GENETICS

Alcohol dehydrogenase 1B genotype and fetal alcohol syndrome: a HuGE minireview

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Fetal alcohol syndrome (FAS), 1 of the most common developmental disabilities in the United States, occurs at a rate of 0.5-2.0:1000 live births. Animal model, family, and twin studies suggest a genetic component to FAS susceptibility. Alcohol dehydrogenases (ADHs) catalyze the rate-limiting step in alcohol metabolism. Studies of genetic associations with FAS have focused on the *alcohol dehydrogenase 1B* (*ADH1B*) gene, comparing mothers and children with the alleles *ADH1B*2* or *ADH1B*3*, associated with faster ethanol metabolism, with those homozygous for *ADH1B*1*. While most studies have found a protective effect for genotypes containing *ADH1B*2* or *ADH1B*3*, results have been conflicting, and further investigation into the association between the *ADH1B* genotype and FAS is needed. Whether increased alcohol intake accounts for the elevated risk reported for the *ADH1B*1/ADH1B*1* genotype should be addressed, and future studies would benefit from consistent case definitions, enhanced exposure measurements, larger sample sizes, and careful study design.

Key words: *ADH1B*, *ADH2*, alcohol dehydrogenase, epidemiology, fetal alcohol syndrome

Gene and Gene Product

Alcohol metabolism occurs in 2 steps (Figure). Alcohol dehydrogenase (ADH) converts ethanol to acetaldehyde, which is then broken down to acetate by aldehyde dehydrogenase (ALDH). Human ADH, a dimeric enzyme, is divided into 5 classes encoded by 7 genes, whose protein products are similar in amino acid sequence and structure but differ in preferred substrates.[1] The majority of ethanol metabolism is performed by the ADHs in Class 1, *ADH1A* (alpha), *ADH1B* (beta), and *ADH1C* (gamma) (previously named *ADH1*, *ADH2*, and *ADH3*, respectively); Class 2, *ADH4*; and Class 4, *ADH7*.[2] Class 1 ADHs are found in the liver, kidney, lung, and mucosa of the stomach and lower digestive tract; Class 2, in the liver; and Class 4, in the mucosa of the upper digestive tract and stomach.[3] High levels of the products of ADH-mediated ethanol oxidation, acetaldehyde and NADH, inhibit ADH activity.[4,5]

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In addition to acting in the rate-limiting step in the conversion of ethanol to acetaldehyde,[6] ADH might also participate in the rate-limiting step in synthesis of retinoic acid from retinol.[7] Retinoic acid, a ligand controlling a nuclear receptor signaling pathway, regulates embryonic development, spermatogenesis, and epithelial differentiation.[8,9] Ethanol acts as a competitive inhibitor of ADH-mediated retinol oxidation, so that increased alcohol consumption can result in decreased retinoic acid levels.[10,11]

Cytosolic ALDH1 and mitochondrial ALDH2 are the main enzymes in humans responsible for metabolizing acetaldehyde to aldehyde. The tetrameric enzymes ALDH1 and ALDH2 are expressed in many tissues, including the liver, with low mRNA levels found in the placenta.[12] Failure to metabolize acetaldehyde adequately leads to increased tissue and circulating levels of acetaldehyde, which can produce flushing, headaches, tachycardia, and nausea upon alcohol ingestion.

Gene Variants

Polymorphisms have been identified in the *ADH* genes *ADH1B* and *ADH1C*, as well as in the *ALDH2* gene. Population frequencies for the *ADH1B*, *ADH1C*, and *ALDH2* polymorphisms have been described in a recent HuGE review.[13] *ADH1A*, *ADH1B*, *ADH1C*, and *ADH4* are found together in a cluster at chromosomal region 4q22. The protein product of the *ADH1B*1* allele, which has an arginine at positions 47 and 369, has a relatively low Vmax and Km for ethanol and is most common in non-Hispanic whites and blacks or African Americans.[13] In contrast, the protein encoded by *ADH1B*2*, which has a histidine at position 47 and an arginine at position 369, has a high Vmax, with increased activity leading to faster ethanol clearance rates, and is found predominantly in Asians.[13] Similarly, the protein product of the *ADH1B*3* allele, which has an arginine at position 47 and a cysteine at position 369, has a high Vmax and high Km and a faster ethanol clearance rate at normal physiological levels of ethanol achieved after drinking. *ADH1B*3* is seen mostly in blacks or African Americans and Native Americans.[13]

The in vivo differences in ethanol clearance rates and acetaldehyde levels

FIGURE
Alcohol metabolism

Ethanol is metabolized by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH)

between the protein products of the *ADH1B* alleles is less clear.[14] Some have suggested that the effects vary by populations, with stronger effects seen in Asians than non-Hispanic whites,[15] which might in part be due to differences in *ALDH2* alleles. The effect of the more active *ADH1B* allele protein products appears to be dominant, with similar alcohol clearance rates for heterozygotes and *ADH1B*2* or *ADH1B*3* homozygotes.[3]

The *ADH1C* polymorphism also shows differences in kinetics, with the protein encoded by *ADH1C*1* having a higher Vmax than the *ADH1C*2* protein product. The protein encoded by *ADH1C*1* has a valine at position 349, while the *ADH1C*2* protein product contains an isoleucine. In blacks or African Americans and Asians, *ADH1C*1* is more common, while non-Hispanic whites show similar frequencies of both alleles. *ADH1C* shows strong linkage disequilibrium with *ADH1B*, and some have suggested that associations detected with the *ADH1C* allele are instead due to the linked *ADH1B* allele.[16,17]

Two polymorphic alleles of *ALDH2* are present as well, the wild type variant *ALDH2*1* and the inactive *ALDH2*2* variant, which encodes a protein with a glutamine to lysine change at position 487. Homozygotes for the *ALDH2*2* allele have almost no mitochondrial ALDH activity, leading to increased levels of acetaldehyde following consumption of alcohol, which in turn inhibit ADH activity and slow alcohol elimination.[4] *ALDH2*2* heterozygotes show markedly reduced ALDH activity and alcohol elimination as well, which might be explained by the dominant effect of *ALDH2*2* products when incorporated into ALDH2 tetramers.[18] *ALDH2*2* is prevalent among Asians but rare in other races and ethnicities.[6,19]

Disease: Fetal Alcohol Syndrome

Alcohol is a teratogen, and prenatal exposure can cause lifelong damage. Maternal alcohol use can result in a spectrum of disabilities, the most severe of which is fetal alcohol syndrome (FAS). FAS prevalences from 0.5-2.0 cases per 1000 live births have been reported and, of the 4 million babies born worldwide each year with prenatal alcohol exposure, approximately 1000-6000 are born with FAS.[20] Children with FAS have dysmorphia, growth problems, and central nervous system (CNS) abnormalities. As published recently in recommendations from the Centers for Disease Control and Prevention (CDC),[20] a diagnosis of FAS requires specific CNS abnormalities, a prenatal or postnatal growth deficit in height or weight, and 3 specific facial abnormalities: smooth philtrum, thin vermilion border, and small palpebral fissures. The CNS anomalies can be structural, neurologic, or functional. Structural defects can include microcephaly or brain abnormalities visible through imaging techniques, while neurologic problems can be seizures, nystagmus, lack of coordination, or lack of motor control. Functional defects can include those indicating damage to the corpus callosum, cerebellum, or basal ganglia, as well as a global cognitive deficit (such as decreased IQ or substantial developmental delay) or deficits in 3 or more functional domains (cognitive, executive, motor functioning, attention/hyperactivity, or social skills).[20]

Several factors indicate that susceptibility to FAS might have a genetic component. In animal model studies, strain-specific susceptibility to fetal alcohol damage has been observed in inbred strains of mice.[21-24] Those studies, which could distinguish between maternal and fetal genotypic effects, found that both maternal and fetal genetic factors contributed significantly to susceptibility to ethanol teratogenesis.[22,23] For example, Gilliam and Irtenkauf[22] found a greater litter weight deficit and increased malformation rate in ethanol-exposed litters carried by the C57BL/6J strain of mice compared with those carried by the LS strain when the 2 strains were crossed. These distinctions were observed for the hybrid, genetically similar progeny, consistent with maternal genetic factors contributing to susceptibility. Gilliam et al[23] had similar findings, except that fetal, not maternal, genotype conferred susceptibility to fetal weight deficits. Gilliam and Irtenkauf [22] and Gilliam et al[23] found that ethanol-exposed progeny with different genotypes that were carried by the same maternal strain showed distinct rates of malformation, indicating that fetal genotype also plays a role in susceptibility. However, in both cases, the effect was only significant when progeny were carried by the more susceptible maternal strain, indicating that maternal genotype had a greater influence than fetal genotype on susceptibility to ethanol teratogenesis. Chernoff[21] showed that fetal abnormalities and weights were directly related to maternal blood alcohol levels, which were inversely related to maternal ADH activity. However, Gilliam and Irtenkauf[22] and Boehm et al[24] did not find significant differences in maternal blood ethanol levels among strains, despite differences in susceptibility.

Family studies indicate high recurrence rates of FAS in siblings,[25] with higher discordance rates in dizygotic than monozygotic twins.[26] Genetic factors can vary by race and ethnicity, and higher rates of FAS have been observed in blacks or African Americans and Native Americans than non-Hispanic whites.[27] After adjusting for frequency of maternal drinking, chronic alcohol problems, and age, a 7-fold increase in FAS risk was seen for blacks or African Americans.[28] Together, these studies suggest that genetic factors may interact with the environmental factor of prenatal alcohol exposure to increase the risk of FAS.

ASSOCIATIONS

Association studies have examined the relationship between *ADH1B* polymorphisms and FAS. The contribution of the *ADH1B* genotype to alcoholism and alcohol-related morbidities has been studied extensively, and the correlation between *ADH1B* and certain cancers has been analyzed as well, including a recent HuGE review.[13] A review of these other associations, particularly alcoholism, will be informative for the understanding of the effects of the *ADH1B* genotype on FAS susceptibility.

ASSOCIATION OF *ADH1B* AND ALCOHOLISM

Genetic background affects susceptibility to alcoholism and patterns of alcohol use, as well as metabolism of alcohol. Increased *ADH1B* activity, especially when coupled with decreased *ALDH2* activity, can lead to elevated acetaldehyde levels following alcohol consumption. These high acetaldehyde levels can result in unpleasant sensations, such as nausea and facial flushing, which might act as deterrents to alcohol consumption.[4] Indeed, homozygotes for the *ALDH2*2* variant, found almost exclusively in Asians, show greatly decreased rates of alcohol dependence, and heterozygotes appear protected as well, although to a somewhat lesser degree.[29]

Likewise, a decreased risk of alcoholism has been found for those with either of the higher activity *ADH1B* alleles, *ADH1B*2* and *ADH1B*3*. This association has been seen for *ADH1B*2* most clearly in Asians.[16,29-43] An association has also been reported in Jews,[44] Hispanics,[17,45] and non-Hispanic whites,[17,43,46-49] as well as in a metaanalysis.[50] However, not all studies have found a correlation.[51,52] A greater level of response to alcohol in those with *ADH1B*2* has also been observed in some studies,[53,54] but not in others.[55] Another way of considering alcohol use is to examine drinking patterns (frequency, number of drinks per occasion), either in people with alcoholism or in a population-based sample. While some studies focusing on *ADH1B*2* and drinking patterns have observed decreased drinking in those carrying the *ADH1B*2* allele,[56-58] others have seen little or no effect of genotype on behavior.[29,59,60] Most participants in these studies have been men, and when women were included, significant associations for women were not identified between *ADH1B*2* and alcoholism[17,35,46-48] or between *ADH1B*2* and drinking patterns.[57]

The connection between *ADH1B*3* and alcoholism or drinking patterns is less established. Associations have been observed with drinking patterns[61] and alcoholism[61] in some studies, with *ADH1B*3* acting as a protective factor. *ADH1B*3* has also been associated with a negative family history of alcoholism[62] and a more intense response to alcohol.[63] However, other investigators have not seen a correlation with alcoholism.[64]

Some studies have reported a relationship between ethanol metabolism and *ADH1B* genotype,[65-69] although others have not seen an association.[14,68,70-72] Furthermore, most of these studies have again included male subjects predominantly.

ASSOCIATIONS OF *ADH1B* AND ALCOHOL-RELATED MORBIDITIES

While the role of *ADH1B* in the susceptibility to alcoholism may be relatively clear, the interaction of this gene, as well as the importance of acetaldehyde levels, in the development of alcohol-related medical problems is less straightforward. Several different mechanisms have been proposed to account for damage caused by exposure to high levels of alcohol. For example, increased levels of acetaldehyde can lead to elevated lipid peroxidation, which then causes oxidative stress.[73,74] Sites of ethanol metabolism, such as the liver, can be especially vulnerable, as well as tissues that are more sensitive to damage, either by the high ethanol or acetaldehyde levels themselves or the pathways activated as a result. The *ADH1B* genotype has been investigated primarily in relation to liver disease, pancreatitis, diabetic complications, and certain cancers.[12,50-51,75-105]

Several studies have found *ADH1B*2* to be protective against liver disease.[75-80] However, when level of alcohol intake is not included in the analysis, as is the case for some studies, the protective effect might be indirect. Those carrying the *ADH1B*2* allele might be genetically inclined to consume less alcohol, which in turn would lead to less alcohol-mediated damage, rather than *ADH1B*2* affecting the damage done to the liver once high levels of alcohol are present. In contrast, because *ADH1B*2* might lead to higher levels of acetaldehyde, this allele might be expected to increase the risk of alcohol-mediated damage. Some studies have found that among people with alcoholism, those with *ADH1B*2* are at increased risk of liver damage.[12,50,75,81,82] However, other studies did not find any association between *ADH1B* genotype and liver disease.[43,51,83-86] Likewise, *ADH1B*2* was more prevalent in people with alcoholism who had pancreatitis than those who did not have this complication in some studies but not in others.[84,87-91]

ADH1B has also been studied in relation to certain cancers. Again, many studies have identified *ADH1B*2* as a protective factor. In several studies, some of which adjusted for alcohol intake, *ADH1B*1* homozygosity was associated with increased risk for oropharyngolaryngeal or esophageal cancers.[88,92-97] However, other studies identified *ADH1B*2* as a risk factor. Sturmer et al[98] found that *ADH1B*2* was more common in women with breast cancer, despite the fact that those with *ADH1B*2* drank less. However, in Lilla et al,[99] *ADH1B*2* was associated with decreased risk of breast cancer as alcohol consumption increased, while *ADH1B*1* was associated with increased risk with higher alcohol consumption. Another study did not find an association between *ADH1B* genotype and cancer for laryngeal cancer.[100]

Other associations have also been examined for *ADH1B*. In people with diabetes, *ADH1B*2*, in combination with *ALDH1B*1*, has been associated with an increased risk of nephropathy and retinopathy, while *ADH1B*1* with *ALDH1B*2* has been associated with an increased neuropathy risk.[101] Homozygosity for the *ADH1B*1* allele has also been associated with increased risk for cerebral infarction and lacunae in

men,[102] testicular atrophy in men with alcoholism,[103] and brain atrophy in men with alcoholism,[104] but a decreased risk for avascular necrosis of the hip joint in people with alcoholism.[105] Chao et al[105] suggest that the *ADH1B* genotype, in combination with variations at other loci, might affect which organ systems are most impacted by increased alcohol levels.

ASSOCIATION OF *ADH1B* AND FAS

To identify studies on the association between *ADH1B* and FAS published before March 2006, we conducted a PubMed search using the MeSH terms "fetal alcohol syndrome" and "genes," as well as "ADH1B." We also searched using the key words "fetal alcohol and associations," "ADH and fetal alcohol," and "ADH1B or ADH2," and we reviewed the reference lists of all published studies to confirm that all relevant papers had been identified. We also performed similar searches using EMBASE and the ISI Web of Knowledge. These searches identified 6 studies on *ADH1B* and FAS. The findings of these studies are summarized in Table 1, which lists the case-control studies, and Table 2, which describes the cohort studies.

One study focused on the *ADH1B*1* and *ADH1B*2* alleles, while 5 of the studies compared *ADH1B*1* and *ADH1B*3*. Most studies found an increased risk for alcohol-related birth defects associated with the *ADH1B*1* homozygous genotype,[106-110] while 1 study found the reverse.[111] However, the characteristics measured as an indication of fetal alcohol syndrome varied between studies.

Viljoen et al[110] performed a case-control study of a mixed-ancestry population in Western Cape Province, South Africa, which has a high prevalence of FAS (Table 1). The study comprised 56 case mothers and their affected children and 178 control individuals. Case children were identified at hospital genetics clinics and through an epidemiological survey. Children were first screened to identify those whose head circumference was less than the 10th percentile or who had both height and weight parameters below the 10th percentile. Those screening positive then received independent physical examinations by dysmorphologists, followed by a maternal interview when both dysmorphologists observed features consistent with FAS. If the interview indicated heavy alcohol exposure during the pregnancy, neurodevelopmental assessment of the child was performed and compared with an unaffected child matched by school, sex, and ethnic group. However, for genotyping, the controls were derived from previously collected specimens from blood donors who were from the same geographic location and were of similar ancestry. No information was available on the sex, drinking habits, or FAS status of control individuals. The *ADH1B*3* allele frequency was low for both case and control participants and did not show significant variation between the groups in this study. This study found a lower frequency of the *ADH1B*2* allele in affected children (.036) and their mothers (.036) compared with that in controls (.107, $P = .025 \pm .004$ for both).

All other studies focused on the *ADH1B*1* and *ADH1B*3* alleles, predominantly in blacks or African Americans. McCarver et al[108] recruited a cohort of 243 maternal-infant pairs based on maternal alcohol intake during pregnancy and maternal *ADH1B* genotype in order to obtain a variety of both (Table 2). No correlation was observed between alcohol intake and maternal *ADH1B* genotype.[108] The Mental Development Index (MDI) from the Bayley Scales of Infant Development was used to measure infant outcome at 12 months of age. Birthweight, birth length, and birth head circumference were also assessed. The authors found an association between maternal or infant *ADH1B*1* homozygosity, or both, and lower MDI scores of those infants whose mothers drank alcohol during pregnancy ($\beta = 0.16$, partial correlation coefficient = 0.16, $P < .01$). Maternal *ADH1B*1* homozygosity also showed an association with smaller birthweights of infants whose mothers drank during pregnancy ($\beta = 0.17$, partial correlation coefficient = 0.22, $P < .001$), as well as an association with decreased head circumference, regardless of maternal drinking status ($\beta = 0.14$, partial correlation coefficient = 0.15, $P < .05$). In a continuation of the McCarver et al[108] study, Das et al[106] studied the relationship between alterations in children's facial morphology, maternal alcohol use, and *ADH1B* genotype (Table 2). To analyze facial morphology, an investigator blinded to genotype and maternal drinking status measured photographs of infants to determine inner canthal distance, palpebral fissure length, and philtrum length. Those measurements, considered both individually and as a composite, were smaller in infants whose mothers drank during pregnancy when both the mother and infant lacked *ADH1B*3* alleles compared with (1) mothers who did not drink and (2) mothers who drank but either the mother or infant, or both, had at least 1 *ADH1B*3* allele ($F = 4.94$, $P = .002$). This correlation was still seen after adjustment for other growth measurements affected by prenatal alcohol exposure.

A study by Jacobson et al[107] was designed to replicate and extend the findings of McCarver et al. In the Jacobson study, 217 mothers and 239 children from 263 black or African American maternal-child pairs were genotyped for *ADH1B*, and the children underwent extensive evaluations at different ages (Table 2). All moderate and heavy drinkers were included in the study, as well as 5% of the lower-level drinkers or abstainers and 53 heavy cocaine and light alcohol users. Jacobson et al found that *ADH1B*1* homozygous mothers reported a higher mean drinking frequency (2.45 drinking days/week) at conception, compared with women with at least one *ADH1B*3* allele (1.82 drinking days/week). For infants, prenatal alcohol exposure was associated with smaller head circumference and decreased Bayley MDI scores only in those whose mothers were homozygous for *ADH1B*1*. For infants assessed at 7.5 years, poorer performance on tests, including Digit Cancellation, Category Fluency, magnitude estimation, and reaction time on the Continuous Performance Test (CPT) AX task, was associated with prenatal alcohol exposure in

TABLE 1
Case-control studies on fetal alcohol syndrome

Study	Geographic area	Race or ethnicity	Case definition	Method of ascertainment: Case participants	Method of ascertainment: Control participants	No. of case/control participants	Prevalence of genotype: Participants	Genotype N (% total): 1/1	1/2	2/2	1/3	2/3	3/3	Odds ratio (95% CI, *P*)
110	South Africa	Khoisan-Caucasian	<10th percentile head circumference or height and weight Dysmorphology evaluation Neurodevelopmental assessment	Hospital, community	Blood donors	56/178	Case children	48 (86%)	4 (7%)	0	4 (7%)	0	0	For *ADH1B*2*-containing genotype: 0.33 (0.12-0.95, $P = .055$) For *ADH1B*2* or *ADH1*B*3*-containing genotypes: 0.48 (0.21-1.07, $P = .101$)
							Mothers of case children	48 (86%)	4 (7%)	0	4 (7%)	0	0	
							Controls	132 (74%)	31 (17%)	2 (1%)	9 (5%)	3 (2%)	1 (1%)	
111	USA	Black or African American, non-Hispanic white	Alcohol-related physical features in newborns: Facial features (broad nasal bridge, depressed nasal bridge, anteverted nares, long philtrum, hypoplastic philtrum, thin vermilion border) Head size Growth restriction	Hospital, substance abuse clinic	Hospital, substance abuse clinic	Maternal: 49/209 Infant: 20/68	Mothers of case children	8 (33%) (black or African American), 30 (63%) (all races)			16 (67%) (black or African American), 18 (38%) (all races)			Adjusted OR for *ADH1B*1/ADH1B*3*: All women: 3.24 (1.56-6.76, $P = .002$) Black or African American women: 2.49 (0.809-7.66, $P = .112$)
							Mothers of control children	34 (57%) (black or African American), 181 (87%) (all races)			26 (43%) (black or African American), 28 (13%) (all races)			
							Case children	6 (40%) (black or African American), 10 (50%) (all races)			9 (60%) (black or African American), 10 (50%) (all races)			
							Control children	20 (71%) (black or African American), 58 (85%) (all races)			8 (29%) (black or African American), 10 (15%) (all races)			
109	USA	Black or African American	Birthweight (BW), small for gestational age (SGA)	Population-based	Population-based	22/284	Case children	17 (77%) (BW), 20 (91%) (SGA)			5* (23%) (BW), 2 (10%) (SGA)			SGA for *ADH1B*3*-containing genotypes: 0.32 (0.07-1.43)
							Control children	211 (74%) (BW), 208 (73%) (SGA)			73* (26%) (BW), 76 (27%) (SGA)			

**ADH1B*3/ADH1B*3 or ADH1B*1/ADH1B*3.*

TABLE 2
Cohort studies on fetal alcohol syndrome

Study	Geographic area	Race or ethnicity	What measured	Method of ascertainment	Cohort size	Associations reported*
108	USA	Black or African American	Growth parameters at birth (head circumference, length and weight) Mental Development Index (MDI) from Bayley Scales of Infant Development at 1 year old	Hospital, matched (alcohol intake similar for different *ADH1B* genotypes)	243†	Lower birthweight and drinking during pregnancy × ADH1B*1/ADH1B*1 maternal: $\beta = 0.17$, partial correlation coefficient = 0.22, $P < .001$ (Model $r^2 = 0.41$, F = 7.9, $P < .0001$) Lower head circumference and ADH1B*1/ADH1B*1 maternal: $\beta = 0.14$, partial correlation coefficient = 0.15, $P < .05$ (Model $r^2 = 0.21$, F = 20.5, $P < .0001$) Lower MDI and drinking during pregnancy × ADH1B*1/ADH1B*1 maternal and infant: $\beta = 0.16$, partial correlation coefficient = 0.16, $P < .01$ (Model $r^2 = 0.09$, F = 55.1, $P < .0001$)
106	USA	Black or African American	Facial morphology at 1 year old	Hospital, matched (alcohol intake similar for different *ADH1B* genotypes)	247†	Smaller facial features in model considering 3 facial features simultaneously and drinking at first prenatal visit × ADH1B*1/ADH1B*1 maternal and infant: F = 4.94, $P = .002$ (Model $r^2 = 0.08$, $P < .01$)
107	USA	Black or African American	Maternal alcohol use At birth: weight, head circumference At 6.5 months: Processing speed assessed with Fagan Test of Infant Intelligence At 12 months: Processing speed and cross-modal transfer assessed with Fagan Test of Infant Intelligence; reaction time with Visual Expectancy Paradigm; complexity of play At 13 months: Mental Development Index (MDI) from Bayley Scales of Infant Development At 7.5 years: Working memory assessed with Digit Span and Arithmetic tests from Wechsler Intelligence Scale for Children, Third Edition; Focused attention with Digit Cancellation test; Executive function/ working memory with Category Fluency measured using Verbal Fluency subtest of McCarthy Scales of Children's Abilities; Sustained attention with Continuous Performance Test; Processing efficiency with Magnitude Estimation Children's classroom teachers completed Achenbach Teacher Report Form to assess social competence and behavioral problems and Barkley-DuPaul ADHD Rating Scale	Hospital	Maternal genotype: 140 *ADH1B*1/ADH1B*1*, 72 *ADH1B*1/ADH1B*3*, 5 *ADH1B*3/ADH1B*3*	Pregnancy drinking patterns at conception, maternal ADH1B*1/ADH1*B vs ADH1B*3/-: Mean oz absolute alcohol/day: 0.96 vs 0.57, t = 2.22 Mean frequency (drinking days/week): 2.45 vs 1.82, t = 2.22 Infant outcomes with prenatal alcohol exposure, maternal *ADH1B*1/ADH1*B* vs *ADH1B*3/-*: Head circumference: r = −0.31 vs −0.05, $\beta = -0.23$ vs 0.04 Bayley MDI scales: r = −0.26 vs −0.12, $\beta = -0.24$ vs −0.10 Elicited symbolic play: r = −0.26 vs −0.06, $\beta = -0.18$ vs −0.06 Processing speed, FTII: r = 0.03 vs 0.23, $\beta = 0.03$ vs 0.31 Processing speed, cross-modal: r = 0.34 vs −0.09, $\beta = 0.26$ vs −0.11 Visual Expectancy Paradigm, reaction time: r = 0.49 vs 0.06, $\beta = 0.46$ vs 0.17 Visual Expectancy Paradigm, proportion quick responses: r = −0.57 vs −0.19, $\beta = -0.55$ vs −0.26 Outcomes at 7.5 years with prenatal alcohol exposure, maternal *ADH1B*1/ADH1*B* vs *ADH1B*3/-*: Cognitive outcomes: Freedom from distractibility: r = −0.12 vs 0.05, $\beta = -0.16$ vs −0.10 Digit cancellation (interference): r = 0.28 vs 0.02, $\beta = 0.23$ vs −0.09 Category fluency: r = −0.19 vs −0.07, $\beta = -0.23$ vs −0.09 CPT RT (AX task): r = 0.15 vs 0.18, $\beta = 0.18$ vs 0.07 Magnitude estimation (slope), number: r = −0.30 vs −0.06, $\beta = -0.30$ vs −0.06 Magnitude estimation (slope), arrows: r = 0.22 vs 0.04, $\beta = 0.22$ vs 0.02 Achenbach Teacher Report Form: Social problems: r = 0.25 vs −0.04, $\beta = 0.24$ vs −0.01 Attention problems: r = 0.26 vs 0.03, $\beta = 0.21$ vs 0.06 Aggressive behavior: r = 0.25 vs −0.03, $\beta = 0.22$ vs −0.06 Delinquent behavior: r = 0.18 vs −0.02, $\beta = 0.14$ vs −0.04 Externalizing: r = 0.25 vs −0.03, $\beta = 0.23$ vs −0.02 Total problems: r = 0.41 vs −0.00, $\beta = 0.38$ vs 0.03 ADHD Rating Scale: Impulsivity: r = 0.32 vs −0.03, $\beta = 0.29$ vs −0.06 Inattention: r = 0.28 vs −0.01, $\beta = 0.22$ vs −0.04 ADHD classification: r = 0.30 vs 0.10, $\beta = 0.30$ vs 0.14 Infant outcomes with prenatal alcohol exposure, child *ADH1B*1/ADH1*B* vs *ADH1B*3/-*: Head circumference: r = −0.33 vs −0.08, $\beta = -0.24$ vs −0.00 Bayley MDI scales: r = −0.18 vs −0.27, $\beta = -0.14$ vs −0.16 Elicited symbolic play: r = −0.17 vs −0.34, $\beta = -0.09$ vs −0.34

Continued on page 18.

TABLE 2
Cohort studies on fetal alcohol syndrome

Continued from page 17.

Study	Geographic area	Race or ethnicity	What measured	Method of ascertainment	Cohort size	Associations reported*
107 (continued)						Processing speed, FTII: r = 0.20 vs 0.01, β = 0.20 vs 0.01 Processing speed, cross-modal: r = 0.14 vs 0.08, β = 0.14 vs 0.08 Visual Expectancy Paradigm, reaction time: r = 0.34 vs 0.19, β = 0.25 vs 0.26 Visual Expectancy Paradigm, proportion quick responses: r = −0.41 vs −0.41, β = −0.34 vs −0.26 Outcomes at 7.5 years with prenatal alcohol exposure, child *ADH1B*1/ADH1*B* vs *ADH1B*3/-*: Cognitive outcomes: Freedom from distractibility: r = −0.06 vs −0.03, β = −0.14 vs −0.05 Digit cancellation (interference): r = 0.16 vs 0.16, β = 0.13 vs 0.10 Category fluency: r = −0.16 vs −0.08, β = −0.22 vs −0.07 CPT RT (AX task): r = 0.13 vs −0.06, β = 0.16 vs −0.02 Magnitude estimation (slope), number: r = 0.22 vs 0.07, β = 0.21 vs 0.07 Magnitude estimation (slope), arrows: r = −0.28 vs −0.07, β = −0.28 vs −0.08 Achenbach Teacher Report Form: Social problems: r = 0.21 vs 0.15, β = 0.20 vs 0.16 Attention problems: r = 0.13 vs 0.38, β = 0.10 vs 0.35 Aggressive behavior: r = 0.18 vs 0.24, β = 0.16 vs 0.21 Delinquent behavior: r = 0.07 vs 0.34, β = 0.08 vs 0.37 Externalizing: r = 0.16 vs 0.27, β = 0.16 vs 0.28 Total problems: r = 0.06 vs 0.47, β = 0.06 vs 0.48 ADHD Rating Scale: Impulsivity: r = 0.23 vs 0.27, β = 0.21 vs 0.24 Inattention: r = 0.15 vs 0.40, β = 0.10 vs 0.32 ADHD classification: r = 0.26 vs 0.10, β = 0.28 vs 0.27

* Pearson "r" is the unadjusted relation of prenatal alcohol exposure to child outcome; standardized "β" coefficient refers to the relation after adjusting for potentially confounding variables.

† Maternal-infant pairs were enrolled on the basis of maternal alcohol intake during pregnancy and maternal *ADH1B* genotype. One hundred seventy-three participants overlapped between the McCarver et al[108] and Das et al[106] studies.

those children whose mothers were *ADH1B*1* homozygotes. Teacher ratings for these children were poorer as well, especially in the areas of social problems, attention, aggressive behavior, inattention, and impulsivity, with higher attention-deficit/hyperactivity disorder (ADHD) scores on the Barkley-DuPaul ADHD scale. Some of the same associations with prenatal alcohol exposure were seen with infants and children who were homozygous for *ADH1B*1*, including reduced head circumference, processing speed, Category Fluency, reaction time on the CPT AX task, and magnitude estimation. However, prenatal alcohol exposure affected elicited symbolic play and reaction time on the Visual Expectancy Paradigm only in those infants with at least 1 *ADH1B*3* allele. Also, teacher ratings were poorer for those children with the *ADH1B*3* allele for attention problems, delinquent problems, externalizing, and total problems, as well as inattention on the ADHD rating scale, although prenatal alcohol exposure affected teachers' rating of social problems only in *ADH1B*1* homozygous children.

Arfsten et al[109] performed a nested study using control children from a larger population-based case-control study, focusing on the association between infant *ADH1B*3* genotype and fetal growth (Table 1). In that study, dried blood spots from 306 black or African American infants were genotyped, and 25% of these children had at least 1 *ADH1B*3* allele. These data were combined with information obtained from the case-control study on maternal drinking status, infant birthweight, and whether the infant was small for gestational age (SGA). Below the 10th percentile of the population fetal growth curve was considered low birthweight, and comparisons to determine SGA status were sex and gestational age-specific; however, actual measurements were based on maternal recall. Maternal drinking showed no association with in-

fant *ADH1B* genotype. Being SGA was associated with *ADH1B*1* homozygosity, with an odds ratio (OR) of 3.15 (95% confidence interval [CI] 0.7-14.26), as well as with maternal alcohol consumption (OR = 2.31, 95% CI 0.77-6.91). SGA infants with prenatal alcohol exposure showed increased odds for being *ADH1B*1* homozygotes, but the authors suggested that this association might have been complicated by the link between maternal drinking and maternal smoking, a known SGA risk factor. The *ADH1B*1/ADH1B*1* genotype showed a slight but nonsignificant association with decreased birthweight in those infants exposed to alcohol prenatally. Arfsten et al[109] suggested that the effects seen with *ADH1B*1* homozygosity alone might have reflected the influence of this allele on retinol metabolism.

In contrast, Stoler et al[111] found an increased risk for FAS with the maternal *ADH1B*1/ADH1B*3* genotype (Table 1). Genotyping was performed on 404 mothers and 139 infants in a nested study. The percentage of black or African American mothers with the *ADH1B*1/ADH1B*3* genotype (46%) was higher than expected (33%), and this genotype was correlated with increased drinking. Newborns were examined to determine affected or unaffected status, based on facial features and size. For a designation of affected, the infant had to show 4 or more of the characteristic facial features (broad nasal bridge, depressed nasal bridge, anteverted nares, long philtrum, hypoplastic philtrum, or thin vermilion border), as well as microcephaly or growth restriction (defined as head size, birthweight, or length 2 standard deviations below the mean for infants of the same race, sex, and gestational age). The *ADH1*1/ADH1*3* genotype was seen more often in black or African American mothers with affected (64%) infants than those with unaffected infants (43%), and 60% of black or African American-affected infants had the *ADH1*1/ADH1*3* genotype, as opposed to 29% of the unaffected infants. Using logistic regression, the authors reported an OR of 3.24 (95% CI 1.55-6.76) for the association between maternal *ADH1*1/ADH1*3* genotype and FAS for all women and an OR of 2.49 (95% CI 0.809-7.66) for black or African American women.

INTERACTIONS

Level of alcohol exposure

The level of prenatal alcohol exposure was assessed differently between studies, and this might explain some of the discrepancies between the results. Uniform measurements of alcohol intake and controlling for this variable are especially important because the *ADH1B* genotype might affect alcohol intake. Thus, risk associated with this genotype might be due either to its influence on alcohol intake or to its role in altering levels of alcohol, acetaldehyde, or other factors (or a combination of both effects).

Most studies used interviews at regular time points to assess alcohol intake and defined heavy alcohol use as 1 drink or more per day. The McCarver[108] and Das[106] studies used interviewer-directed patient recall of a day-by-day history to review the number of drinks each day by beverage for the 2-week period before each antenatal visit, as well as a typical week in the periconceptional period at the first antenatal visit. Average daily alcohol consumption for each time period was calculated, and heavy alcohol use was defined as 0.5 ounces or more of absolute alcohol per day and light use as less than 0.5 ounces/day. The median alcohol intake for mothers in these studies was 0.5 ounces/day in the preconception period and 0.17 ounces/day in the 2 weeks before the first antenatal visit. Since recruitment for these studies was based on maternal genotype and alcohol use, these studies were not able to analyze how much of the protective effect of *ADH1B*3* was due to decreased maternal alcohol intake. Jacobson et al[107] used a similar timeline follow-back interview technique to measure maternal alcohol intake and the same definition of heavy drinking. In addition, they administered the Michigan Alcoholism Screening Test (MAST) to assess level of alcohol dependence. Among drinkers, alcohol intake did decrease during pregnancy, going from an average alcohol intake of 1.9 days/week to 0.9 days/week and 4.5 drinks/occasion to 3.6 drinks/occasion. Stoler et al[111] also used the timeline follow-back procedure to assess alcohol intake in the 4 weeks prior to each antenatal appointment, as well as the 4 weeks before the first visit. Participants also filled out a self-administered alcoholism screening questionnaire (TWEAK, which is an acronym for Tolerance, Worry about drinking, Eye-opener [morning drinking], Amnesia [blackouts], and Cut down on drinking [K/C]). In their analysis, Stoler et al combined the drinking categories "very high," defined as drinking at least 1 drink/day or 28 drinks over a 4-week period, and "high," defined as drinking more often than weekly but less than daily, for a total of 34 very high/high drinkers. Stoler et al[111] adjusted for maternal weight gain and smoking, although these factors might correlate with alcohol use.

In the study by Arfsten et al,[109] maternal alcohol intake was assessed using parent interviews within 1 year of the infant's birth, which asked about alcohol consumption in the 3 months before the mother's last period, the first 3 months of pregnancy, the second and the third trimesters. Most analyses used a dichotomous variable for alcohol intake (none vs any), although the average number of drinks/day was used for some linear regression analyses. In contrast, Viloen et al[110] did not provide any measures of maternal alcohol intake, instead stating that all mothers of FAS children were assumed to be heavy drinkers.

Demographic and other factors

Demographic factors have been associated with an increased risk of FAS, including black or African American race, low socioeconomic status (SES), and advanced maternal age.[27,112-114] In addition, poor maternal nutrition, smoking, and multiparity have also been associated with increased risk. The participants in some of the studies have shared some of these risk factors, including low SES, poor nutrition, smoking, and multiparity.[110]

LABORATORY TESTS

As mentioned in a recent HuGE review,[13] the ADH1B polymorphism can be genotyped using polymerase chain reaction or restriction fragment length polymorphism techniques. The ADH1B genotype can also be detected by single nucleotide polymorphism (SNP) analysis.

POPULATION TESTING

Currently, studies on genetic testing for *ADH1B* are not available. The effect of the *ADH1B* genotype on FAS requires further clarification prior to any systematic population-level testing. Furthermore, alcohol exposure in utero can be hazardous to the fetus regardless of *ADH* genotype. Approaches have been suggested that supplement the population-wide public health measures to strongly discourage any alcohol use by women who are pregnant, planning a pregnancy, or at risk for a pregnancy. In the clinical setting, universal screening for alcohol use among all women of childbearing age could identify both women who drink above recommended levels and those who drink and could become pregnant.[20] For those identified through such screening, a brief motivational intervention that focused on both risk drinking and ineffective contraception use has been demonstrated to reduce the risk of an alcohol-exposed pregnancy.[115]

GAPS AND RESEARCH PRIORITIES

Consistent case definitions must be used

To compare data across studies, a consistent case definition of FAS is required. The different studies described previously focused on different aspects of the FAS phenotype and assessed children at different ages, making comparison of findings difficult and metaanalysis of results impossible. Furthermore, 3 of the studies[106-108] focused on the more common nonsyndromal prenatally exposed offspring, rather than on children with FAS, and these studies consisted of comparisons of average measurements between *ADH1B* genotypes. While the detection of adverse outcomes predicted by FAS studies tended to validate the method used for ascertainment of the independent variable and the moderating influence of the genotype, the lack of categorization of children as affected or not is problematic. Ascertainment of FAS status has been challenging, with the absence of uniformly accepted diagnosis criteria and referral guidelines, as well as FAS features that overlap with other conditions. The criteria presented in a recent CDC report should assist in addressing some of these issues.[20]

Exposure measurements should be improved

Documentation and confirmation of prenatal alcohol exposure has been difficult to establish. Self-reporting of alcohol use in pregnancy is not always accurate.[116] Most measurements are based on maternal recall, which can lead to imprecise exposure information. Furthermore, the stigmatization associated with drinking alcohol while pregnant can cause mothers to underreport alcohol intake. Studies have investigated the use of biomarkers to detect alcohol levels, which would provide an objective measurement of alcohol intake. These studies have shown improvements in self-reporting if participants are aware of potential laboratory confirmation.[117,118] However, these tests have lower sensitivity in women, especially in pregnant women, and no biomarkers are currently available that are sensitive enough to detect the relatively low levels of alcohol that would still place the fetus at risk. As with case definitions, consistent assessments and groupings of alcohol intake will be essential if data are to be compared between studies. Ideally, information on the quantity of alcohol consumed, the time period over which it is consumed, and the frequency of drinking occasions would be obtained. For analysis, alcohol intake at specific stages would be used, rather than the average intake across the entire pregnancy. This will most likely only be accomplished in a prospective study, and even then problems relating to maternal self-reporting will remain.

Alcohol-related studies in women are needed

The effect of the *ADH1B* genotype, especially the *ADH1B*3* allele, on alcohol intake and metabolism, particularly in women, must be better established. Most studies on alcoholism have been done predominantly in men, and the women who were included in the studies showed lower overall alcohol consumption; thus, results are not necessarily generalizable to women. Women are known to metabolize alcohol differently and are more susceptible to the development of alcohol-related diseases. Women show higher peak blood alcohol levels than men after ingestion of the same amount of alcohol, explained in part by slower gastric emptying of ethanol, a higher rate of hepatic ethanol oxidation, a decreased volume of distribution, and potentially by lower gastric metabolism secondary to decreased ADH activity in the stomach (decreased first pass metabolism). All of this can lead to higher levels of hepatotoxic metabolites (eg, acetaldehyde) in women.[119] Furthermore, hormonal influences might also influence alcohol metabolism. Pregnancy might affect alcohol metabolism, so truly comprehensive studies would need to establish the effect of the *ADH1B* genotype on alcohol metabolism in pregnant women.

Definitive studies are needed

Ideally, a case-control study of FAS children could be performed using 2 control populations: 1 whose mothers did not drink, and thus would not have been exposed to alcohol-related teratogens, and 1 whose mothers drank amounts comparable with those of case mothers but who remained unaffected by exposure to alcohol-related teratogens.[120] Better exposure measurements would allow investigators to control more accurately for alcohol intake so that the question of whether the association between *ADH1B* genotypes and FAS is mediated solely through its effects on drinking propensity might be resolved.

Also, some studies analyzed those with the *ADH1B*1/ADH1B*3* and *ADH1B*3/ADH1B*3* genotypes together.[106-109] However, examining the 2 genotypes

separately might be of value. A recent meta-analysis by Lewis and Smith[121] found that while *ALDH2*2* homozygotes showed reduced risk of esophageal cancer compared with *ALDH2*1* homozygotes, presumably related to decreased alcohol intake, *ALDH2*1/ALDH2*2* heterozygotes showed increased risk, likely because of the increased acetaldehyde levels following alcohol consumption that result from this genotype. A similar scenario might be possible for *ADH1B*, and an increased risk for *ADH1B*1/ADH1B*3* heterozygotes was observed for the Stoler et al study,[111] which examined heterozygotes only, rather than *ADH1B*1/ADH1B*3* heterozygotes and *ADH1B*3* homozygotes together as in the other studies.[106-109] Larger sample sizes than those of the previous studies would increase the power to find associations and allow separate evaluation of heterozygotes and homozygotes.

However, a single study enrolling enough children with FAS to have suitable power might not be feasible. An alternative would be establishment of multicenter studies that include maternal and child DNA collection, standardized exposure information, and well-defined case definitions, so that data from the different centers could be combined. A multicenter study using already available data and samples from international cohorts, which are more current than those in the United States, might also be an option. Future studies might also incorporate use of microarrays, rather than being limited to the very few polymorphisms that have been studied.

Association with additional genes should be explored

In addition to *ADH1B*, other genes have been suggested as candidates for association with FAS. The *cytochrome P450 E1* (*CYP2E1*) gene acts in the microsomal ethanol oxidizing system, which also functions in ethanol metabolism, particularly at high ethanol concentrations.[120-122] Rasheed et al[125] reported an association between increased placental *CYP2E1* expression and smaller head size in infants of mothers who drank heavily. McCarver et al[126] identified a 96 base pair insertion in the *CYP2E1* regulatory region that results in increased *CYP2E1* activity in the presence of ethanol intake, likely through increased transcription.[124,126] Taken together, these results suggest that women with the *CYP2E1* polymorphism might be at increased risk for having a child with FAS. McCarver et al[126] detected the polymorphism in 31% of black or African American participants tested and 6.9% of white participants. Unlike the *ADH1B* findings, an increased genetic risk for *CYP2E1* is consistent with the elevated FAS risk observed in blacks or African Americans, which is present even after controlling for alcohol intake.[28] Also, some drugs have been shown to alter alcohol metabolism—aspirin, for example, decreases first pass metabolism of alcohol.[127] Thus, genes, such as *cytochrome P450 C9*, whose products are responsible for metabolizing these drugs and thus regulating their levels in the body, might also be candidates for association with FAS, especially in combination with drug use.

CYP2E1 and other placental cytochrome P450 enzymes metabolize ethanol to generate cytotoxic reactive oxygen species (ROS).[128,129] Furthermore, ethanol reduces antioxidant activity.[130] Studies in animal models have indicated that increased levels of oxidative stress can mediate the damage caused by prenatal alcohol exposure. These studies found that prenatal ethanol exposure led to defects similar to those observed in humans and resulted in reduced levels of the neural markers including paired-box transcription factor 6 (Pax6). Restoration of Pax6 expression was sufficient to partially rescue the defects seen with ethanol exposure.[131-133] Overexpression of the antioxidants catalase or peroxiredoxin 5 partially protected against the ethanol-mediated defects and restored Pax6 and other neural marker expression. Thus, polymorphisms in antioxidant genes that decrease oxidative stress, in addition to those in ROS-producing enzymes like CYP2E1, might be candidates to examine in relation to FAS. Those polymorphisms that increase antioxidant activity or decrease ROS production would likely be protective against FAS, while those that decrease antioxidant activity or increase ROS production would be expected to increase risk. These results also suggest that increased dietary antioxidant intake might be protective against FAS, as has been suggested by animal model studies.[134,135]

Conclusion

The effects of prenatal alcohol exposure vary greatly between individuals, which may be explained in part by different genetic susceptibilities. Most studies on the association between FAS and the *ADH1B* genotype suggest an increased risk for the maternal and possibly fetal *ADH1B/ADH1B* genotype. However, this might be due to the indirect effect of *ADH1B* genotype on alcohol intake. Furthermore, this association does not explain the increased incidence of FAS in black or African American populations, which have a lower prevalence of the *ADH1B/ADH1B* genotype. These concerns can be addressed in future studies by consistent case definitions, enhanced ethanol intake measurements, and careful study design. In addition, the mechanism by which prenatal ethanol exposure causes damage, as well as which other genetic pathways are involved, must be further addressed.[59,60,123] ■

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APPENDIX

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