middle of that linkage peak, and was extensively analyzed. Many variations and haplotypes in *GABRA2*, encoding the α2 subunit of the $GABA_A$ receptor, were associated with alcohol dependence as well as with the β-EEG phenotype [73]. This has since been confirmed in many studies of different populations [86–92]. The association in the COGA sample is with the most severe half of the alcoholic subjects, as defined by comorbid drug dependence [93], which also correlates with early onset of alcoholism and many other measures of severity [94]. Other studies have shown association also with the *GABRG1* gene, adjacent to *GABRA2* and in LD with it [96].

One of the large linkage peaks in the COGA sample was on chromosome 4q [77, 80]; this region was also implicated in the Irish study [82]. The *ADH* genes lie under this peak. As discussed above, these were targeted by many SNPs, and associations found with SNPs in *ADH4, ADH1A*, and *ADH1B* [37]. These findings were supported and extended by other groups (see above). However, we hypothesized that a broad linkage peak was likely to reflect the combined contribution of several genes, and continued our analyses of other genes within this region. COGA has, thus far, identified several additional genes within this linkage peak in which variations affect alcohol dependence or a closely-related phenotype. *SNCA*, encoding α-synuclein, was a top candidate gene based upon studies in a rat model of alcohol preference [65, 96, 97] and on data from monkeys [98] and humans [98–101]. In the COGA subjects, variations in *SNCA* were not significantly associated with dependence per se, but were associated with craving for alcohol [102]. Continuing our analysis of genes in the chromosome 4 linkage peak, we demonstrated that *TACR3*, encoding the tachykinin 3 (neurokinin B) receptor, was associated with alcohol dependence, as was *NFKB1* [103], encoding a subunit of the ubiquitous transcription factor NF-κB, which regulates many genes in the brain. The association of both *TACR3* and *NFKB1* were strongest with the most severely affected subjects [103, 104]. Thus the hypothesis that multiple genes contribute to this linkage peak was supported.

A second major linkage peak in the COGA sample was on chromosome 7q [77, 105–107]. A systematic screen across an 18 Mb (2-LOD) interval was carried out, selecting SNPs that efficiently report on the variations within this region based upon patterns of LD [108]. Several SNPs gave significant or suggestive evidence of association with alcoholism; the most consistent evidence was for several SNPs in the *ACN9* gene [108], related to gluconeogenesis and the assimilation of ethanol and acetate. Additional genes within this region are being examined.

Genome-wide association studies

Recently, genome-wide association studies (GWAS) have largely replaced linkage studies [109, 110]. These studies take advantage of modern multiplexed methods for simultaneously genotyping 1 million SNPs or more. They allow association testing of a very large fraction of the genome, and have been successful for several complex diseases [109]. There are limitations, however. The most obvious is the risk of false positives due to the extraordinary amount of multiple testing; less obvious is that the corrections used to avoid false positives are likely to lead to many false negatives. The problem of multiple testing leads to a requirement for very large sample sizes, with cases and controls very well matched for ethnicity. The use of correction factors using ancestry informative markers can accommodate multiple ethnicities in the same study. Another limitation is that GWAS are designed to find relatively common polymorphisms that contribute to the risk for a disease; if a collection of rare variants in a gene can independently increase risk, this will often be missed by GWAS (but can be captured by linkage studies).

To date, only one GWAS on alcoholism has been published. Treutlein et al. [111] studied 487 male alcoholic inpatients from Germany and 1358 controls, and followed up the more significant findings in another group of 1024 patients and 996 controls. No SNP met criteria for genome-wide significance in the initial study, but two did in the combined sample. Other SNPs provided consistent evidence in the initial sample and follow up, at less significant levels. The need for large samples and replications means that results expected within the next few years will be important for assessing which SNPs are truly associated with alcohol dependence.

Gene × environment interaction

A substantial gene × environment interaction was shown dramatically in the Japanese population by Higuchi [25]. The degree of protection against alcoholism afforded by the *ALDH2*2* allele changed significantly between the years 1979 and 1992: in that time, the fraction of Japanese alcoholics carrying the *ALDH2*2* allele in heterozygous form increased from 2.5 to 13% [25]. This time was far too small for any change in the underlying frequency of the polymorphism in the Japanese population as a whole, so the only explanation is that its protective effect was reduced, presumably by sociological changes leading toward more alcohol consumption. In that same study, no alcoholics were found to be homozygous for *ALDH2*2* (although 120 would have been expected based on the allele frequency), suggesting that the protection afforded by having two copies of the *ALDH2*2* allele is much stronger and was not as susceptible to the environmental changes [25].

Genes and environment in treatment

It is likely that particular genes and combinations of genes will differentially affect risk for different manifestations of alcoholism, such as co-occurrence with other disorders, and that different combinations of genes will also affect the response to particular treatments. There is already evidence that variations in some genes primarily affect alcoholism that shows early onset and comorbidity with other drugs of abuse (e.g. *GABRA2, ADH4, CHRM2, NFKB1*) [73, 93, 95, 103, 104]. As we learn more about the genetic underpinnings of alcoholism, we are likely to find that different combinations of genetic variants lead to different responses to different treatments, which will improve our ability to design individualized therapies [112].

Summary

There has been much progress in the genetics of alcohol dependence. Variations in several genes have clearly been shown to affect the risk for developing alcohol dependence. Certain variations in *ADH* and *ALDH* genes have very strong effects on the risk for alcoholism. Variations in other genes appear to have a much smaller effect on risk. In populations of European ancestry, in which the coding variations in *ADH* and *ALDH* that have the strongest effects are uncommon, most of the individual difference in risk is still

unexplained, and probably reflects the summation of many genes of small effect, along with gene × gene and gene × environment interactions. Linkage studies and their follow-up, along with candidate gene studies and GWAS, are beginning to fill the gaps. Initial findings must be confirmed in independent studies, and much work remains to elucidate the mechanisms involved. Nevertheless, with the new technologies and larger samples being studied, progress should accelerate. The future will involve studies of epigenetic factors, copy number variants, and gene expression, as well as tests for rare variants of large effect in specific families [113].

It should be remembered that although variations in genes clearly affects an individual's risk for alcoholism, the disease is not determined solely by genes. The environment and individual choices plays a major role. Understanding the genetic contributions to risk should lead to better understanding of the disease processes and assist in tailoring treatments to individuals.

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