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Critical Review

Alcohol Dehydrogenases, Aldehyde Dehydrogenases, and Alcohol Use Disorders: A Critical Review

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Alcohol use disorders (AUDs) 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 2 genes involved in alcohol (ethanol [EtOH]) 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 AUDs in both cases is alteration in the rate of metabolism of EtOH 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.

Key Words: Alcohol Dependence, Alcohol Metabolism, Alcohol Consumption, ADH Genes, ALDH Genes, Linkage Disequilibrium.

ALCOHOL USE DISORDERS (AUDs) 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 (DSM-5) requires meeting at least 2 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 AUDs in 2,036 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 AUDs. The requirement for alcohol consumption adds additional complexity, 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 AUDs (from 0.37 to 0.70) (Walters et al., 2018).

Ethanol (EtOH) 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) (Fig. 1). Metabolism by cytochrome P450s and catalase makes 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 EtOH 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 EtOH can get high: The blood alcohol concentration that is defined as legal intoxication in the United States (0.08%) corresponds to 17 mM EtOH. The oxidation of acetaldehyde is extremely efficient, such that circulating levels of acetaldehyde are usually more than 1,000-fold less; they are generally barely detectable, ≤ 3 μM (Harada et al., 1983; Mizoi et al., 1994; Nuutinen et al., 1984; Peng et al., 2014a), although

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

they are higher in liver (~15 μM after ingestion of 0.8 g/kg EtOH) (Nuutinen et al., 1984).

The contribution of genetic variants to risk for AUDs 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; Hart and Kranzler, 2015; Rietschel and Treutlein, 2013). 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 AUDs, the *ADH* and *ALDH* genes. There is very strong evidence that variations in *ADH* and *ALDH* genes affect alcohol consumption and the risk for AUDs.

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; Edenberg and Bosron, 2018; Hurley et al., 2002). Their pattern of expression in tissues differs (Fig. 2). ADH1A, ADH1B, and ADH1C are called class I ADHs; they are more than 90% identical in amino acid sequence and can heterodimerize with each other. These 3 ADHs have K_m for EtOH in the range of 0.013 to 27 mM (Chi et al., 2018; Hurley and Edenberg, 2012; Hurley et al., 2002) (Table 1) and carry out most of the EtOH oxidation in liver. The other ADH enzymes function as homodimers. When EtOH levels are high (e.g., intoxicating), ADH4 could contribute substantially, perhaps one-third 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 EtOH oxidation and local generation of acetaldehyde primarily in the stomach and esophagus. ADH5 is ubiquitously expressed; although it does not make a major contribution to EtOH oxidation in liver, it can contribute to metabolism in other tissues, including the gastrointestinal 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.

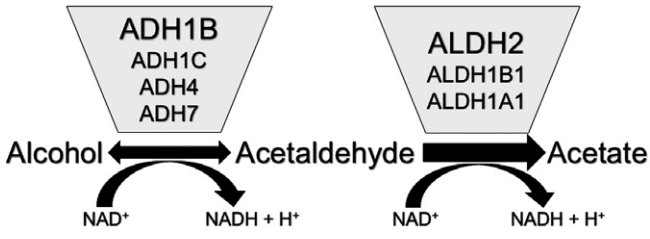


Fig. 1. Primary pathway of alcohol metabolism. The oxidation of alcohol to acetaldehyde is reversible in vitro, but in vivo the overall reaction goes strongly toward acetate due to the activity of ALDH2. The ADH and ALDH enzymes that carry out most of the metabolism are shown.

The *ADH* region of the genome (Fig. 3) arose from repeated gene duplication, and many genetic variations in this region are in high linkage disequilibrium (LD), that is, are inherited together. There are many and often large ethnic differences in allele frequencies and LD patterns. For example, out of 110 single nucleotide polymorphisms (SNPs) analyzed in a set of European American and African American families, 88 had minor allele frequencies (MAFs) that differed between the 2 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 AD; several aspects were reviewed recently (Edenberg and Bosron, 2018; Polimanti and Gelernter, 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 (Fig. 2). There are many SNPs that affect its expression in 1 or more tissues (expression quantitative trait locus [eQTLs]), with many concentrated in the region between *ADH1C* and *ADH7* and others between *ADH4* and *ADH6* (Fig. S1; 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 EtOH 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 EtOH much faster than ADH1B*1 (Table 1). Computer modeling suggests that at 17 mM EtOH, ADH1B*2 homodimers could oxidize EtOH 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 to contributions of the other ADH enzymes and limitations by cofactor levels. Neumark and colleagues (2004) found a small (~14%) but significant difference in alcohol elimination rate between subjects of European descent with at least 1 *ADH1B*2* allele compared

[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 call these 47 and 369.

Table 1. *ADH* Genes and Enzyme Kinetics

Approved wregene symbol[a]	Approved gene name[a]	Synonyms[b]	RNA: RefSeq accession ID	Subunit encoded[c]	K_M, ethanol (mM)	Activity V_{max} (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	–[d]	–	–	–	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	1,800	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* and proteins in roman font.

[d]RNA detected and protein not detected.

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 EtOH, ADH1B*3/*3 could oxidize EtOH 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* (Supporting 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 and colleagues (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 ALDH; 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: The 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; Li et al., 2011; Luczak et al., 2006; Park et al., 2013; Whitfield, 2002; Zintzaras et al., 2006).[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 to 0.26) (Chen et al., 1999b; Luczak et al., 2006; Park et al., 2013; Whitfield, 2002). Logistic regression of combined *ADH2* and *ALDH2* genotypes in Han Chinese found that in the presence of active ALDH2 (*ALDH2*1* homozygosity), a

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

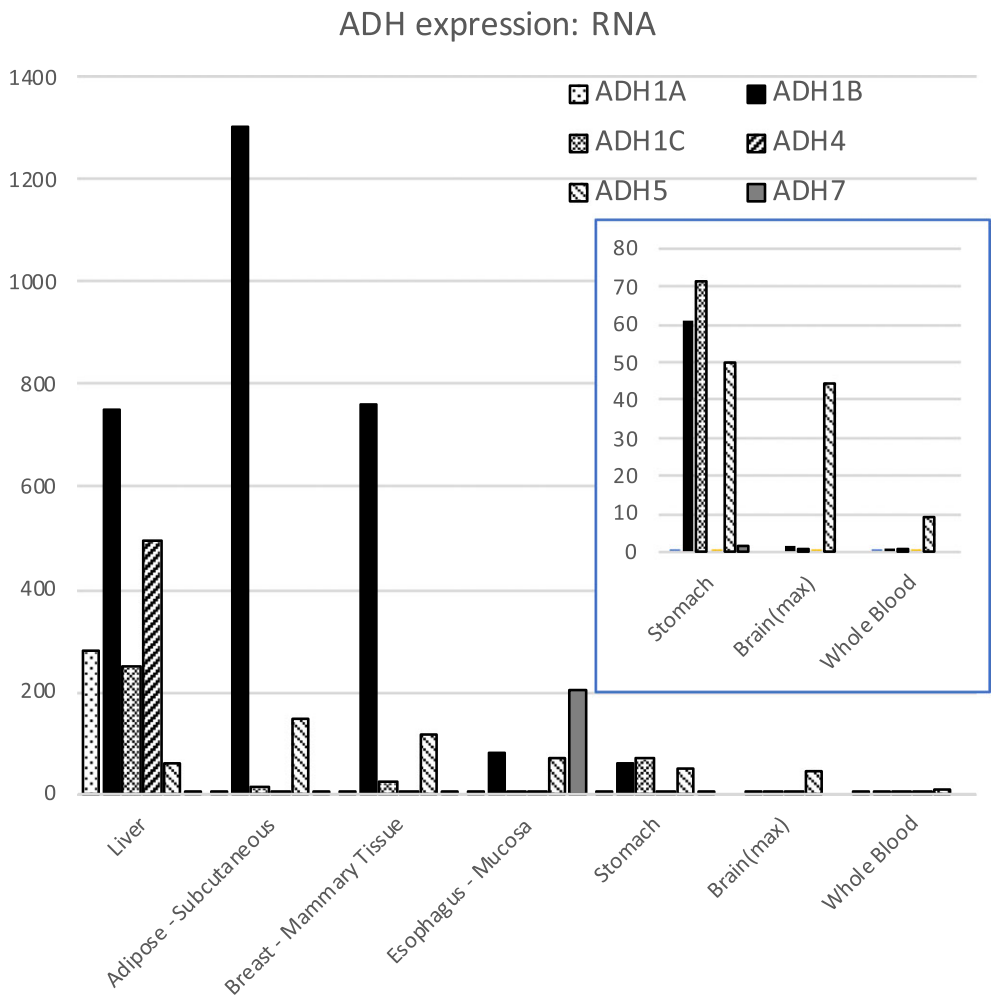


Fig. 2. Expression of ADH mRNA in selected tissues. Data are in median transcripts per million transcripts (tpm), from GTEx version 7 (gtexportal.org, exported April 15, 2018) (GTEx Consortium, 2013). *ADH* genes are shown in numerical order, left to right, within each tissue. Inset shows enlarged image of stomach, brain (maximum tpm across all brain tissues), and whole blood.

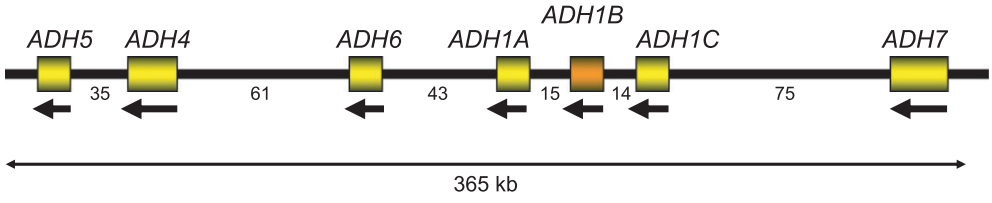


Fig. 3. ADH region of chromosome 4. ADH genes are arranged head-to-tail along chromosome 4 and transcribed in the opposite direction. Numbers below the line are distances between genes, in kb.

single *ADH1B*2* allele gave an OR of 0.22, and 2 *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}) (Li et al., 2011; Luczak et al., 2006; Whitfield, 1997; Zintzaras et al., 2006). Because drinking was not as common among Asian women, their overall risk was less, and therefore, the protective effect was also less (Luczak et al., 2006; Zintzaras et al., 2006).

In a small genomewide association study (GWAS) plus follow-up in Koreans, rs1229984 *(ADH1B*2)* gave by far the strongest association with AD (OR = 0.42; $p = 2.6 \times 10^{-21}$), and 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

Table 2. *ADH* and *ALDH2* Allele Frequencies

			*ADH1B*2*	*ADH1B*3*	*ADH1C*1*	*ALDH2*2*
		dbSNP ID	rs1229984	rs2066702	rs1693482[a]	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 Caribbeans in Barbados	0.010	0.193	0.891	0.005
AFR	ASW	Americans of African ancestry in the SW United States		0.205	0.861	
AFR	ESN	Esan in Nigeria		0.273	0.929	
AFR	GWD	Gambian in Western Divisions 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, Nigeria		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 Beijing, 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.

[a]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).

associated with the count of DSM-IV AD symptoms ($p = 2.7 \times 10^{-5}$) (Gelernter et al., 2018). rs1229984 was associated with drinking versus nondrinking in Japan (OR = 1.20, $p < 3.6 \times 10^{-4}$) (Takeuchi et al., 2011). Surprisingly, the East Asians in a U.S. 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 (Carr et al., 2002; Hasin et al., 2002; Meyers et al., 2015; 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/wk and less heavy drinking in both men and women (Linneberg et al., 2010; Tolstrup et al., 2008). 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 ($p = 1.8 \times 10^{-9}$) (Treutlein et al., 2014). A U.S. study showed the protective effect of *ADH1B*2* on risk for AD was close to that seen in East Asians (OR = 0.34, $p = 6.6 \times 10^{-10}$) and reduced the maximum drinks in a 24-h period ($p = 3 \times 10^{-13}$) (Bierut et al., 2012). A study in Great Britain showed a similar effect, OR = 0.26 versus all

controls, 0.19 versus screened controls ($p = 2.7 \times 10^{-8}$) (Way et al., 2015).

In European Americans, rs1229984 was associated with Maxdrinks ($p = 6 \times 10^{-15}$) (Hart et al., 2016; Xu et al., 2015) and with the number of DSM-IV and DSM-5 criteria ($p = 1.4 \times 10^{-13}$, 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 ($p = 8.2 \times 10^{-7}$), a lower number of Maxdrinks ($p = 2.7 \times 10^{-6}$), lower total alcohol consumption ($p = 8.9 \times 10^{-8}$), and fewer DSM-IIIR symptoms of dependence ($p = 0.0016$) (Macgregor et al., 2009). Jorgenson and colleagues (2017) found rs1229984 was associated with drinker versus nondrinker status in Americans of both European ($p = 2.5 \times 10^{-20}$) and Hispanic ($p = 4.4 \times 10^{-7}$) descent, and with average drinks per week ($p = 1.9 \times 10^{-35}$ in European Americans and 2.6×10^{-6} in Hispanics). 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, $p = 4.8 \times 10^{-10}$) 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 ($p = 1.2 \times 10^{-31}$) and symptom count ($p = 1.9 \times 10^{-23}$) (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 ($p = 9.8 \times 10^{-13}$) (Walters et al., 2018).

Data on rs1229984 are not available in many GWAS, because it was not included in many genotyping arrays and is not well imputed, its MAF in Europeans falls below the usual cutoff (0.05), and it may fail quality control due to differences in MAF among subgroups that lead to apparent violation of Hardy–Weinberg equilibrium (e.g., Clarke et al., 2017). In the Psychiatric Genomics Consortium Substance Use Disorders (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 Alcohol Use Disorders Identification Test (AUDIT) score ($p = 5.8 \times 10^{-72}$), AUDIT-C (items 1 to 3, consumption; $p = 2.6 \times 10^{-56}$), and AUDIT-P (items 7 to 10, problems; $p = 9.9 \times 10^{-46}$) (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 ($p = 10.7 \times 10^{-36}$) (Sanchez-Roige et al., 2018); that SNP (and other associated SNPs in the region) is in LD with rs1229984 ($D' = 1$; $r^2 = 0.54$) (Fig. S2).

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 DSM-5 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 AUDs 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 EtOH 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 (Gizer et al., 2011; Wall et al., 2003). It appears to be protective against fetal alcohol syndrome, likely by reducing consumption (Scott and Taylor, 2007; Warren and Li, 2005). In a GWAS of African Americans, rs2066702 was associated with the number of DSM-IV and DSM-5 criteria ($p = 1.9 \times 10^{-9}$, 1.4×10^{-9}, respectively), among which tolerance was the strongest, and with Maxdrinks ($p = 6.4 \times 10^{-8}$) (Hart et al., 2016). A meta-analysis of that sample plus samples from SAGE (Bierut et al., 2010) found strong association with AD (OR ~0.7; $p = 3.7 \times 10^{-13}$), DSM-IV symptom counts ($p = 6.3 \times 10^{-17}$) (Gelernter et al., 2014), and Maxdrinks ($p = 2.5 \times 10^{-10}$) (Xu et al., 2015). The most recent meta-analysis of African Americans ($n = 6{,}280$) showed association of *ADH1B*3* with AD ($p = 2.2 \times 10^{-9}$) (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 (Fig. S2).

ADH1C

ADH1C is expressed at modest levels in liver (one-third that of *ADH1B*), and to a smaller extent in stomach, with little expression in other tissues (Fig. 2). There are 2 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 (Chi et al., 2018; Hurley et al., 2002) (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 two ($r^2 = 0.97$ 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 AD is less robust than that of *ADH1B*. *ADH1C*2* is associated with AD and consumption in East Asians (e.g., Matsuo et al., 2007; Thomasson et al., 1991, 1994), 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 (Chen et al., 1999b; Choi et al., 2005; Osier et al., 1999). 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, $p = 4 \times 10^{-33}$) 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 (Borras et al., 2000; Luo et al., 2006b; Neumark et al., 2004) or only nominal (Agrawal et al., 2011; Edenberg et al., 2006; 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 AD 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 AD, 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 AD provided evidence of association of rs1614972 (in LD with rs698 and rs1693482, $D' = 1$, $r^2 = 0.31$) with AD ($p = 1.4 \times 10^{-4}$), but it did not withstand correction for multiple testing (Treutlein et al., 2009). Enlarging that sample provided genomewide significant evidence for association of a different SNP, rs1789891 (D' with rs1693482 = 1, $r^2 = 0.22$), with AD (1.3×10^{-8}, OR[4] = 0.68) (Frank et al., 2012). A follow-up of SNPs from the Treutlein study 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 AD in a study of British and Irish ($p = 7.2 \times 10^{-5}$; OR = 0.71), and the association remained significant when conditioned on rs1229984 (*ADH1B*2;* $p = 1.7 \times 10^{-4}$) (Way et al., 2015). In the PGC-SUD trans-ancestral meta-analysis, rs1789912 was associated with AD ($p = 1.47 \times 10^{-9}$) (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; $p_{\text{conditional}} = 7.7 \times 10^{-4}$, 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 population provided evidence for association with rs141973904, an uncommon allele (MAF = 0.016) in *ADH1C* ($p = 4.4 \times 10^{-7}$) (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 ($p = 7 \times 10^{-4}$, with 50 SNPs tested) (Macgregor et al., 2009). Several studies reported no independent effect of *ADH1C*1* on average drinking (Drogan et al., 2012; Latella

[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.

et al., 2009) or upon likelihood of very heavy drinking (Munoz et al., 2012). In a meta-analysis of average drinking (g/kg/d) among Europeans, rs1789891 was nominally significant ($p = 1.2 \times 10^{-3}$) 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 to 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 AD, 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 EtOH of 34 mM (Table 1). Its expression is relatively high in liver and extremely low elsewhere. A paradox is that there are over 5,500 eQTLs 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 EtOH (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 AD 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 nonsynonymous 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 ($p = 2.0 \times 10^{-13}$); 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 (Fig. 2). It has very low affinity for EtOH, 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 2,667 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; Kendler et al., 2011; Kuo et al., 2008; 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 (Fig. 2). It has a high turnover number, and its high K_m suggests it will be most active when EtOH concentrations are high, as they are during EtOH 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 EtOH (Dohmen et al., 1996).

A single SNP in *ADH7* (rs284786) was nominally associated with a DSM-IIIR-based definition of AD (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/d) among Europeans, the most significant SNP in the *ADH* region was rs2584448 in *ADH7* ($p = 3.9 \times 10^{-4}$); when the analysis restricted the controls to drinkers, the top SNP was rs2165672, also in *ADH7* (Schumann et al., 2011); neither was genomewide significant.

ADH1A

ADH1A is expressed at lower levels in liver than *ADH1B* or *ADH1C* and is barely expressed in other adult tissues (Fig. 2). *ADH1A* is expressed early in fetal development and may play a role there (Smith et al., 1971). Coding variations are essentially nonexistent, 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, b). 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,b). 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* (Fig. S1).

The large trans-ethnic meta-analysis of subjects of European and African descent carried out by the PGC-SUD working group found that rs10516440 (associated with AD at $p = 9.9 \times 10^{-8}$; p conditioned on rs1229984 = 7.4×10^{-5}) was a significant eQTL for *ADH1B* in a trans-tissue analysis ($p = 1.4 \times 10^{-76}$; 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 2 coding variants in *ADH1B* that affect its kinetic properties (rs1229984 and rs2066702; *ADH1B*2* and *ADH1B*3*, respectively) affect alcohol consumption and risk for AD. 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. Table S1 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. Figure S2 shows the strong LD among all of the SNPs in the *ADH* region that are listed in Table S1. 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 EtOH, the oxidation of acetaldehyde to acetate, is important for eliminating the potentially toxic acetaldehyde (Zakhari, 2006). Unlike the oxidation of EtOH to acetaldehyde, this step is essentially irreversible (Hurley et al., 2002). There are 19 human ALDHs, but 3 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 3 act as homotetramers and have broad substrate specificities.

ALDH2

ALDH2, the mitochondrial ALDH, has a very high affinity for acetaldehyde ($K_M = 0.2\ \mu M$) 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 1,000-fold less than the levels of EtOH (Harada et al., 1983; Mizoi et al., 1994; Nuutinen et al., 1984; Peng et al., 2014a). ALDH2 is expressed ubiquitously, with highest levels in liver and adipose (Fig. 4); it is among the top

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		–	–	12:111766887-111809985
	*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	9:38392664-38398665
ALDH1A1	Aldehyde dehydrogenase 1 family member A1	*ALDH1; ALDH-E1; ALDH11; RALDH1; ALDC*	NM_000689		180	380	9:72900662-72953317

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

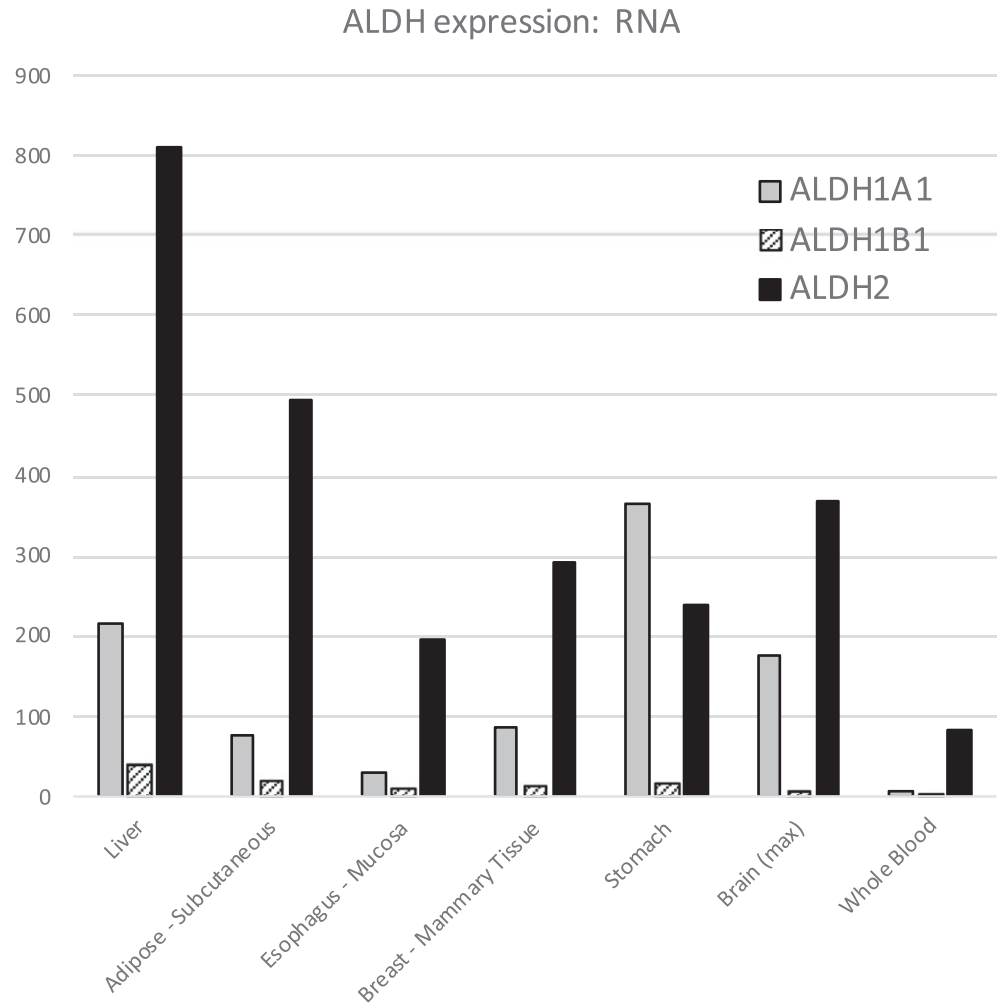


Fig. 4. Expression of key ALDH RNAs in selected tissues. Data are median tpm, from GTEx version 7 (exported April 15, 2018) (GTEx Consortium, 2013).

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; Hurley et al., 2002; Zhou and Weiner, 2000), and it is also more rapidly degraded (Xiao et al., 1996).

The presence of a single *ALDH2*2* allele is protective against heavy drinking and AD in a semidominant manner (Crabb et al., 1989). People carrying even 1 *ALDH2*2* allele can have blood acetaldehyde levels of 30 to 75 μM or higher, more than 10 times the normal level (Adachi et al., 1989; Harada et al., 1983; Peng et al., 2014a). This causes a severe form of flushing that includes increased skin temperature, nausea, vomiting, headaches, and increased pulse rate (Goedde et al., 1979, 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 AUDs. This aversive reaction reduces the propensity to drink, the amount consumed per occasion, and thereby the risk for alcoholism (Bosron and Li, 1981; Chen et al., 1999b, 2009; Crabb et al., 1989; Edenberg, 2007, 2012; Goedde et al., 1992; Harada et al., 1982; Hurley and Edenberg, 2012; Hurley et al., 2002; Luczak et al., 2006; Thomasson et al., 1991; Whitfield, 2002). 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 data sets 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 to 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 AD because they cannot tolerate even 1 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 AD ($p = 4.7 \times 10^{-8}$) (Quillen et al., 2014). SNPs in nearby genes also appeared to be associated (Table S2), due to the extensive LD in the region (D' between rs671 and many SNPs across 1 Mb is over 0.6; Fig. S3): 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 AD ($p = 8.4 \times 10^{-8}$; OR = 0.22) (Park et al., 2013). A recent GWAS in Thai subjects (ascertained for methamphetamine dependence or use) found 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/d 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 versus nondrinkers (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 United States, 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 × environment interaction.

ALDH1B1

ALDH1B1 is 75% identical to ALDH2 and is also located in mitochondria (Jackson et al., 2011; Stagos et al., 2010; Stewart et al., 1995; Vasiliou et al., 2013). It is expressed at much lower levels than ALDH2 (Fig. 4). Because of both 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 EtOH 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/wk 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 AD 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 (Fig. 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 United States (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 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 to 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 (Fig. S3), 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 AD. The effect sizes for *ADH1B*2* (rs1229984) and *ALDH2*2* (rs671) are high for a complex disease. The 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 data sets 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.

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[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.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig. S1. Location of eQTLs for *ADH1B* in adipose tissues.

Fig. S2. Linkage disequilibrium (D') among ADH SNPs with $p < 10^{-6}$.

Fig. S3. Linkage disequilibrium (D') among ALDH SNPs with $p < 5 \times 10^{-8}$.

Table S1. ADH SNPs associated with AD or related traits.

Table S2. ALDH SNPs associated with AD and related traits.