Published in final edited form as:
Alcohol Clin Exp Res. 2018 December ; 42(12): 2281–2297. doi:10.1111/acer.13904.

Alcohol dehydrogenases, aldehyde dehydrogenases and alcohol use disorders: a critical review

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Abstract

Alcohol use disorders (AUD) are complex traits, meaning that variations in many genes contribute to the risk, as does the environment. Although the total genetic contribution to risk is substantial, most individual variations make only very small contributions. By far the strongest contributors are functional variations in two genes involved in alcohol (ethanol) metabolism. A functional variant in alcohol dehydrogenase 1B (*ADH1B*) is protective in people of European and Asian descent, and a different functional variant in the same gene is protective in those of African descent. A strongly protective variant in aldehyde dehydrogenase 2 (*ALDH2*) is essentially only found in Asians. This highlights the need to study a wide range of populations. The likely mechanism of protection against heavy drinking and AUD in both cases is alteration in the rate of metabolism of ethanol that at least transiently elevates acetaldehyde. Other *ADH* and *ALDH* variants, including functional variations in *ADH1C*, have also been implicated in affecting drinking behavior and risk for alcoholism. The pattern of linkage disequilibrium in the ADH region, and the differences among populations, complicate analyses, particularly of regulatory variants. This critical review focuses upon the *ADH* and *ALDH* genes as they affect AUDs.

Introduction

Alcohol use disorders (AUD) are common, complex disorders, the risk for which is contributed by genetic differences, environmental differences, and their interactions. AUDs lack an objective test. The current clinical definition (The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DSM-5) requires meeting at least 2 out of 11 criteria that reflect problems caused by consuming alcohol (American Psychiatric Association, 2013). The checklist definition means that theoretically one can meet DSM-5 criteria for AUD in 2036 different ways. Many studies have used DSM-IV definitions of alcohol dependence (AD; 3 or more of 7 criteria), which is more severe than a minimal DSM-5 definition, but still heterogeneous (99 possible combinations). This heterogeneity has obvious implications for the study of AUD. The requirement for alcohol consumption adds additional complexity,

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because there are large environmental differences in access to and acceptance of alcohol in different social groups and across time and location, and these can vary even within an individual's life. Average drinks per week is widely studied, but is highly skewed, with most people consuming less than 2 drinks per week and with a small fraction consuming very large quantities. It does not capture the pattern of drinking (e.g., bingeing). There is only a modest genetic correlation between average drinks per week and AUD (from 0.37 – 0.70) (Walters et al., 2018).

Ethanol is absorbed from the gastrointestinal tract, primarily in the small intestine, then travels to the liver, and from there is distributed throughout the body water (Hurley et al., 2002). The first step in the major pathway of its metabolism is oxidation to acetaldehyde by alcohol dehydrogenases (ADHs) (Figure 1). Metabolism by cytochrome P450s and catalase make only minor contributions (Hurley et al., 2002). Acetaldehyde binds readily to proteins, RNA and DNA, and can be aversive and toxic (Zakhari, 2006). Acetaldehyde is rapidly oxidized to acetate by aldehyde dehydrogenases (ALDHs). First pass metabolism (metabolism before the ethanol reaches the general circulation) occurs in the digestive tract and on its first pass from there through the liver. From then on, most metabolism occurs in the liver, catalyzed by ADH and ALDH enzymes[1]. Levels of ethanol can get high: the blood alcohol concentration that is defined as legal intoxication in the US (0.08%) corresponds to 17 mM ethanol. The oxidation of acetaldehyde is extremely efficient, such that circulating levels of acetaldehyde are usually more than 1000-fold less; they are generally barely detectable, ≤ 3 μM (Mizoi et al., 1994, Peng et al., 2014a, Harada et al., 1983, Nuutinen et al., 1984), although they are higher in liver (~15 μM after ingestion of 0.8 g/kg ethanol) (Nuutinen et al., 1984).

The contribution of genetic variants to risk for AUD is spread across a large number of genes, probably at least hundreds, that act through many pathways and interact with the environment (for recent reviews see (Edenberg and Foroud, 2013, Rietschel and Treutlein, 2013, Hart and Kranzler, 2015)). Most variants have very small effects on risk. This critical review will focus on the set of genes with the strongest effect on risk for AUD, the alcohol dehydrogenase *(ADH)* and aldehyde dehydrogenase *(ALDH)* genes. There is very strong evidence that variations in *ADH* and *ALDH* genes affect alcohol consumption and the risk for AUD.

Alcohol dehydrogenases

There are 6 closely related ADHs whose structure and enzymology have been studied; a seventh (ADH6) has not been found as a protein *in vivo* (Table 1) (Bosron et al., 1993, Hurley et al., 2002, Edenberg and Bosron, 2018). Their pattern of expression in tissues differs (Figure 2). ADH1A, ADH1B, and ADH1C are called class I ADHs; they are more than 90% identical in amino acid sequence, and can hetero-dimerize with each other. These three ADHs have K_m for ethanol in the range of 0.013 to 27 mM (Chi et al., 2018, Hurley et al., 2002, Hurley and Edenberg, 2012) (Table 1), and carry out most of the ethanol oxidation in liver. The other ADH enzymes function as homodimers. When ethanol levels are high

[1] *Genes* are in *italics*, proteins in roman font.

(e.g., intoxicating), ADH4 could contribute substantially, perhaps 1/3 of the overall metabolism (Lee et al., 2004), although a recent model shows a smaller contribution (Chi et al., 2018). ADH7 is the only ADH enzyme not expressed in liver; it contributes to ethanol oxidation and local generation of acetaldehyde primarily in the stomach and esophagus. ADH5 is ubiquitously expressed; although it doesn't make a major contribution to ethanol oxidation in liver, it can contribute to metabolism in other tissues, including the GI tract and brain, and thereby generate acetaldehyde locally. ADH6 has never been isolated from human tissue, although its RNA is present; computational modeling suggests it is likely to be both highly unstable and inactive (Ostberg et al., 2016) and therefore not likely to impact alcohol metabolism.

The *ADH* region of the genome (Figure 3) arose from repeated gene duplication, and many genetic variations in this region are in high linkage disequilibrium (LD), i.e. are inherited together. There are many and often large ethnic differences in allele frequencies and LD patterns. For example, out of 110 SNPs analyzed in a set of European-American and African-American families, 88 had minor allele frequencies (MAF) that differed between the two groups by more than 0.05 (Edenberg et al., 2006) (Table 2). These factors complicate interpretation of the genetic association data and emphasize that it is important to separately analyze different populations and combine data only at the meta-analysis stage.

ADH1B

The kinetic properties of ADH1B and its high levels of expression in liver suggest that it has the largest impact on alcohol consumption and the risk for alcohol dependence; several aspects were reviewed recently (Polimanti and Gelernter, 2018, Edenberg and Bosron, 2018). It is among the top 100 genes expressed in liver, adipose and mammary tissues. It is expressed at lower levels in many other tissues, but at barely detectable levels in brain and whole blood (Figure 2). There are many single nucleotide polymorphisms (SNPs) that affect its expression in one or more tissues (eQTLs), with many concentrated in the region between *ADH1C* and *ADH7* and others between *ADH4* and *ADH6* (Supplementary Figure 1; all eQTL data are from gtexportal.org (GTEx Consortium, 2013)); many of these SNPs are in strong LD.

There are 3 isoforms of ADH1B that are relatively common in at least some populations. The ADH1B enzyme with arginine at both positions 48 and 370[2] is commonly known as ADH1B*1 (in earlier literature it is called β1-ADH or ADHB*1; Table 1). ADH1B*1 metabolizes ethanol at the slowest rate among the 3 isoforms. It is the most common isoform globally except in much of East Asia, and is the form to which others are compared. The isoform with histidine at position 48 is called ADH1B*2 (β2-ADH or ADHB*2), and differs only due to rs1229984. *In vitro*, ADH1B*2 oxidizes ethanol much faster than ADH1B*1 (Table 1). Computer modeling suggests that at 17 mM ethanol, ADH1B*2 homodimers could oxidize ethanol at about 11 times the rate of ADH1B*1 homodimers (interpolated from (Chi et al., 2018)); heterodimers behave as equal mixtures of the homodimers (Edenberg and Bosron, 2018). The difference in metabolic rate is much smaller *in vivo*, due

[2]Current nomenclature counts from the initiating methionine of the initially synthesized peptide. Older literature and the protein database count from the first amino acid of the mature protein, and therefore calls these 47 and 369

to contributions of the other ADH enzymes and limitations by cofactor levels. Neumark et al. (Neumark et al., 2004) found a small (~14%) but significant difference in alcohol elimination rate between subjects of European descent with at least one *ADH1B*2* allele compared to those homozygous for *ADH1B*1*; there was an apparently linear relationship with the number of *ADH1B*2* alleles, but the number of *ADH1B*2* homozygotes tested was too small for that difference to reach significance. *ADH1B*2* increased the frequency of facial flushing in Asians, although the intensity of the flushing was not nearly as great as caused by *ALDH2*2* alleles (Takeshita et al., 1996).

The isoform with cysteine at position 370, called ADH1B*3 (β3-ADH or ADHB*3), differs from ADH1B*1 due to rs2066702. The turnover number for ADH1B*3 is more than 60-fold that of ADH1B*1 *in vitro* (Table 1); at 17 mM ethanol, ADH1B*3/*3 could oxidize ethanol at about 3 times the rate of ADH1B*1/*1 (interpolated from (Chi et al., 2018)). There are only 2 other coding variants with frequencies over 1%, and these have not, in general, been studied for any *ADH* (Supplementary Information).

ADH1B*2

The kinetic properties of ADH1B*2 and its high frequency in China and Japan (~0.70, Table 2) prompted candidate gene studies founded upon the hypothesis that a variant that affects alcohol metabolism would affect drinking behavior and thereby the risk for AD. Thomasson et al. (Thomasson et al., 1991) found the protective effect of *ADH1B*2* was strong (allelic odds ratio (OR) = 0.33) in male Chinese, and independent of that of *ALDH2*2* (the inactive aldehyde dehydrogenase; see below). This was followed by many candidate gene studies and meta-analyses in Asian populations. Wherever the frequency of *ADH1B*2* was high enough, the same result was obtained: presence of a single *ADH1B*2* allele strongly reduced the risk for alcoholism, and in those homozygous for *ADH1B*2*, the risk was even further reduced (Chen et al., 1999b, Luczak et al., 2006, Whitfield, 2002, Li et al., 2011, Zintzaras et al., 2006, Park et al., 2013)[3].

There is heterogeneity among Asian populations in the allele frequency and in the strength of the protection. Han Chinese and Japanese men show the strongest protection (the OR for heterozygotes = 0.18–0.26) (Whitfield, 2002, Chen et al., 1999b, Luczak et al., 2006, Park et al., 2013). Logistic regression of combined *ADH2* and *ALDH2* genotypes in Han Chinese found that in the presence of active ALDH2 (*ALDH2*1* homozygosity), a single *ADH1B*2* allele gave an odds ratio (OR) of 0.22, and two *ADH1B*2* alleles gave OR = 0.14, both with $p<10^{-6}$ (Chen et al., 1999b). Minority populations in Asia show less protection (Shen et al., 1997, Thomasson et al., 1994). Meta-analyses that lump all Asian groups show less protection (OR ~ 0.4; $p = 10^{-33}$ to 7×10^{-42}) (Zintzaras et al., 2006, Li et al., 2011, Luczak et al., 2006, Whitfield, 1997). Because drinking was not as common among Asian women, their overall risk was less and therefore the protective effect were also less (Luczak et al., 2006, Zintzaras et al., 2006).

In a small genome-wide association study (GWAS) plus follow-up in Koreans, rs1229984 *(ADH1B*2)* gave by far the strongest association with AD (OR = 0.42; $p = 2.6\times10^{-21}$), and

[3]References to many earlier studies are in the reviews cited.

once conditioned on rs1229984, no other associations in the region remained significant (Park et al., 2013). In a GWAS among methamphetamine dependent subjects and users in Thailand, rs1229984 was associated with the count of DSM-IV AD symptoms ($p = 2.7\times10^{-5}$) (Gelernter et al., 2018). Rs1229984 was associated with drinking *vs.* non-drinking in Japan (OR = 1.20, $P < 3.6 \times 10^{-4}$) (Takeuchi et al., 2011). Surprisingly, the East Asians in a US study did not show a significant effect of *ADH1B*2* on alcohol consumption (Jorgenson et al., 2017), perhaps due to low overall consumption.

The frequency of *ADH1B*2* is very low in most European populations and near zero in African populations (Table 2), making studies of *ADH1B*2* outside Asia difficult. An exception is among individuals of Middle Eastern descent (Li et al., 2007), and small studies have shown that the presence of *ADH1B*2* in individuals of Jewish descent (MAF ~ 0.2) was associated with reduced consumption, binge drinking, risk, and severity of alcoholism (Hasin et al., 2002, Meyers et al., 2015, Carr et al., 2002, Neumark et al., 1998). Early meta-analysis of small European studies showed that *ADH1B*2* was protective, with an OR of 0.28 in men and 0.41 in women (p = 0.0016) (Borras et al., 2000) or 0.47 (Whitfield, 2002). It was also protective in Mexican Americans (OR = 0.28) (Ehlers et al., 2012).

Stronger evidence for association of rs1229984 with alcohol-related phenotypes in individuals of European descent began to accumulate from larger studies. In Denmark, *ADH1B*2* was associated with hospitalization for AD (OR = 0.26 in men, 0.37 in women) and with fewer drinks/week and less heavy drinking in both men and women (Tolstrup et al., 2008, Linneberg et al., 2010). Germans with an *ADH1B*2* allele drank less per day than those without (Drogan et al., 2012), and *ADH1B*2* was strongly associated with AD ($p=1.8\times10^{-9}$) (Treutlein et al., 2014). A US study showed the protective effect of *ADH1B*2* on risk for AD was close to that seen in East Asians (OR = 0.34, $p= 6.6\times10^{-10}$) and reduced the maximum drinks in a 24 h period ($p=3\times10^{-13}$) (Bierut et al., 2012). A study in Great Britain showed a similar effect, OR = 0.26 *vs.* all controls, 0.19 *vs.* screened controls ($p=2.7\times10^{-8}$) (Way et al., 2015).

In European Americans, rs1229984 was associated with Maxdrinks ($p = 6\times10^{-15}$)(Hart et al., 2016) (Xu et al., 2015) and with the number of DSM-IV and DSM5 criteria ($p = 1.4\times10^{-13}$, 5.3×10^{-14} respectively), among which withdrawal was the strongest (Hart et al., 2016). In Australian twins, 97% of European descent, those carrying an *ADH1B*2* allele reported more flushing after consuming small amounts of alcohol ($p = 8.2\times10^{-7}$), a lower number of Maxdrinks ($p = 2.7\times10^{-6}$), lower total alcohol consumption ($p = 8.9\times10^{-8}$), and fewer DSM-IIIR symptoms of dependence (p = 0.0016) (Macgregor et al., 2009). Jorgenson et al. found rs1229984 was associated with drinker *vs.* nondrinker status in Americans of both European ($p=2.5\times10^{-20}$) and Hispanic ($p=4.4\times10^{-7}$) descent, and with average drinks per week ($p=1.9\times10^{-35}$ in EA and 2.6×10^{-6} in Hispanics) (Jorgenson et al., 2017). In a Spanish cohort selected for heavy alcohol consumption and matched controls, *ADH1B*2* was associated with protection from heavy drinking in both men (OR = 0.19, $p = 4.8\times10^{-10}$) and women (OR = 0.48 p = 0.0067); other ADH SNPs were not significant when conditioned upon rs1229984 (Munoz et al., 2012). Interestingly, rs12299842 was recently associated with attendance at a pub or social club in Great Britain ($p = 4.2 \times 10^{-25}$) (Day et al., 2018).

A meta-analysis provided strong evidence for association of *ADH1B*2* with AD ($p=1.2\times10^{-31}$) and symptom count ($p=1.9\times10^{-23}$) (Gelernter et al., 2014). The latest and largest meta-analysis to date also provides strong evidence for the association of *ADH1B*2* with AD in individuals of European ancestry, $p= 9.8\times10^{-13}$ (Walters et al., 2018).

Data on rs1229984 are not available in many GWAS, because it was not included in many genotyping arrays, is not well imputed, its MAF in Europeans falls below the usual cutoff (0.05), and it may fail QC due to differences in MAF among subgroups that lead to apparent violation of Hardy-Weinberg equilibrium (e.g. (Clarke et al., 2017)). In the PGC-SUD meta-analysis, there are data on rs1229984 in only 40% of the subjects (Walters et al., 2018). Thus, in some studies the strongest association of AD is with other SNPs that are in LD with rs1229984.

An initial study from the UK Biobank found 4 SNPs across the *ADH* region were associated with alcohol consumption, rs145452708, rs29001570, rs35081954, and rs193099203; rs1229984 was not tested because it deviated from Hardy Weinberg equilibrium (Clarke et al., 2017). Their findings at least in part reflect the effects of *ADH1B*2*, since the associated SNPs are in LD with rs1229984 (D' = 1, 0.74, 0.91, 0.56, respectively, based on 5 EUR populations, Table 2). In a later UK Biobank GWAS of a partially overlapping sample, *ADH1B*2* was very strongly associated with total AUDIT score ($p = 5.8\times10^{-72}$), AUDIT-C (items 1–3, consumption; $p = 2.6\times10^{-56}$), and AUDIT-P (items 7–10, problems; $p = 9.9\times10^{-46}$) (Sanchez-Roige et al., 2018). Conditioning the analysis on rs1229984 rendered other nearby SNPs (except rs13107325) no longer significant, demonstrating that the signal derived from *ADH1B*2* (Sanchez-Roige et al., 2018). Meta-analysis of AUDIT scores in the UK biobank and 23andme participants of European ancestry (rs1229984 was not available in 23andme (Sanchez-Roige et al., 2017)) showed rs138495951, in *ADH1B*, was strongly associated with total AUDIT score ($p = 10.7\times10^{-36}$) (Sanchez-Roige et al., 2018); that SNP (and other associated SNPs in the region) is in LD with rs1229984 (D' = 1; $r^2 = 0.54$) (Supplementary Figure 2)

The effects of an allele even as strong as *ADH1B*2* can be modulated by the environment: the delayed age of first intoxication and first DSM5 symptom in adolescents was reduced if most of their friends drink (Olfson et al., 2014). *ADH1B*2* has a stronger effect on alcohol consumption and risk for AUD among those who experience childhood adversity (Meyers et al., 2015).

ADH1B*3

*ADH1B*3* is found almost exclusively in individuals of African origin (Table 2). Individuals with an *ADH1B*3* allele (ADH1B*369Cys; rs2066702) metabolize ethanol somewhat faster than those with only *ADH1B*1* alleles (Thomasson et al., 1995). Within Africa and in African Americans, allele frequencies for *ADH1B*3* range from 0.09 to 0.28; in other populations it is essentially absent (Table 2). There are many fewer studies of African populations, an omission that needs to be corrected.

*ADH1B*3* has a significant protective effect on risk for alcoholism in African Americans (Edenberg et al., 2006, Gelernter et al., 2014, Walters et al., 2018), and Afro-Trinidadians

(Ehlers et al., 2007), and with AD and withdrawal symptoms in Native Americans in southwest California (Wall et al., 2003, Gizer et al., 2011). It appears to be protective against fetal alcohol syndrome, likely by reducing consumption (Warren and Li, 2005, Scott and Taylor, 2007). In a GWAS of African-Americans, rs2066702 was associated with the number of DSM-IV and DSM5 criteria ($p = 1.9\times10^{-9}$, 1.4×10^{-9}, respectively), among which tolerance was the strongest, and with maxdrinks ($p = 6.4\times10^{-8}$) (Hart et al., 2016). A meta-analysis of that sample plus samples from SAGE (Bierut et al., 2010) found strong association with alcohol dependence (OR ~ 0.7; $p = 3.7\times10^{-13}$), DSM-IV symptom counts ($p = 6.3\times10^{-17}$) (Gelernter et al., 2014), and Maxdrinks ($p = 2.5\times10^{-10}$) (Xu et al., 2015). The most recent meta-analysis of African Americans (n = 6280) showed association of *ADH1B*3* with AD ($p = 2.2\times10^{-9}$) (Walters et al., 2018). Many SNPs extending across most of the ADH region, from *ADH1C* to past *ADH5*, are in LD with rs2066702, and provided supporting evidence (Supplementary Figure 2).

ADH1C

ADH1C is expressed at modest levels in liver (1/3 that of *ADH1B*), and to a smaller extent in stomach, with little expression in other tissues (Figure 2). There are two major isoforms of ADH1C, and they differ at 2 sites simultaneously: ADH1C*1 (γ1 ADH, ADH1C[Arg272; Ile350]) and ADH1C*2 (γ2 ADH, ADH1C[Gln272;Val350]). The Arg/Gln at position 272 is encoded by rs1693482 and the Ile/Val at 350 by rs698. *In vitro* kinetic assays show ADH1C*1 is about 1.5 to 2-fold more active than ADH1C*2 (Hurley et al., 2002, Chi et al., 2018) (Table 1). These kinetic differences are almost certainly due to the difference at amino acid 272 (Arg/Gln; rs1693482). Most genetic literature focuses on the other SNP, rs698, for historic and technical reasons (Xu et al., 1988). This does not affect conclusions, because Arg272 is virtually always found together with Ile350, and Gln272 with Val350: the correlation between these SNPs is complete ($r^2 = 1.0$) in 24 of the 26 populations in the 1000 genomes database, and nearly so in the other 2 ($r^2 = 0.97$ in ITU, 0.93 in YRI). Thus measuring either SNP gives essentially the same information. Many other SNPs are highly correlated with rs698/rs1693482. In both Asians (e.g. CHB) and European-Americans (e.g. CEU) more than 100 SNPs with $r^2>0.90$ span a 38 kb region that also covers much of *ADH1B*.

The association of *ADH1C* with alcohol dependence is less robust than that of *ADH1B*. *ADH1C*2* is associated with AD and consumption in East Asians (e.g. (Thomasson et al., 1991, Thomasson et al., 1994, Matsuo et al., 2007)), where *ADH1C*1* (the higher activity, protective form) is at high frequency (Table 2) and tends to travel with *ADH1B*2* (higher activity, protective); D' = 0.78 in CHB+JPT. The LD pattern led to suggestions that the evidence for an effect of *ADH1C*1* independent of *ADH1B*2* was weak (Osier et al., 1999, Chen et al., 1999b, Choi et al., 2005). A meta-analysis suggested that *ADH1C*1* was protective (OR = 0.52) (Zintzaras et al., 2006). A later meta-analysis found stronger evidence that *ADH1C*1* was protective against AD in Asians (OR = 0.47, $p = 4\times10^{-33}$) but was not significant in Europeans (Li et al., 2012a). Neither meta-analysis explicitly examined whether the effect was independent of *ADH1B* genotype.

In people of European origin, where *ADH1B*2* is at very low frequency, there is less confounding. Several studies have shown no (Neumark et al., 2004, Luo et al., 2006b, Borras et al., 2000) or only nominal (Edenberg et al., 2006, Agrawal et al., 2011, Kuo et al., 2008, Li et al., 2012a) allelic association between AD and rs698, rs1693482 or rs1789891 (D' = 1) in Europeans. In a GWAS of a factor score derived from symptoms of alcohol dependence among controls from a study of schizophrenia, no SNP reached significance, but the strongest result from a candidate-gene-based analysis was *ADH1C* (p = 0.003 in European-Americans)(Kendler et al., 2011); this was not a finding for a single SNP, but rather a group of SNPs in the region.

Several more recent studies have provided evidence for an independent effect of *ADH1C*1* on alcohol dependence, but extensive LD in the *ADH* region has led to associations of different SNPs. A GWAS and follow-up of key SNPs in German males with early onset alcohol dependence provided evidence of association of rs1614972 (in LD with rs698 and rs1693482, D'=1, r^2 = 0.31) with AD ($p = 1.4\times10^{-4}$) but it did not withstand correction for multiple testing (Treutlein et al., 2009). Enlarging that sample provided genome-wide significant evidence for association of a different SNP, rs1789891 (D' with rs1693482 =1, r^2 = 0.22) with alcohol dependence (1.3×10^{-8}, OR[4] = 0.68) (Frank et al., 2012). A follow up of SNPs from the Treutlein study and provided limited statistical support (p=0.0017) for association of rs1614972 with AD in a different population (OR = 0.8) (Biernacka et al., 2013). Rs1789891 was associated with alcohol dependence in a study of British and Irish ($p = 7.2\times10^{-5}$; OR =0.71), and the association remained significant when conditioned on rs1229984 (*ADH1B*2;* $p = 1.7\times10^{-4}$) (Way et al., 2015). In the PGC-SUD trans-ancestral meta-analysis, rs1789912 was associated with alcohol dependence ($p = 1.47\times10^{-9}$) (Walters et al., 2018); it is in complete LD with rs698/rs1693482 (r^2 = 1). In analyses of Europeans, conditional on *ADH1B*2*, the 2 SNPs that define *ADH1C*1* and 2 others (rs1789912, rs1154445; $p_{conditional} = 7.7\times10^{-4}$, 1.7×10^{-4}) that were in complete LD (r^2 = 1) with them retained some evidence of association (Walters et al., 2018).

A GWAS on AUDIT score in a basically healthy European-American (EA) population provided evidence for association with rs141973904, an uncommon allele (MAF = 0.016) in *ADH1C* ($p = 4.4\times10^{-7}$) (Sanchez-Roige et al., 2017). The minor allele of rs141973904 is found with the allele of rs1693482 that encodes *ADH1C*1* (D'=1) but because of the large difference in allele frequencies their correlation is very low (r^2 = 0.01). Rs141973904 is also in high LD with rs1229984 (*ADH1B*2;* D' = 1, r^2 = 0.54), which was not available for testing but might well have been the functional allele responsible for the finding.

Association with alcohol consumption among Europeans has given mixed results. A study of alcohol elimination in Australian twins did not find evidence for an effect of either rs698 or rs1693482 (Birley et al., 2009), but a later study showed an effect of rs1693482 on maxdrinks that was still nominally significant after controlling for rs1229984 ($p=7\times10^{-4}$, with 50 SNPs tested) (Macgregor et al., 2009). Several studies reported no independent effect of *ADH1C*1* on average drinking (Latella et al., 2009, Drogan et al., 2012) or upon

[4]Some report the OR for *ADH1C**2 (risk allele), but to be consistent with how we discuss *ADH1B*, these have been converted to show the OR for the protective allele.

likelihood of very heavy drinking (Munoz et al., 2012). In a meta-analysis of average drinking (g/kg/day) among Europeans, rs1789891 was nominally significant ($p = 1.2\times10^{-3}$) if controls were restricted to drinkers (Schumann et al., 2011). A larger follow-up showed suggestive evidence for association of SNPs in the *ADH* region (1.4×10^{-6} to 8.5×10^{-5}), most in *ADH1C* and *ADH7* (Schumann et al., 2016); many of those SNPs were in complete LD with rs698 ($r^2>0.99$, D'=1) and also in LD with rs1229984 (D'>0.9). A large study in Denmark found an association of rs698 with heavy drinking in both men and women (OR for *ADH1C*1* ~ 0.75), excessive drinking in men (OR = 0.63) and hospitalization for AD in women (OR = 0.71 – 0.45 for heterozygotes and homozygotes) (Tolstrup et al., 2008); secondary analysis excluding individuals carrying *ADH1B*2* gave similar results.

Overall, there is evidence that *ADH1C*1* is protective against alcohol dependence, but the LD in the region, particularly across *ADH1B* and *ADH1C*, makes interpretation of many of the studies difficult. In particular, the high LD with *ADH1B*2* (D' = 0.91 in Europeans, although r^2 is low) is generally not acknowledged. Given the strong effect of *ADH1B*2* on these phenotypes conditional analyses are important. Another way to disambiguate the situation would be to separately analyze the data in the large group without any *ADH1B*2* alleles, as was done in the Danish study (Tolstrup et al., 2008).

ADH4

ADH4 (π-ADH) has K_m for ethanol of 34 mM (Table 1). Its expression is relatively high in liver and extremely low elsewhere. A paradox is that there are over 5500 eQTL for *ADH4*, but all are in tissues in which expression is extremely low; there are no significant eQTLs affecting the expression of *ADH4* in liver. There are few coding variants in *ADH4*, one of which (Ile309Val, rs1126671) affects the stability of the enzyme and its binding of ethanol (Stromberg et al., 2002); it is relatively common in Europeans (MAF = 0.30) and Africans (MAF=0.14) but rare in East Asians (MAF ~ 0.001).

In a family-based study that used the pedigree disequilibrium test, 12 SNPs in and near *ADH4* were associated with DSM-IV-defined alcohol dependence in European American families; the top SNP was rs4148886 (Edenberg et al., 2006). Eleven of the SNPs are in LD and mark a region from intron 1 past the 3' untranslated region that contains many additional SNPs (Edenberg et al., 2006). Neither of 2 non-synonymous SNPs, rs1126671 and rs1126673 nor a functional promoter SNP, rs1800759 (Edenberg et al., 1999) were significant, although rs1800759 had been in an earlier study in Brazil (Guindalini et al., 2005). None of a set of 7 SNPs (in nearly complete LD) showed significant association, but deviation from Hardy-Weinberg equilibrium in European Americans suggested a recessive effect; there was no evidence for association in African Americans (Luo et al., 2006a). In the Irish, there was no association of *ADH4* with AD (Kuo et al., 2008). A rare variant downstream of *ADH4* (rs187709743) was associated with symptom count in American Indians (Peng et al., 2017). An Australian study found suggestive evidence for association of rs1800759 with lifetime maxdrinks (p = 0.0075), frequency of drinking (p = 0.0055), and total consumption (p = 0.0023), and of rs3762894 with maxdrinks during the past year (p = 0.00048) and usual number of drinks (p = 0.00078) (Macgregor et al., 2009). The evidence dropped substantially after conditioning on *ADH1B*2*, but some evidence for association of

rs3762894 with maxdrinks remained (p = 0.004) (Macgregor et al., 2009). In Koreans, several *ADH4* SNPs were significant, the best being rs3805322 ($p = 2.0\times10^{-13}$); however conditioning the analysis on *ADH1B*2* genotype reduced all of the SNPs to not significant (p>0.23) (Park et al., 2013).

ADH5

ADH5 encodes χ-ADH (Table 1), which is also a glutathione-dependent formaldehyde dehydrogenase. *ADH5* is the most widely expressed of the *ADHs*, present in essentially all tissues (Figure 2). It has very low affinity for ethanol, but mouse studies suggest that its role might be more significant than originally thought when alcohol levels are high (Haseba and Ohno, 2010). In a small study of first pass metabolism, ADH5 made a contribution when the concentration of alcohol ingested was high (40%) (Dohmen et al., 1996).There are 2667 eQTLs affecting expression of *ADH5* in various tissues, 221 in liver and 228 in cerebellum.

A number of studies have provided modest evidence for association of SNPs in the *ADH4-ADH5* region with AD (Edenberg et al., 2006) (Kuo et al., 2008) (Kendler et al., 2011) (Luo et al., 2006b). A key issue to keep in mind is that there is a very strong LD block that extends across *ADH4* and *ADH5*, so findings in *ADH5* might relate to effects in *ADH4*, to regulatory effects on other genes, or to LD with rs1229984 in *ADH1B*. In a Korean GWAS, the initial evidence for association of 2 SNPs in *ADH5* with AD disappeared when conditioned on *ADH1B*2* (Park et al., 2013).

ADH7

ADH7 (σ-ADH or μ-ADH; Table 1), is the only member of the ADH family that is not expressed in liver (Figure 2). It has a high turnover number, and its high Km suggests it will be most active when ethanol concentrations are high, as they are during ethanol consumption in the esophagus (where its level of expression is affected by 62 eQTLs) and stomach, precisely its locations. A small study showed a significant contribution of ADH7 to first pass metabolism, particularly after low concentrations of oral ethanol (Dohmen et al., 1996).

A single SNP in *ADH7* (rs284786) was nominally associated with a DSM-IIIR-based definition of alcohol dependence (Edenberg et al., 2006), one downstream of ADH7 was suggestively associated with AD in Mexican-Americans (Norden-Krichmar et al., 2014), and several in that region were associated with maxdrinks in Native Americans (Peng et al., 2014b). Analysis of alcohol levels after an oral alcohol challenge with 103 SNPs across the *ADH* region showed early effects from SNPs in and near the 5' region of *ADH7* through intron 6, with only nominally significant effects of SNPs across the region between *ADH7* and *ADH1A* (Birley et al., 2009). In a meta-analysis of average drinking (g/kg/day) among Europeans the most significant SNP in the *ADH* region was rs2584448 in *ADH7* ($p=3.9\times10^{-4}$); when the analysis restricted the controls to drinkers, the top SNP was rs2165672, also in *ADH7* (Schumann et al., 2011), neither was genome-wide significant.

ADH1A:

ADH1A is expressed at lower levels in liver than *ADH1B* or *ADH1C*, and is barely expressed in other adult tissues (Figure 2). *ADH1A* is expressed early in fetal development,

and may play a role there (Smith et al., 1971). Coding variations are essentially non-existent, with none having an allele frequency of 1% or above in any population studied (Lek et al., 2016). The lack of coding variants and low level of expression in adults suggests that variations in *ADH1A* are not likely to play major roles in affecting risk for alcoholism. There is nominal evidence that several SNPs are associated with AD (Edenberg et al., 2006, Kuo et al., 2008) but that is likely due to LD with SNPs in *ADH1B*.

ADH Regulatory variants

The strong effect of *ADH1B* and *ADH1C* coding variants may obscure more modest effects of regulatory variants. Coding SNPs that lead to more active ADH enzymes are protective, so it is logical to anticipate that regulatory variants that increase expression of those enzymes have a similar, if more modest, effect. Individual SNPs and haplotypes have been shown to affect expression of *ADH* genes, including *ADH1B* (Pochareddy and Edenberg, 2011), *ADH1C* (Chen et al., 2005), *ADH4* (Edenberg et al., 1999, Pochareddy and Edenberg, 2010), and *ADH7* (Jairam and Edenberg, 2014a, Jairam and Edenberg, 2014b). Some mapped regulatory elements that affect ADH1B expression in liver-derived cells lie in the region between *ADH1B* and *ADH7* (Chen et al., 2005, Jairam and Edenberg, 2014a, Jairam and Edenberg, 2014b). There are many eQTLs, extending broadly across the region, that affect expression of one or more *ADH* genes. These differ in different tissues; for example, in subcutaneous adipose there is a dense cluster between *ADH7* and *ADH1C* and a small cluster over 700 kb away, whereas in visceral adipose there is a cluster between *ADH4* and *ADH6*, extending beyond *ADH5* (Supplementary Figure 1).

The large trans-ethnic meta-analysis of subjects of European and African descent carried out by the Psychiatric Genomics Consortium Substance Use Disorders working group (PGC-SUD) found that rs10516440 (associated with AD at $p = 9.9\times10^{-8}$; p conditioned on rs1229984 $=7.4\times10^{-5}$) was a significant eQTL for *ADH1B* in a trans-tissue analysis ($p = 1.4\times10^{-76}$, gtexportal.org), although only nominally significant in liver (Walters et al., 2018). The major allele of rs10516440 (A) was associated with increased *ADH1B* expression and reduced AD risk, concordant with the expected direction.

ADH results to date

There is very strong evidence, both biochemical and genetic, that two coding variants in *ADH1B* that affect its kinetic properties (rs1229984 and rs2066702; *ADH1B*2* and *ADH1B*3* respectively) affect alcohol consumption and risk for alcohol dependence. Their effect on risk for AD is among the strongest of any variant. There is also good evidence for an independent effect of a coding variant in *ADH1C* (rs698 and rs1693482), although with less effect. There is weaker evidence that other *ADH* genes affect risk and consumption. Supplementary Table 1 shows ADH SNPs reported at p values $< 10^{-6}$. The extensive LD in the region, however, makes association of specific SNPs other than the coding variants in *ADH1B* and *ADH1C* with AD difficult. Supplementary Figure 2 shows the strong LD among all of the SNPs in the *ADH* region that are listed in Supplementary Table 1. SNPs that lie within or near the other *ADH* genes, as well as some outside the area, are in strong

LD with those coding variants, and might also act by altering expression of one of the *ADH* genes.

Aldehyde dehydrogenase enzymes

The second step in the metabolism of ethanol, the oxidation of acetaldehyde to acetate, is important for eliminating the potentially toxic acetaldehyde (Zakhari, 2006). Unlike the oxidation of ethanol to acetaldehyde, this step is essentially irreversible (Hurley et al., 2002). There are 19 human aldehyde dehydrogenases, but three closely related ones (68% amino acid sequence identity) are most relevant to the metabolism of acetaldehyde: ALDH1A1, ALDH1B1 and ALDH2 (Jackson et al., 2011, Vasiliou et al., 2004). All three act as homotetramers, and have broad substrate specificities.

ALDH2

ALDH2, the mitochondrial ALDH, has a very high affinity for acetaldehyde (K_M = 0.2 μM) and a high reaction velocity (V_{max} = 280/min) (Hurley et al., 2002, Klyosov, 1996) (Table 3). ALDH2 rapidly eliminates most of the acetaldehyde, unless it is inhibited by disulfiram or by an inactivating mutation (see below). In individuals with active ALDH2 enzyme, acetaldehyde in the bloodstream ranges from undetectable to about 3 μM, roughly 1000-fold less than the levels of ethanol (Mizoi et al., 1994, Peng et al., 2014a, Harada et al., 1983, Nuutinen et al., 1984). ALDH2 is expressed ubiquitously, with highest levels in liver and adipose (Figure 4); it is among the top 100 genes expressed in liver. No eQTLs affect its expression in liver.

There are 2 main isoforms of the ALDH2 enzyme. The one common in most of the world, ALDH2*1, has glutamate at amino acid 487 of the mature protein (504 of the precursor). A variant, ALDH2*2, has a lysine there instead, encoded by rs671. Allele frequencies for *ALDH2*2* are highest in Han Chinese and Japanese, with lower frequencies elsewhere in Asia; it is rarely found outside Asia (Table 2). Even a single ALDH2*2 subunit renders the tetrameric enzyme nearly inactive under physiological conditions (Crabb et al., 1989, Zhou and Weiner, 2000, Hurley et al., 2002) and it is also more rapidly degraded (Xiao et al., 1996).

Presence of a single *ALDH2*2* allele is protective against heavy drinking and alcohol dependence in a semi-dominant manner (Crabb et al., 1989). People carrying even one *ALDH2*2* allele can have blood acetaldehyde levels of 30 – 75 μM or higher, more than 10 times the normal level (Peng et al., 2014a, Harada et al., 1983, Adachi et al., 1989). This causes a severe form of flushing that includes increased skin temperature, nausea, vomiting, headaches, and increased pulse rate (Goedde et al., 1979, Goedde et al., 1983, Harada et al., 1981, Mizoi et al., 1983, Shibuya et al., 1989). The effects are similar to those of disulfiram (Antabuse®), a drug approved for treatment of AUD. This aversive reaction reduces the propensity to drink, the amount consumed per occasion, and thereby the risk for alcoholism (Bosron and Li, 1981, Harada et al., 1982, Thomasson et al., 1991, Hurley et al., 2002, Edenberg, 2007, Crabb et al., 1989, Chen et al., 2009, Luczak et al., 2006, Goedde et al., 1992, Edenberg, 2012, Chen et al., 1999b, Whitfield, 2002, Hurley and Edenberg, 2012). In Han Chinese, the presence of a single *ALDH2*2* allele in a background of homozygous

*ADH1B*1* gave an OR of 0.40; when combined with a single *ADH1B*2* allele the OR dropped to 0.06 (Chen et al., 1999b). Meta-analysis of 22 datasets showed an OR of 0.22 for *ALDH2*2* heterozygotes (Luczak et al., 2006). A later meta-analysis showed similarly strong protection against AD: OR = 0.22 ($p = 1 \times 10^{-44}$) under a dominant model that is probably close to the physiological effects of the variant (Li et al., 2012b). The protective alleles at *ADH1B* and *ALDH2* act synergistically to give a relative risk of alcoholism in Asians of 1–10% (Chen et al., 1999a, Luczak et al., 2006).

Heterozygotes have a small fraction of ALDH2*1 homotetramers that provide some residual activity. Homozygotes for *ALDH2*2* have no detectable ALDH2 activity and are essentially completely protected against alcohol dependence because they cannot tolerate even one standard drink of alcohol (Higuchi et al., 1994).

In Chinese subjects from rural Northern Hunan Province *ALDH2*2* was associated with flushing ($p=4.8 \times 10^{-26}$), reduced the number of maxdrinks ($p = 1.5 \times 10^{-16}$), and was protective against alcohol dependence ($p=4.7 \times 10^{-8}$) (Quillen et al., 2014). SNPs in nearby genes also appeared to be associated (Supplementary Table 2), due to the extensive LD in the region (D' between rs671 and many SNPs across 1 Mb is over 0.6; Supplementary Figure 3): conditioning on rs671 did not leave any others significant, including a previously reported association in *CCDC63* (Quillen et al., 2014). *ALDH2*2* explained a substantial fraction of the total phenotypic variance, 7.9% for AD, 22.9% for maxdrinks and 29.3% for flushing (Quillen et al., 2014). Women in that study had very low levels of alcohol consumption, so analyses of women had little or no power. A GWAS on a small number of Korean men found rs671 was associated with alcohol dependence ($p = 8.4 \times 10^{-8}$; OR = 0.22) (Park et al., 2013). A recent GWAS in Thai subjects (ascertained for methamphetamine dependence or use) gave similar results: significant association of rs671 with flushing (5.2×10^{-14}), maxdrinks (1.3×10^{-10}) and DSM-IV criterion count (4.5×10^{-9}) (Gelernter et al., 2018).

Ten SNPs on chromosome 12 were significantly associated with the log of the average drinks/day in Korea (Baik et al., 2011). Surprisingly, they did not test rs671; all 10 SNPs are in LD with rs671 (D' = 0.54 to 0.85), which was almost certainly driving the associations. In Japan, rs671 was very strongly associated with drinkers *vs.* non-drinkers (OR = 0.16, $p = 3.6 \times 10^{-211}$); the significance of other SNPs within 0.7 Mb disappeared when adjusted for rs671 (Takeuchi et al., 2011).

Among young adult students of Asian background in the US, those with *ALDH2*1/*2* drank less frequently and lower quantities of alcohol, and had fewer heavy drinking episodes and lower maxdrinks (Otto et al., 2013). In a GWAS of Americans of East Asian background, rs671 was very strongly associated with drinking status (drinking at least once per week, OR = 0.40, $p = 2.3 \times 10^{-72}$), but had a weaker effect on typical number of drinks per week among drinkers ($p = 5.4 \times 10^{-4}$) (Jorgenson et al., 2017); conditional analysis showed no other significant signals in the *ALDH2* region.

Regulation of the amount of ALDH2 enzyme produced would also be expected to alter the reaction to alcohol, but studies of the promoter variant rs886205 (Chou et al., 1999) have not

shown an independent effect on AD (Harada et al., 1999, Kimura et al., 2006) or risky drinking (Haschemi Nassab et al., 2015).

In Japan, the protection against AD from a single *ALDH2*2* allele dropped sharply from 1979 to 1992, as the pressure to drink socially and as part of business culture increased (Higuchi et al., 1994). This is a striking example of gene x environment interaction.

ALDH1B1

ALDH1B1 is 75% identical to ALDH2, and is also located in mitochondria (Stagos et al., 2010, Jackson et al., 2011, Vasiliou et al., 2013, Stewart et al., 1995). It is expressed at much lower levels than ALDH2 (Figure 4). Both because of its lower expression and its much lower affinity for acetaldehyde (Table 3) ALDH1B1 does not normally play a large role in acetaldehyde oxidation. However, knocking out *Aldh1b1* in mice led to a significant increase in blood acetaldehyde after ethanol consumption (Singh et al., 2015).

Two missense variants in *ALDH1B1* are predicted to be damaging (Way et al., 2017). The Ala86Val variant (*ALDH1B1*2;* rs2228093) was inactive when expressed *in vitro* (Jackson et al., 2015). In a Danish allergy cohort, rs2228093 was correlated with fewer drinks/week and alcohol-induced hypersensitivity (rash, itch), although rs2073478, in LD with it, was not (Husemoen et al., 2008, Linneberg et al., 2010). Rs2073478 *(Arg107Leu)* was associated with heavy drinking in Inuit in Greenland (Bjerregaard et al., 2014). However, neither rs2228093 nor rs2073478 was associated with alcohol dependence in a larger study of British individuals (Way et al., 2017).

ALDH1A1

ALDH1A1 is a cytosolic enzyme that has a low affinity for acetaldehyde (Table 3). It is expressed at lower levels than ALDH2 in most tissues except stomach (Figure 4). As with ALDH1B1, it probably plays only a small role in acetaldehyde elimination, predominantly when ALDH2 is not active and thus acetaldehyde levels are high. Low activity of this enzyme (measured in erythrocytes) correlated with a mild flushing reaction in Europeans that did not affect alcohol consumption (Ward et al., 1994, Yoshida et al., 1989).

There are several low frequency variants of *ALDH1A1* that have been nominally associated with alcoholism-related phenotypes, including *ALDH1A*2*, a 17 bp promoter deletion, and *ALDH1A*3*, a 3 bp promoter insertion[5] that showed a weak trend toward association with alcoholism in African Americans (Spence et al., 2003). *ALDH1A1*2* variant was reported to be associated with higher consumption and increased risk for AD among Trinidadians of Indian descent (Moore et al., 2007), but in Mission Indians it showed the opposite direction (Ehlers et al., 2004), and there was no association with drinking in young adult students of Asian background in the US (Otto et al., 2013). An uncommon intronic variant, rs8187974 was nominally associated with both DSM-IV AD and maxdrinks in European Americans (Sherva et al., 2009). Three SNPs were nominally associated with an alcohol consumption score factor in European American women (Agrawal et al., 2011), and several with problem

[5]These sequences were not found in dbSNP, but there are two 17 bp deletions at approximately the site of *ALDH1A1**2, rs81887866 and rs6151031.

drinking and AD in European populations (Lind et al., 2008). None have shown up in GWAS. Taken together, the evidence that variants affect AD or drinking behavior is weak.

ALDH results to date

There is overwhelming evidence, both biochemical and genetic, that *ALDH2*2* reduces alcohol consumption, particularly heavy drinking, and greatly reduces the risk for AD, through its triggering of a strong flushing reaction. Reports of association of other genes on chromosome 12 within 1 – 2 Mb of *ALDH2* in populations in which *ALDH2*2* is present are nearly certain to be due to strong LD with this functional variant (Supplementary Figure 3), and the evidence for effects of the other variants disappears when conditioned on rs671. Evidence for association of *ALDH1A1* and *ALDH1B1* is very weak.

Conclusions

The coding variants *ADH1B*2, ADH1B*3, ADH1C*1* and *ALDH2*2* all provide some protection against excessive alcohol consumption and thereby against alcohol dependence. The effect sizes for *ADH1B*2* (rs1229984) and *ALDH2*2* (rs671) are high for a complex disease. Presence of even a single *ALDH2*2* allele leads to high levels of acetaldehyde in blood and a very strong flushing reaction. Although the *ADH1B*2, ADH1B*3* and *ADH1C*1* variants do not by themselves lead to high levels of acetaldehyde because an active ALDH2 enzyme so efficiently oxidizes it to acetate, they also provide significant protection. Allele frequencies of these coding SNPs differ widely among populations, as do the patterns of LD, and the impact of a variant can be modified by different environments, so it is important to broaden studies to a wider range of populations.

The evidence for effects of other *ADH* and *ALDH* genes is much weaker. Regulatory variants and other coding variants in and around the *ADH* region and the key *ALDHs* are also likely to affect risk for AUDs and alcohol consumption, but because they have much smaller effects and because analyses are complicated by the LD in the region, larger and more diverse datasets are needed to reliably determine their independent effects.

Beyond the genes encoding these metabolic enzymes, there are probably at least hundreds to thousands of additional genes, interacting with the environment, that affect the risk for AUDs and excessive alcohol consumption. With the exception of the protection offered by homozygosity for *ALDH2*2*, no one gene or combination of genes is determinative. Understanding which other genes affect risk, and the mechanisms by which they do, should enable progress in prevention and treatment. Much larger, well-characterized samples are needed to identify these variants of small effect, and thereby to better understand AUDs and the other effects of alcohol. Even variants that individually make only a very small contribution to risk can reveal key pathways and mechanisms of risk, which can then be targeted for treatment and prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

Related work in the authors' laboratory is supported by NIH Grants U10AA008401 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and U01MH109532 from the National Institute on Mental Health (NIMH) and the National Institute on Drug Abuse (NIDA).

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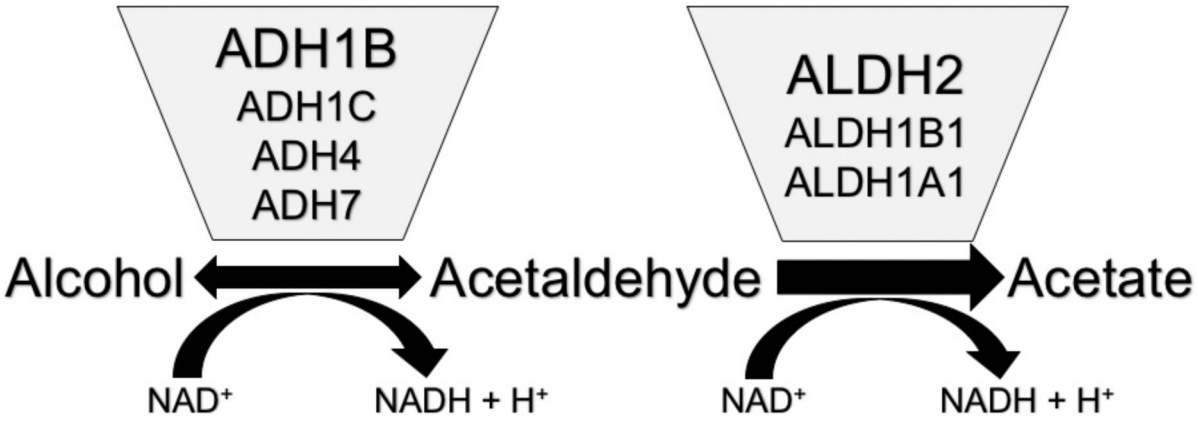

Figure 1. Primary pathway of alcohol metabolism.

The oxidation of alcohol to acetaldehyde is reversible *in vitro*, but *in vivo* the overall reaction goes strongly toward acetate due to the activity of ALDH2. The ADH and ALDH enzymes that carry out most of the metabolism are shown.

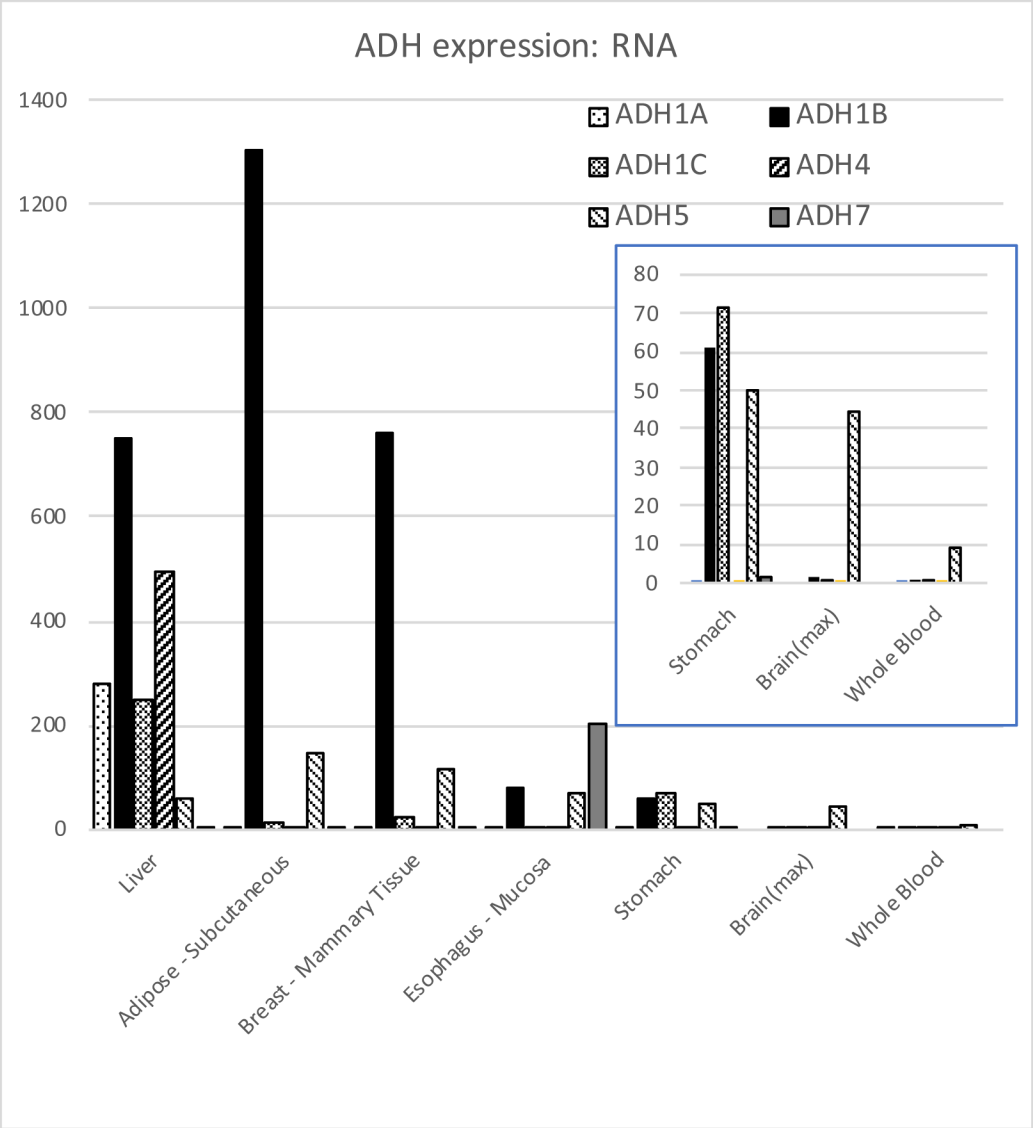

Figure 2. Expression of ADH mRNA in selected tissues.

Data are in median transcripts per million transcripts (tpm), from GTEx version 7 (gtexportal.org, exported 15 April 2018) (GTEx Consortium, 2013). *ADH* genes are shown in numerical order, left to right, within each tissue. Inset shows enlarged image of stomach, brain (maximum tpm across all brain tissues) and whole blood.

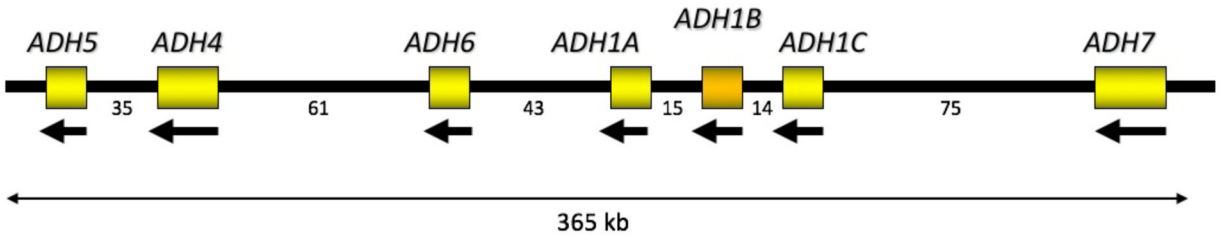

Figure 3. ADH region of chromosome 4.

ADH genes are arranged head-to-tail along chromosome 4, and transcribed in the opposite direction. Numbers below the line are distances between genes, in kb.

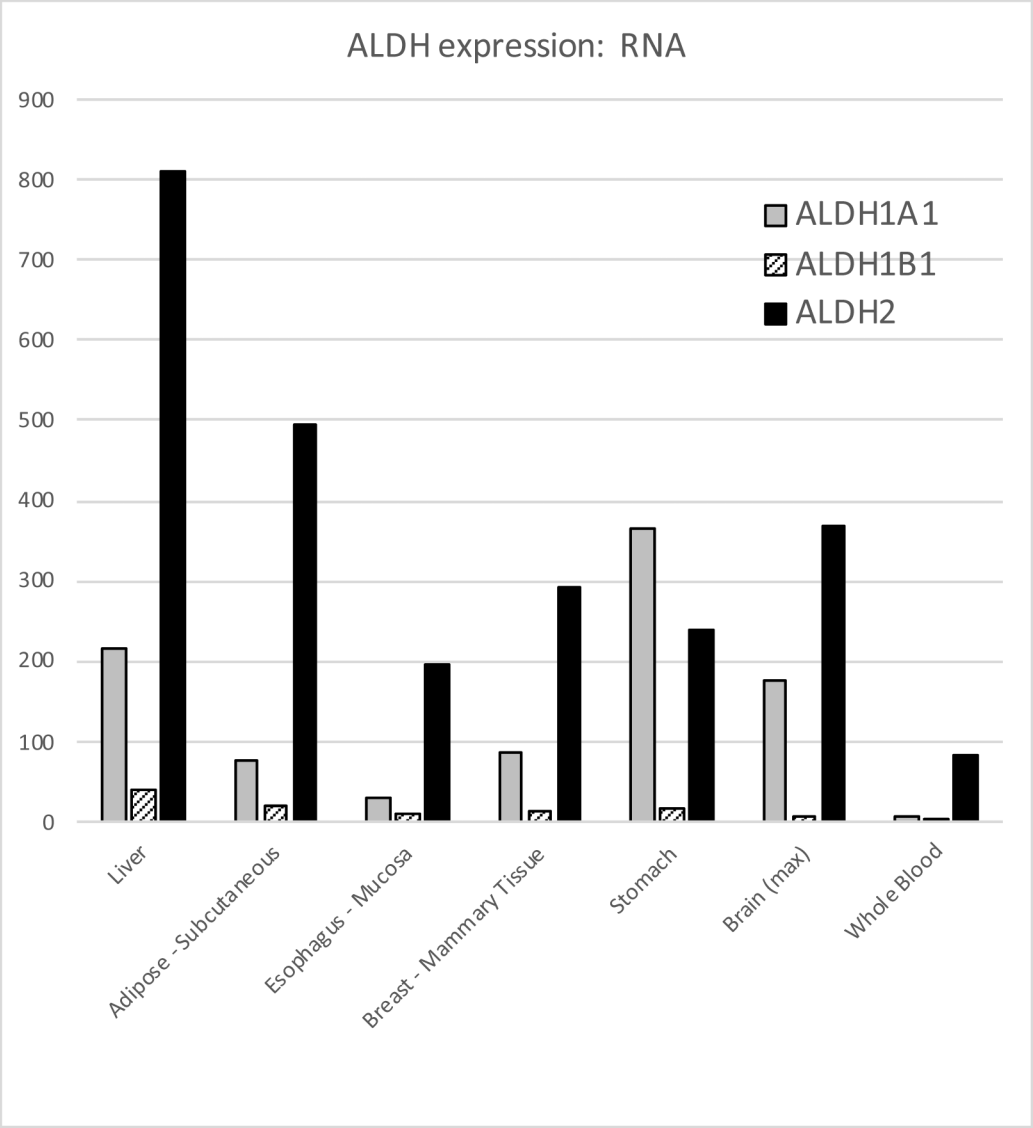

Figure 4. Expression of key ALDH RNAs in selected tissues.
Data are median tpm, from GTEx version 7 (exported 15 April 2018) (GTEx Consortium, 2013).

Table 1.

ADH genes and enzyme kinetics

Approved Gene Symbol[a]	Approved Gene Name[a]	Synonyms[b]	RNA: RefSeq Accession ID	Subunit encoded[c]	K_M, ethanol (mM)	Activity Vmax (min)-1	Activity at 22 mM ethanol	RefSeq position
ADH1A	alcohol dehydrogenase 1A (class I), alpha polypeptide	*ADH1*	NM_000667	α-ADH, ADH1	4	30	25	4:99,276,366-99,291,028
ADH1B	alcohol dehydrogenase 1B (class I), beta polypeptide	*ADH2*	NM_000668	β-ADH, ADH2				4:99,306,387-99,321,442
	*ADH1B*1; ADH1B[Arg48/Arg370]*	*ADH2*1*		β1-ADH, ADH2*1	0.013	5.2	5.2	
	*ADH1B*2; ADH1B[His48/Arg370]*	*ADH2*2*		β2-ADH, ADH2*2	1.8	190	176	
	*ADH1B*3; ADH1B[Arg48/Cys370]*	*ADH2*3*		β3-ADH, ADH2*3	61	140	37	
ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	*ADH3*	NM_000669	γ-ADH, ADH3				4:99,336,492-99,353,045
	*ADH1C*1; ADH1C[Arg272/Ile350]*	*ADH1C*1*		γ1-ADH, ADH1C*1	0.1	32	32	
	*ADH1C*2; ADH1C[Gln272/Val350]*	*ADH1C*2*		γ2-ADH, ADH1C*2	0.14	20	20	
ADH4	alcohol dehydrogenase 4 (class II), pi polypeptide	*class II ADH, ADH2*	NM_000670	π-ADH, ADH4	11	9	6	4:99,123,667-99,144,298
ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide	*class III ADH, ADH3*	NM_000671	χ-ADH, ADH5	>1,000	100	<2	4:99,070,978-99,088,788
ADH6	alcohol dehydrogenase 6 (class V)	*class V ADH, ADH5*	NM_000672	-	-	-	-	4:99,202,638-99,219,246
ADH7	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide	*class IV ADH, ADH4*	NM_000673	μ-ADH, σ-ADH, ADH7	30	1800	760	4:99,412,261-99,435,510

Data on kinetics are from studies at 0.1 M sodium phosphate, pH 7.5, 25C (Chi et al., 2018). RefSeq positions are from the Human GRCh38/hg38 genome assembly.

[a] HUGO Gene Nomenclature Committee.

[b] Synonyms based on class designations (Duester et al., 1999) create much confusion in the literature, because one must determine what is meant by, for example, “ADH4”: class II (officially ADH4) or class IV (officially ADH7). We use the approved symbols throughout this article.

[c] Protein subunits have traditionally been named with Greek symbols, but can also be named based upon the gene encoding them; *genes* are in *italics*, proteins in roman font.

[d] RNA detected, protein not detected.

Table 2.

ADH and *ALDH2* allele frequencies

			ADH1B*2	***ADH1B*3***	***ADH1C*1***	***ALDH2*2***
			rs1229984	rs2066702	rs1693482 **	rs671
		Position	4:99,318,162	4:100,229,017	4:99,304,835	12:111,803,962
		Genome Allele	T	A	C	A
		RNA Allele	A	T	G	A
		Amino acid	His48	Cys370	Arg272	Lys504
Group	**Code**	**Population**				
AFR	ACB	African Carribbeans in Barbados	0.010	0.193	0.891	0.005
AFR	ASW	Americans of African Ancestry in SW USA		0.205	0.861	
AFR	ESN	Esan in Nigera		0.273	0.929	
AFR	GWD	Gambian in Western Divisons in The Gambia		0.142	0.912	0.004
AFR	LWK	Luhya in Webuye, Kenya		0.141	0.859	
AFR	MSK	Mende in Sierra Leone		0.088	0.906	
AFR	YRI	Yoruba in Ibadan, Nigera		0.282	0.926	
AMR	CLM	Colombians from Medellin, Colombia	0.074		0.755	
AMR	MXL	Mexican Ancestry from Los Angeles USA	0.086		0.719	0.008
AMR	PEL	Peruvians from Lima, Peru	0.012		0.824	0.006
AMR	PUR	Puerto Ricans from Puerto Rico	0.063		0.635	
ASN	CDX	Chinese Dai in Xishuangbanna, China	0.634		0.887	0.043
ASN	CHB	Han Chinese in Bejing, China	0.709		0.951	0.160
ASN	CHS	Southern Han Chinese	0.757		0.929	0.271
ASN	JPT	Japanese in Tokyo, Japan	0.731		0.928	0.240
ASN	KHV	Kinh in Ho Chi Minh City, Vietnam	0.646		0.919	0.136
EUR	CEU	Utah Residents (CEPH) with Northern and Western European ancestry	0.015		0.525	
EUR	FIN	Finnish in Finland			0.490	
EUR	GBR	British in England and Scotland	0.005		0.560	
EUR	IBS	Iberian population in Spain	0.065		0.692	
EUR	TSI	Toscani in Italia	0.051		0.692	
SAN	BEB	Bengali from Bangladesh	0.017		0.820	
SAN	GIH	Gujarati Indian from Houston, Texas	0.024		0.718	
SAN	ITU	Indian Telugu from the UK	0.015		0.765	
SAN	PJL	Punjabi from Lahore, Pakistan	0.042		0.672	
SAN	STU	Sri Lankan Tamil from the UK	0.005		0.662	

Allele corresponding to the variant noted is shown on the genomic reference strand and in the RNA (note that the ADH transcripts run in the opposite direction). Positions are on the GRCh38/hg38 human genome assembly. Data are from the 1000 genomes project, Phase 3 (The 1000 Genomes Project Consortium et al., 2015). Blanks are <0.001. Groups: AFR = African, AMR=American, ASN=East Asian, EUR=European, SAN=South Asian. Code: 3 letter identifier for population.

** Frequencies are identical to the more frequently studied SNP rs698 (genome C, RNA G, Val350), except that for rs698, YRI=0.931, ITU= 0.760. For data on a wider range of populations and SNPs, see the alfred database https://alfred.med.yale.edu (Rajeevan et al., 2012).

Table 3.

ALDH genes and enzyme kinetics

Approved Gene Symbol[a]	Approved Gene Name[a]	Synonyms	RNA: RefSeq Accession ID	Subunit encoded	K_M, acetaldehyde (mM)	Activity Kcat (min-1)	RefSeq position
ALDH2	aldehyde dehydrogenase 2	*ALDHI; ALDH-E2; ALDM*	NM_000690		-	-	12:111766887-1118
	*ALDH2*1*	*ALDH2*Glu504*		ALDH2*1 ALDH2[Glu504][b]	0.2	280	
	*ALDH2*2*	*ALDH2*Lys504*		ALDH2*2 ALDH2[Lys504][b]		c	
ALDH1B1	aldehyde dehydrogenase 1 family member B1	*ALDH5; ALDHX*	NM_000692		55	655	9:38392664-38398
ALDH1A1	aldehyde dehydrogenase 1 family member A1	*ALDH1; ALDH-E1; ALDH11; RALDH1; ALDC*	NM_000689		180	380	9:72900662-72953

RefSeq positions are from the Human GRCh38/hg38 genome assembly. Data on kinetics are from (Klyosov, 1996) (ALDH2, ALDH1A2) and (Stagos et al., 2010) (ALDH1B1).

[a] HUGO Gene Nomenclature Committee.

[b] Position in precursor protein; aa487 in the mature protein.

[c] ALDH2 is essentially inactive under physiological conditions.