Genetics and alcoholism

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Abstract | Alcohol is widely consumed; however, excessive use creates serious physical, psychological and social problems and contributes to the pathogenesis of many diseases. Alcohol use disorders (that is, alcohol dependence and alcohol abuse) are maladaptive patterns of excessive drinking that lead to serious problems. Abundant evidence indicates that alcohol dependence (alcoholism) is a complex genetic disease, with variations in a large number of genes affecting a person's risk of alcoholism. Some of these genes have been identified, including two genes involved in the metabolism of alcohol (*ADH1B* and *ALDH2*) that have the strongest known affects on the risk of alcoholism. Studies continue to reveal other genes in which variants affect the risk of alcoholism or related traits, including *GABRA2*, *CHRM2*, *KCNJ6* and *AUTS2*. As more variants are analysed and studies are combined for meta-analysis to achieve increased sample sizes, an improved picture of the many genes and pathways that affect the risk of alcoholism will be possible.

Edenberg, H. J. & Foroud, T. *Nat. Rev. Gastroenterol. Hepatol.* **10**, 487–494 (2013); published online 28 May 2013;
doi:10.1038/nrgastro.2013.86

Introduction

Alcohol (ethanol) is consumed by many people throughout the world. Taken in low amounts (up to one drink per day for women who are not pregnant or two drinks per day for men) it can have some beneficial effects, including reduced risk of cardiovascular disease and of all-cause mortality among middle-aged and older individuals.[1] However, excessive consumption (more than three drinks a day for women or four for men) of alcohol creates many serious problems, including physical, psychological and social problems. Alcohol use disorders (AUD) are risk factors for many other diseases and can worsen outcomes, including alcoholic cirrhosis, alcoholic pancreatitis, cancers of the upper gastrointestinal tract and liver, cardiovascular diseases, breast cancer, diabetes and foetal alcohol syndrome.[2] Men tend to drink more heavily and more frequently than women, putting them at increased risk of disease and death.[3,4] The WHO Global Status Report on Alcohol and Health[3] and The Global Burden of Disease Study 2010[4] both list alcohol as the third leading risk factor for death and disability. The WHO estimates that alcohol consumption causes ~2.5 million deaths per year, almost 4% of total deaths worldwide: 6.2% of all male deaths and 1.1% of all female deaths.[3]

Alcohol abuse and alcohol dependence are maladaptive patterns of drinking that cause repeated, serious problems for the drinker. According to a definition in the Diagnostic and Statistical Manual of Mental Disorders[5] (DSM-IV-TR, henceforth DSM-IV), individuals must meet at least three of seven criteria to be diagnosed with alcohol dependence (Table 1). Alcohol abuse is defined by meeting at least one of four criteria but not meeting criteria for dependence; the criteria for alcohol abuse are often met before the patient fulfils the criteria for alcohol dependence. On the basis of data from the 2001–2002 National Epidemiological Survey on Alcohol and Related Conditions (NESARC; a large general population sample from the USA), 3.8% of the US population met DSM-IV criteria for alcohol dependence and an additional 4.7% met DSM-IV criteria for alcohol abuse during the previous year.[6] A follow-up study in 2004–2005 showed that 4.4% of the US population met the criteria for alcohol dependence and an additional 5.3% met the criteria for alcohol abuse during the previous year.[7,8] When considering the lifetime risk of developing an AUD, the rates are increased: 12.5% of individuals meet the criteria for alcohol dependence at some stage during their life, and another 17.8% meet the criteria for alcohol abuse.[6]

The diagnostic criteria are being modified. Instead of separate categories for abuse and dependence, DSM-5 now uses AUD. This category requires an individual to meet at least two of 11 criteria, 10 of which are from DSM-IV, with the addition of alcohol craving (Table 1).[9] DSM-5 differentiates moderate AUD (two or three criteria) from severe AUD (four or more criteria). On the basis of the 2004–2005 NESARC dataset, 80.5% of the individuals who met criteria for DSM-IV alcohol dependence also met criteria for DSM-5 severe AUD.[7,8] In the NESARC 2004–2005 dataset, 10.8% of all individuals met the diagnostic criteria of AUD during the preceding year.[7,8] Similarly, the prevalence of AUD, as defined by DSM-5, was 9.7% in an Australian population sample.[10]

The genetics of alcohol dependence

Alcohol dependence (also termed alcoholism), the most severe AUD, is a complex genetic disease. Alcoholism has long been noted to run in families,[11,12] but that observation alone is not sufficient to demonstrate that genetic factors contribute to risk. Many independent lines of

Competing interests
The authors declare no competing interests.

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Key points

- Alcohol dependence is a common, complex genetic disease, with many variants in numerous genes contributing to the risk of developing this disorder
- Genes involved in alcohol metabolism have strong effects on risk; functional variants of *ADH1B* and *ALDH2* exist that protect against alcoholism, with ORs of 0.2–0.4
- Several other genes, including *GABRA2* and *CHRM2*, have been associated with alcohol dependence in many studies; evidence suggests numerous other genes affect the disease and traits associated with it
- As samples of increased size are assembled for meta-analyses and an extended range of alleles are tested, the roles of many additional genes will probably be uncovered
- Excessive alcohol consumption, particularly binge drinking, contributes to many other diseases, including cirrhosis and cancers of the upper aerodigestive tract, colon, rectum and liver
- Genes that alter how much alcohol a person consumes and how often affect the risk of many of these diseases

evidence point to genetic contributions to the aetiology of alcoholism. Adoption studies show that alcoholism in adoptees correlates more strongly with their biological parents than their adoptive parents.[13–16] Twin studies in the USA and Europe suggest that ~45–65% of the susceptibility to alcoholism is attributable to genetic factors.[11,17–19] Animal studies also demonstrate that genes are involved in alcoholism; mice and rats have been selectively bred for many traits associated with alcohol dependence, including alcohol preference, alcohol sensitivity and withdrawal sensitivity.[20,21] The ability to genetically select for these traits demonstrates that the traits have a genetic basis, and that different genes contribute to different aspects of the phenotype. Taken together, overwhelming evidence indicates that genetic variations contribute to the risk of alcohol dependence.

Even though genetic differences affect risk, no 'gene for alcoholism' exists, and both environmental and social factors make substantial contributions to a person's risk of alcoholism. Genetic factors affect the risk not only of alcohol dependence, but also the level of alcohol consumption and the risk of alcohol-associated diseases, including cirrhosis and cancers of the upper gastrointestinal tract. However, knowing that genetic factors affect risk does not mean that we know which specific variants contribute, or how. This area of research is very active, as new genes and variants are constantly being identified.

As for most complex diseases, alcohol dependence and AUDs are probably the result of variations in hundreds of genes, which interact with different social environments. An additional challenge in the search for genetic variants that affect the risk of AUDs is that extensive clinical heterogeneity is present among patients who meet the criteria. As the diagnosis of an AUD requires the presence of a set of symptoms from a checklist, many different ways to meet the criteria are possible. One could pick three criteria from seven (DSM-IV alcohol dependence) in 35 different ways and four from 11 (DSM-5 severe AUD) in 330 different ways. The clinical heterogeneity probably reflects the genetic heterogeneity of the disease. The difficulties of genetic studies are compounded by environmental heterogeneity in access to alcohol and social norms related to drinking.

Alcohol metabolism and the risk of AUD

The genes with the clearest contribution to the risk of alcoholism and high levels of alcohol consumption are alcohol dehydrogenase 1B class I, beta polypeptide *(ADH1B)* and aldehyde dehydrogenase 2 family (mitochondrial) *(ALDH2)*, two genes that are central to the metabolism of alcohol (Figure 1).[22] Alcohol is primarily metabolized in the liver, although some metabolism occurs in the upper gastrointestinal tract and stomach. The first step in ethanol metabolism is oxidation to acetaldehyde, catalyzed

Table 1 | Criteria for alcohol use disorders

Criteria	DSM-IV		DSM-5
	Alcohol abuse*	Alcohol dependence‡	Alcohol use disorder‖
Failure to meet major role obligations	Included	NA	Retained
Recurrent hazardous use	Included	NA	Retained
Recurrent alcohol-related legal problems	Included	NA	Omitted
Continued use despite recurrent social problems	Included	NA	Retained
Tolerance	NA	Included	Retained
Alcohol withdrawal (or drinking and/or taking drugs to avoid withdrawal)	NA	Included	Retained
Drinking more than intended	NA	Included	Retained
Unsuccessful attempts to cut down on use	NA	Included	Retained
Excessive time related to alcohol (obtaining, hangover)	NA	Included	Retained
Impaired social or work activities due to alcohol	NA	Included	Retained
Use despite known physical or psychological consequences	NA	Included	Retained
Alcohol craving	NA	Omitted	Included

DSM-IV is hierarchical: if an individual meets criteria for alcohol dependence that diagnosis is given; abuse is only diagnosed if the individual does not meet criteria for dependence. DSM-5 is subdivided into moderate (two or three criteria) and severe (four or more criteria) alcohol use disorder. *Defined as one or more of the criteria. ‡Defined as three or more of the criteria during 1 year. ‖Defined as two or more of the criteria. Abbreviation: NA, not applicable.

primarily by alcohol dehydrogenases; seven closely related alcohol dehydrogenases are clustered on chromosome 4.[22] The second step is metabolism of the acetaldehyde to acetate by aldehyde dehydrogenases; again, many aldehyde dehydrogenases exist, among which ALDH2 has the largest affect on alcohol consumption.[22]

Acetaldehyde is a toxic intermediate produced during alcohol metabolism, and systemic build-up of acetaldehyde results in unpleasant feelings such as dizziness, nausea and tachycardia. Individuals carrying just a single copy of the *ALDH2* 504E>K (*ALDH2*2* allele; rs671) display the 'Asian flushing reaction' when they consume even small amounts of alcohol. This reaction includes prominent facial flushing, tachycardia and nausea, and deters most individuals carrying this allele from excessive consumption of alcoholic drinks, although some individuals can drink large quantities of alcohol and develop alcoholism despite experiencing this reaction. *ALDH2* 504E>K is fairly common in east Asia, where up to 30–40% of Han Chinese people and Japanese people carry at least one copy. However, it is extremely rare in people who are not of Asian descent, with almost no individuals of European or African descent carrying this allele.[23–25]

Several studies have revealed the mechanism by which the *ALDH2* 504E>K allele works. The replacement of a glutamic acid residue at position 504 of the ALDH2 enzyme with lysine severely inhibits the enzyme's activity.[22,26,27] Most of the ALDH2 enzyme, which functions as a tetramer, is inactivated and degraded in people who carry even a single *ALDH2* 504E>K allele.[27] This inactivation leads to a major build-up of acetaldehyde in the circulation. The effect is similar to having disulfiram (a drug that blocks the action of aldehyde dehydrogenase, thus increasing sensitivity to alcohol) in one's system at all times. *ALDH2* 504E>K has repeatedly been demonstrated to have a protective effect against AUDs.[22,23,28,29] However, the protection against alcoholism afforded by a single copy of *ALDH2* 504E>K is not complete, and is affected by societal circumstances. Higuchi[30] demonstrated that the relative protection afforded by carrying a single copy of this allele declined dramatically in Japan between 1970 and 1992, a period that coincided with increased social pressure to drink alcohol as part of the business culture. The protection against alcoholism afforded by carrying two copies of the *ALDH2* 504E>K allele is essentially complete, with these individuals typically unable to consume more than a very small amount of alcohol before experiencing adverse events. The effects of the *ALDH2* 504E>K allele are a dramatic demonstration both of the strong effect a genetic variant can have on risk of alcohol dependence, and also of how the effects of a protective allele can be overridden by environmental and social factors.

The enzyme encoded by *ADH1B* (β-ADH), the cytosolic alcohol dehydrogenase with the highest concentration in adult livers, has three known functional variants.[22,31] The reference allele, with a frequency of >95% in populations of European descent, is generally known as *ADH1B* (*ADH1B*1*; known as *ADH2*1* in the older literature), and encodes an enzyme (β1-ADH) with arginine at positions 48 and 370. *ADH1B* 48R>H (*ADH1B*2*; rs1229984) encodes β2-ADH, with a histidine at position 48, and *ADH1B* 370R>C (*ADH1B*3;* rs2066702) encodes β3-ADH with cysteine at position 370. The β2-ADH and β3-ADH enzymes metabolize ethanol *in vitro* at 30–40-fold higher rates than does β1-ADH,[31] although the difference in ethanol metabolism in the liver of an individual carrying one of these alleles would be reduced as a result of the presence of other ADHs and the limitation of NAD/NADH recycling. A Japanese study of individuals checking into a hospital the day after heavy drinking showed that those with two copies of *ADH1B*1* had higher blood alcohol concentrations than those with at least one copy of *ADH1B* 48R>H, indicating that a measurable effect exists *in vivo*.[32] Although some individuals with the *ADH1B* 48R>H allele report flushing upon consuming alcohol, it does not approach the dramatic Asian flushing reaction caused by the *ALDH2* 504E>K allele, nor does it lead to the large increase in circulating levels of acetaldehyde characteristic of *ALDH2* 504E>K carriers. Nevertheless, the *ADH1B* 48R>H allele is nearly as protective as the heterozygous state of *ALDH2* 504E>K, with ORs for heterozygous carriers between 0.2 and 0.4.[22,23,33–35]

The faster metabolism of ethanol by β2-ADH and β3-ADH than β1-ADH is thought to produce at least a transient increase in levels of acetaldehyde in the liver, which in turn triggers an aversive reaction to alcohol. The protective *ADH1B* 48R>H allele is found at high frequencies in east Asia, with over 90% of people of Chinese or Japanese descent carrying at least one copy of the allele; it is found at low frequency in people of European and African descent (generally <5%), and

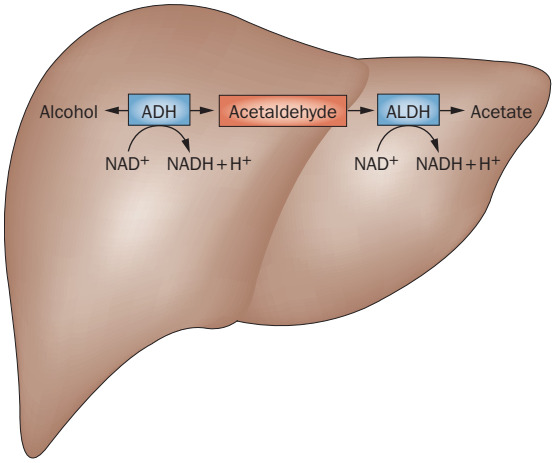

Figure 1 | Major pathway of alcohol metabolism. Ethanol is oxidized to acetaldehyde in a reversible reaction primarily in the cytosol, catalysed primarily by members of the alcohol dehydrogenase family of enzymes. The acetaldehyde is further oxidized to acetate, primarily by the mitochondrial aldehyde dehydrogenase ALDH2 with smaller contribution from cytosolic aldehyde dehydrogenases. The intermediate, acetaldehyde, is a reactive and toxic molecule. Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase.

at modest frequency (~20%) in populations of Middle Eastern descent.[28,36–38] As a result of its low allele frequency in Europeans, and its absence from arrays used in genome-wide association studies (GWAS), the effects of *ADH1B* 48R>H in people of European descent have, until the past few years, been hard to establish. A study published in 2012 demonstrated that *ADH1B* 48R>H has a similar effect on risk of alcoholism in European individuals as it does in Asian people, with an OR of 0.34 ($P = 6.6 \times 10^{-10}$).[34] *ADH1B* 370R>C is found almost only in populations of eastern African descent, where as many as half of the individuals might carry the allele; it is rare in populations from Europe or Asia. *ADH1B* 370R>C also has a protective effect against alcohol dependence,[39] but populations carrying this allele are understudied.

ALDH2 and *ADH1B* have the largest effect on risk of alcoholism of any known genes. Variants in other alcohol dehydrogenases have smaller effects, particularly *ADH1C* and *ADH4*, and reports exist of modest effects of other genes that code for aldehyde dehydrogenases.[22,35,39–41] However, studies have been complicated by the fact that many variants among the *ADH* genes are in high linkage disequilibrium (that is, they are frequently co-inherited). Another complication is that some of the functional variants with the strongest effects on drinking (*ADH1B* 48R>H, *ADH1B* 370R>C and *ALDH2* 504E>K) are rare in European populations, making many studies underpowered. Despite the strong effects of variations in these metabolism-related genes, they do not account for all of the genetic contribution to risk of alcoholism, particularly in populations (such as those from Europe) in which the allele frequencies for the variants with the strongest effects are very low.

Genetic risk of alcohol dependence

Several other genes have been shown to contribute to the risk of alcohol dependence and to several key endophenotypes (a measurable, heritable trait related to the disease, generally found at higher frequency even in family members who do not have the disease than in the general population). The earliest genes associated with alcohol dependence (for example, *GABRA2*) were typically identified as a result of family-based analyses. In most cases, studies recruited families containing multiple members with alcohol dependence (multiplex families); such families are likely to segregate variants that affect the risk of alcohol dependence. The most common initial approach was linkage analysis, in which markers throughout the genome were measured to identify chromosomal regions that segregate with the disease across many families.[42,43] Linkage studies are fairly robust to population differences in allele frequencies (because they test within-family inheritance), and can find a signal even if different variants in the same gene or region are responsible for the risk in different families. The drawback to this approach is that linkage studies find broad regions of the genome, often containing many hundreds of genes. In many cases, the initial linkage studies were followed by more detailed genetic analyses employing single nucleotide polymorphisms (SNPs) that were genotyped at high density across the linked regions.[39,44] Some of the genes identified through this approach have been replicated across a number of studies and seem to produce robust genetic findings.[45–52] Others have not yet been replicated.

GABRA2

Linkage analysis of multiplex families recruited in the Collaborative study on the Genetics of Alcoholism (COGA) identified a region on chromosome 4p that was linked to alcohol dependence;[42] linkage in this region was supported by other studies.[43] SNP genotyping was performed in candidate genes within the linked region—notably in the genes that encode $GABA_A$ receptors. A group of SNPs within the *GABRA2* (γ-amino butyric acid receptor A2) gene, which were in high linkage disequilibrium with each other (that is, tightly correlated), were associated with alcohol dependence and seemed to at least partly underlie the observed linkage finding.[44] This association has been replicated in many different samples of people with European[45–48] and African ancestry.[49] The finding was strongest in people with alcoholism who had early onset of alcoholism or comorbid drug dependence.[46,53] Evidence indicates that the association might extend beyond *GABRA2* and might also include the adjacent *GABRG1* gene.[50,51] Analyses raise the possibility that there might be distinct effects in each gene[49,50] or there might be long-range haplotypes that contribute to the risk of alcohol dependence.[51]

In parallel with analyses of alcohol dependence, the COGA investigators also examined the evidence of linkage with other alcohol-related phenotypes, such as electroencephalograms (EEG)-β. EEG-β are high frequency oscillations in electrical activity of the brain that are important in short-range neural communication. People with alcoholism have increased power in the β frequency of the electroencephalogram,[54,55] as do their offspring who have not been exposed to alcohol.[56,57] Thus, EEG-β is an endophenotype rather than simply a marker of excessive exposure to alcohol. Of note, the initial linkage peak on chromosome 4p was stronger with EEG-β than with alcohol dependence.[58,59] A set of SNPs in *GABRA2*, which overlapped with SNPs associated with alcohol dependence, was associated with this electrophysiological phenotype.[44] SNPs in *GABRA2* have also been associated with excess EEG fast activity in a sample of patients with alcohol dependence and control individuals from the UK.[60] SNPs in *GABRA2* are also associated with impulsiveness and variation in insula activity responses as measured in a functional MRI monetary incentive delay task.[48]

CHRM2

The muscarinic cholinergic receptor 2 gene (*CHRM2*) was also associated with alcohol dependence in a linkage study followed up by genotyping candidate genes in the region.[61] Other groups have replicated this finding,[52] and, like *GABRA2*, the effect seems to be strongest in people with alcoholism who have early onset of the disease or comorbid drug dependence.[62] Again, like *GABRA2*,

an electrophysiological endophenotype resulted in researchers focusing their studies on this gene.[63,64]

GWAS

With the advent of microarrays that can measure hundreds of thousands to millions of SNPs across the genome, GWAS provide a reasonably unbiased method to identify specific genes that contribute to a phenotype. To date, GWAS have focused on common variants, with allele frequencies of ≥5%. Most GWAS are case–control studies or studies of quantitative traits in unrelated participants; however, family-based GWAS provide an alternative approach. GWAS are beginning to yield robust findings, although the experience in many diseases is that very large numbers of patients will be needed. To date, individual GWAS on alcohol dependence and related phenotypes have been of fairly modest size, and most do not reach genome-wide significance. This feature might reflect both the limited sample sizes and the clinical and genetic heterogeneity of the disease. As noted previously, the functional *ADH1B* polymorphism is not represented on GWAS platforms; genes that encode GABA receptors are often nominally significant but well below genome-wide significance in these studies. Thus, the genes and SNPs found through GWAS have had little overlap with previous findings based on candidate genes and/or pathways and linkage analyses. In the following sections, we highlight a few studies and results that utilize key alcohol-related phenotypes and that illustrate several points. Rietschel and Treutlein[65] have recently published a comprehensive review of GWAS studies on alcoholism.

PECR

An initial GWAS of German male inpatients, followed by targeted genotyping of top SNPs and joint analysis provided evidence that alcohol dependence was associated with two SNPs in the 3' flanking region of peroxisomal trans-2-enoyl-coA reductase (*PECR*),[66] a member of the short-chain dehydrogenase family of enzymes. *PECR* is located within broad linkage peaks for several alcohol-related traits, including alcoholism,[67] comorbid alcoholism and depression,[68] level of response to alcohol[69] and amplitude of the P300 response (a neuronal feature related to decision-making).[70,71]

KCNJ6

A notable success in GWAS of alcohol-related endophenotypes focused on frontal θ band event-related oscillations (ERO). ERO are highly heritable neuroelectric correlates of cognitive processes that exhibit deficits in people with alcoholism and their offspring (who are at high risk of developing alcoholism and thus are a good endophenotype). Analyses in 117 families with high levels of alcohol dependence revealed genome-wide significant association of θ band ERO with several SNPs in *KCNJ6* ($P = 4.7 \times 10^{-10}$).[72] *KCNJ6* encodes a potassium inward rectifier channel, GIRK2, whose activation contributes to slow inhibitory postsynaptic potentials that modulate neuronal excitability, and therefore influences neuronal networks.[73,74] *KCNJ6* modulates opioid effects on analgesia and addiction in humans.[75] Animal models have shown that GIRK channels are directly activated by ethanol, are important effectors in analgesia induced by opioids and ethanol[75,76] and are considered a viable drug target.

AUTS2

A large meta-analysis of alcohol consumption (measured as g per day per kg body weight) in 12 European population-based samples detected genome-wide significant evidence ($P = 4 \times 10^{-8}$) of association with SNPs in the autism susceptibility candidate 2 (*AUTS2*) gene.[77] The association was supported by evidence that expression of *AUTS2* in human brain tissue was related to genotype, and that mouse lines selected for alcohol preference differed in their expression of *AUTS2*.[77] Furthermore, studies in *Drosophila melanogaster* found that downregulation of an *AUTS2* homologue resulted in reduced alcohol sensitivity.[77] Subsequent analyses suggest that the expression of *AUTS2* might be downregulated in individuals who are dependent on heroin, compared with control individuals.[78] The molecular function of *AUTS2* is not known.

IPO11–HTR1A

Some genes might contribute to an increased susceptibility to addictions in general. One study used a staged meta-analysis to explore comorbid alcohol and nicotine dependence and detected genome-wide evidence of associations with SNPs spanning a region on chromosome 5 that includes both *IPO11* (importin 11) and *HTR1A* (5-hydroxytryptamine [serotonin] receptor 1A, G protein-coupled).[79] Importins are involved in transport of proteins and RNA between the nucleus and cytoplasm, and serotonin has been implicated in many neural processes; HTR1A agonists reduce the anxiety-like behaviour induced by repeated ethanol withdrawals in rats.[80] Analyses of RNA expression in lymphoblastoid cell lines suggested that SNPs within this region on chromosome 5 had *cis*-acting regulatory effects on the expression of *HTR1A* or *IPO11*.

In the study of complex disorders, it has become apparent that quite large sample sizes, perhaps tens of thousands, are critical if robust association results are to be identified that can be replicated across studies. Unfortunately, studies of alcohol dependence have not yet attained these sample sizes. Meta-analyses, which combine results across a number of studies to attain the critical sample sizes needed, are being developed.

Genetics of alcohol-associated diseases

Alcohol affects a large number of diseases. A meta-analysis published in 2010 found that alcohol consumption was causally related to a large number of diseases, ranging from infectious diseases such as tuberculosis and pneumonia to cardiovascular diseases, cirrhosis and many cancers, particularly of the upper aerodigestive tract, colon, rectum and liver.[2] Genes that affect alcohol consumption can affect the risk of developing a disease

caused in part by alcohol.[31] They might raise the overall risk by increasing the likelihood that the carrier will drink heavily, or lessen the risk by reducing the propensity to drink heavily. Some alleles that reduce the likelihood of heavy drinking can, nevertheless, increase the risk of developing alcohol-associated disease in the subset of individuals who drink heavily even though they are carriers of the alleles.

The gastrointestinal tract is exposed to very high levels of alcohol as it passes through. Most ethanol also passes through the liver before entering the circulation. Alcohol levels in common drinks range from ~5% (1.1 M) for beer, 11–15% for wine (~3 M) and 40% for spirits (~9 M). The oral cavity and oesophagus are directly exposed to those levels, and the liver is exposed to high levels from the portal circulation. Thus, it is not surprising that the risk and severity of diseases of the gastrointestinal system, including cirrhosis, pancreatitis and cancers of the upper gastrointestinal tract, are affected by alcohol consumption.[81–87]

Evidence indicates that heavy episodic (binge) drinking, which results in exposure of tissues to high levels of alcohol, is particularly harmful.[82,88,89] Binge drinking is generally defined as a man consuming five standard drinks within 2 h; women are typically smaller and have a lower percentage of body water than men, so four standard drinks can reach similar alcohol levels. A standard drink is defined in the USA as 12 ounces of beer, 5 ounces of wine or 1.5 ounces of spirits, all of which are approximately equivalent to 14 g of pure ethanol. The strong effects of binge drinking suggest that merely calculating an average number of drinks per week will probably obscure many effects of alcohol, as it treats two standard drinks per day (14 per week) the same as seven drinks on each of 2 days per week.

As a result of their obvious relationship to the metabolism of alcohol in the body, studies have examined the relationship between genes encoding alcohol dehydrogenases and aldehyde dehydrogenases and several gastrointestinal diseases. Variants in *ADH* and *ALDH* genes that at least transiently increase acetaldehyde levels generally reduce the likelihood of heavy drinking and the risk of developing alcoholism, as noted above. However, among those who drink heavily despite this increase in acetaldehyde levels, the same genes might increase cancer risk by increasing levels of acetaldehyde in the tissues.[31,81,83–87] Studies have been complicated by the difficulty in disentangling these effects, and by the fact that many variants among the *ADH* genes are in high linkage disequilibrium.

Future directions

A whole spectrum of allele frequencies and effect sizes are now recognised to have potential roles in alcoholism, from common variations with small effects through to rare variants with large effects. As whole-exome and whole-genome sequencing technologies come down in cost, they are being applied to the identification of rare variants. For studies of rare variants, families are quite valuable for sorting out true positives from the background of individual variations that we all harbour.

Conclusions

Family studies have consistently demonstrated that genes make a substantial contribution to alcohol dependence. Over the past two decades, several genes underlying susceptibility have been identified. Extensive study of the genes involved in alcohol metabolism has demonstrated their important role in disease risk. Additional genes have been identified that have expanded our understanding of the genes and pathways involved; however, the number of findings to date is modest. Several reasons probably account for this paucity of data. First and perhaps foremost, most studies of alcohol-related phenotypes have been small, including just hundreds or a few thousand samples. Most robust associations that have been reported in common diseases have used tens of thousands of samples; several studies of this magnitude are now being combined into even larger meta-analyses. The alcohol research community has begun to form large consortia for meta-analyses and it is anticipated that with the resulting increase in sample sizes the number of robust associations will increase. A second approach that will probably benefit the alcohol research community will be increased examination of pathways or gene sets. These approaches have been quite fruitful for some studies and need to be employed in analyses of alcohol-related traits and phenotypes. Over the next few years, we anticipate the identification of additional common and rare variants that contribute to the risk of alcohol dependence.

Review criteria

In January 2013, we searched PubMed using the following search terms: “genome-wide association studies” combined with “alcoholism” and also with “alcohol dependence”. The references from initial papers identified were searched to identify additional references. From these, we chose key illustrative examples, and also refer the reader to a more detailed and comprehensive review of GWAS (Treutlein and Reitschel). We focused only on papers written in English.

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Acknowledgements

Related work in the authors' laboratories is supported by grants from the National Institutes of Health, AA008401, AA006460, AA020892, AA007611.

Author contributions

Both authors contributed equally to all aspects of this article.