Do Alcohol-Metabolizing Enzyme Gene Polymorphisms Increase the Risk of Alcoholism and Alcoholic Liver Disease?

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Case–control studies that have investigated the association between alcoholism and alcohol-induced liver damage and the *ADH2, ADH3, CYP2E1*, and *ADLH2* polymorphisms have reported controversial or inconclusive results. Thus, we conducted a meta-analysis of 50 association studies of the above polymorphisms. We explored potential sources of heterogeneity and bias, performed subgroup analyses by racial background and sex, performed sensitivity analyses for studies not in Hardy-Weinberg equilibrium, and performed a subgroup analysis for cases that met strict criteria for alcoholism. The present meta-analysis underscores significant associations of *ADH2*1, ADH3*2*, and *ALDH2*1* alleles and the risk of alcoholism (OR = 1.89 [95% CI 1.56-2.28], 1.32 [95% CI 1.12-1.57], and 4.35 [95% CI 3.04-6.23], respectively). The subsequent subgroup analyses showed association for ADH2*1 and ADH3*2 only in East Asians (OR = 2.23 [95% CI 1.81–2.74] and 1.91 [95% CI 1.45-2.53], respectively) and East Asian males (OR = 2.21 [95% CI 1.57-3.10], 1.69 [95% CI 1.10-2.59], respectively). In East Asian males, the OR for ALDH2*1 was 3.66 (95% CI 1.68-7.96). In Caucasians, sensitivity analysis revealed an association for ADH2*1 in alcoholism (OR = 1.62 [95% CI 1.22-1.89]). When strict criteria were imposed, the pattern of results remained unaltered. For liver disease, there were no significant associations for ADH2*1, ADH3*2, or ALDH2*1 in all subpopulations. The *CYP2E1* polymorphism showed no association whatsoever. There is evidence that alleles are mainly dominant. In conclusion, there was heterogeneity between studies in alcoholism for ADH2, ADH3, and ALDH2, and lack of bias in all polymorphisms. The above findings reinforce the need for more rigorous studies, and for regular synthesis of studies' results. *Supplementary material for this article can be found on the HEPATOLOGY website (http://interscience.wiley.com/jpages/0270-9139/suppmat/index.html).* (HEPATOLOGY 2006;43:352-361.)

Over the last few years, an increasing number of studies have provided compelling evidence for the involvement of genetically defined predisposing factors in alcoholism and alcohol-induced cirrhosis. The strongest support comes from the fact that not all subjects with a high daily intake of alcohol develop alcohol-induced liver disease. Mostly metabolized in the liver by the successive action of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), the rate of conversion of ingested ethanol to acetaldehyde, and of acetaldehyde to acetate, is influenced by genetic polymorphisms at both loci. *ALDH2* is the most important gene that affects predisposition to alcoholism in Asian populations. Thus, the prevalence in these populations of the inactive ALDH enzymatic form encoded by the *ALDH2*2* allele appears to protect against alcoholism.[1] Furthermore, alcoholics with this inactive allele may be at great risk for advanced alcoholic liver disease.[2-4]

Regarding the *ADH* gene cluster, polymorphisms are also detected at the *ADH2* and *ADH3* loci with two alleles (referred to as **1* and **2*) each. Alleles *ADH2*2* and *ADH3*1* encode, respectively, for the highly active β_2 and γ_1 allozymes,[5] and a low prevalence of both alleles has been reported in alcoholic Asians—although some studies did not detect associations between *ADH3* polymor-

Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; HWE, Hardy-Weinberg equilibrium; FE, fixed effect; RE, random effect.

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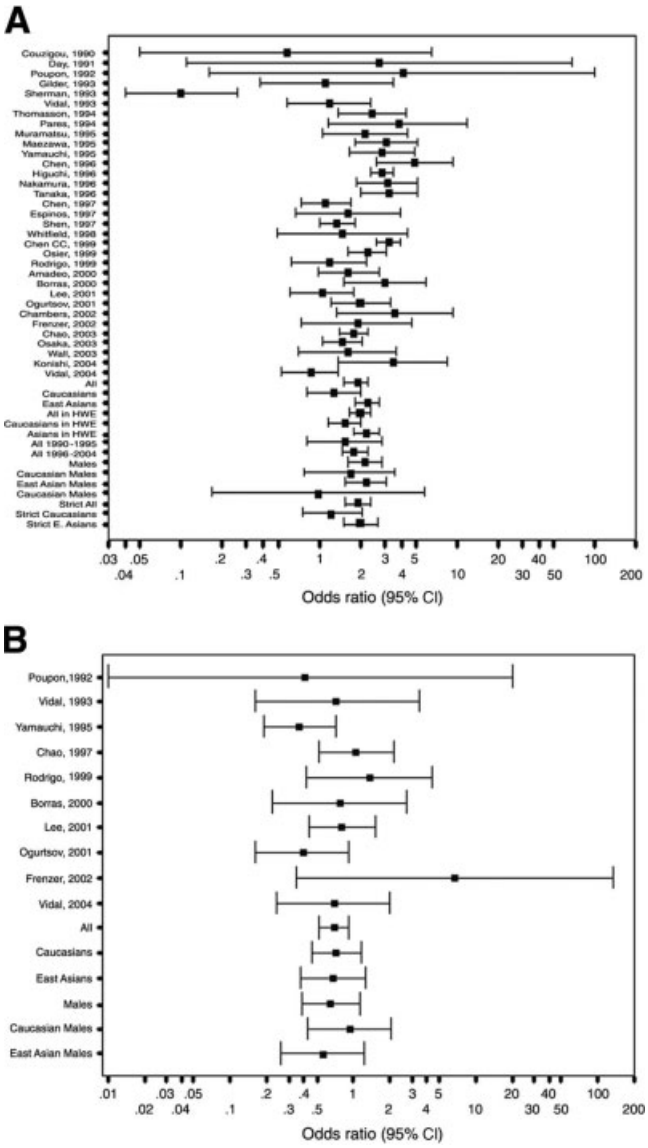

Fig. 1. *ADH2* polymorphism and the risk of (A) alcoholism and (B) liver disease: contrast of allele **1* against **2*. Each study is shown by an OR estimate with the corresponding 95% CI. The horizontal axis is plotted on a log scale. HWE, Hardy-Weinberg equilibrium.

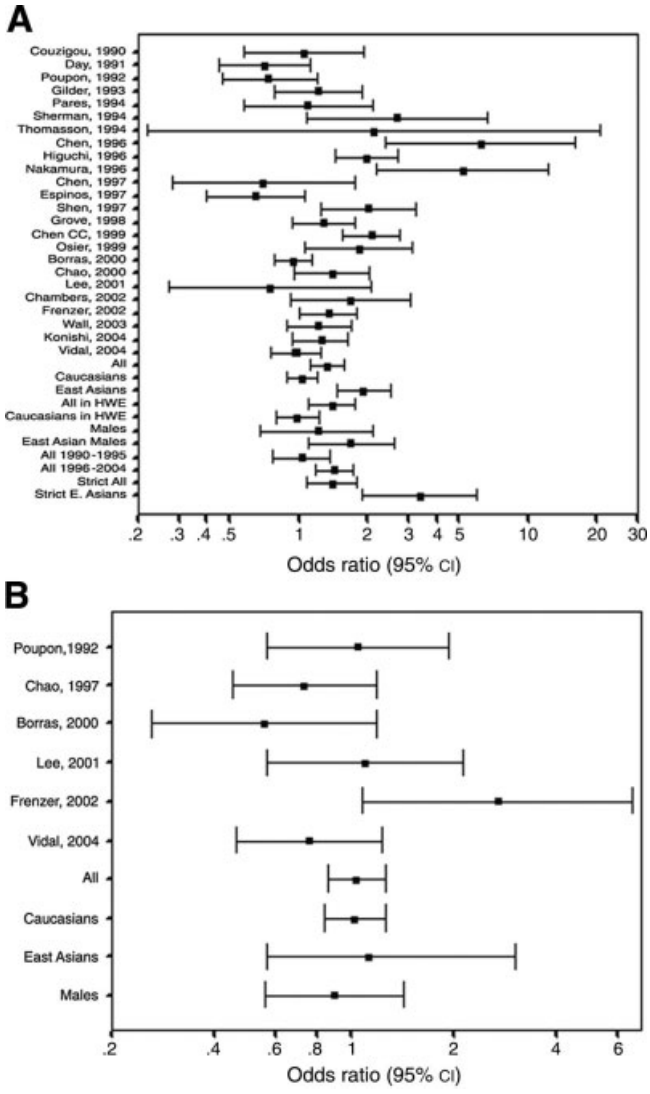

Fig. 2. *ADH3* polymorphism and the risk of (A) alcoholism and (B) liver disease: contrasts of allele **2* against **1*. Each study is shown by an OR estimate with the corresponding 95% CI. The horizontal axis is plotted on a log scale. HWE, Hardy-Weinberg equilibrium.

phism and alcoholism in these populations. On the other hand, the results are far less conclusive for Caucasians because here allele *ADH2*2* is found at very low frequency.[6] In addition, there is evidence that *ADH2*2* and *ADH3*1* alleles are in linkage disequilibrium,[7,8] which clearly indicates that their contribution to the associated risk of alcoholism is not independent.

The cytochrome $CYP_{450}2E1$ is also involved in alcohol metabolism—though to a lesser extent than *ADH* and *ALDH*—and can be induced in the human liver via chronic alcohol administration.[9] This gene is also polymorphic, and 2 point mutations in the 5′ flanking region (*Pst-I*, *Rsa-I*) that are in close linkage disequilibrium are known to alter the transcriptional activity of the gene.[10] These point mutations produce the *CYP2E1*1* (*c1*) and *CYP2E1*2* (*c2*) alleles and have been reported to be associated with alcoholic liver disease in Japanese subjects.[11] As for the *ADH2* polymorphism, the association is far less clear in Caucasians.

The case–control studies that have investigated the association between alcoholism and alcohol-induced liver damage—as well as the *ADH2*, *ADH3*, *CYP2E1*, and *ADLH2* polymorphisms—provide some controversial or nonconclusive results, partly because each typically involved few cases and few controls and, therefore, there was not enough information to demonstrate association.[12] Furthermore, the interpretation is complicated by the fact that different populations, sampling strategies, genotyp-

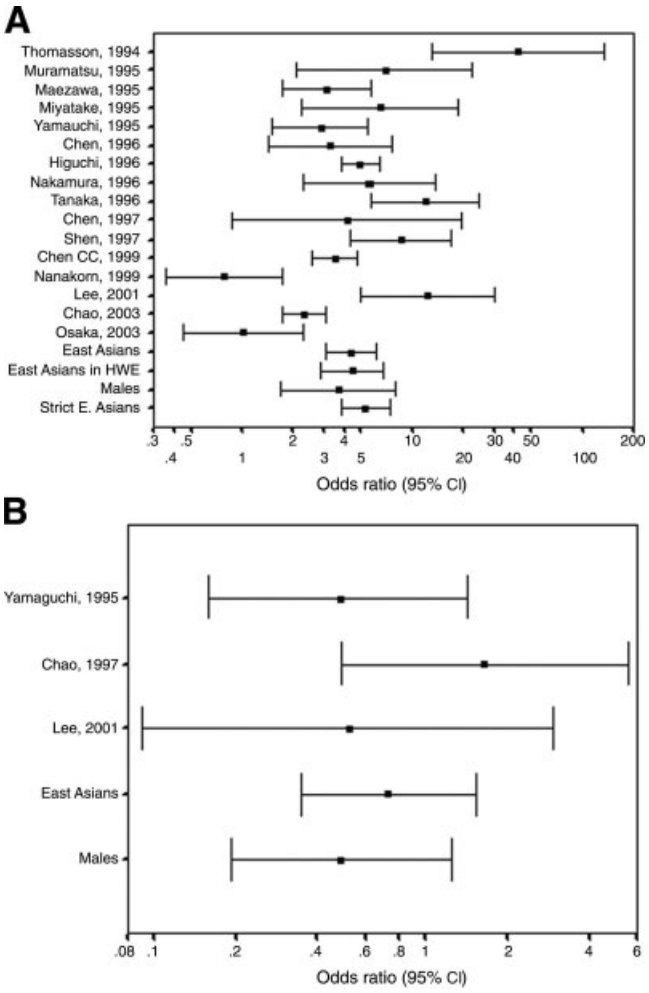

Fig. 3. *ALDH2* polymorphism and the risk of (A) alcoholism and (B) liver disease: contrasts of allele **1* against **2*. Each study is shown by an OR estimate with the corresponding 95% CI. The horizontal axis is plotted on a log scale. HWE, Hardy-Weinberg equilibrium.

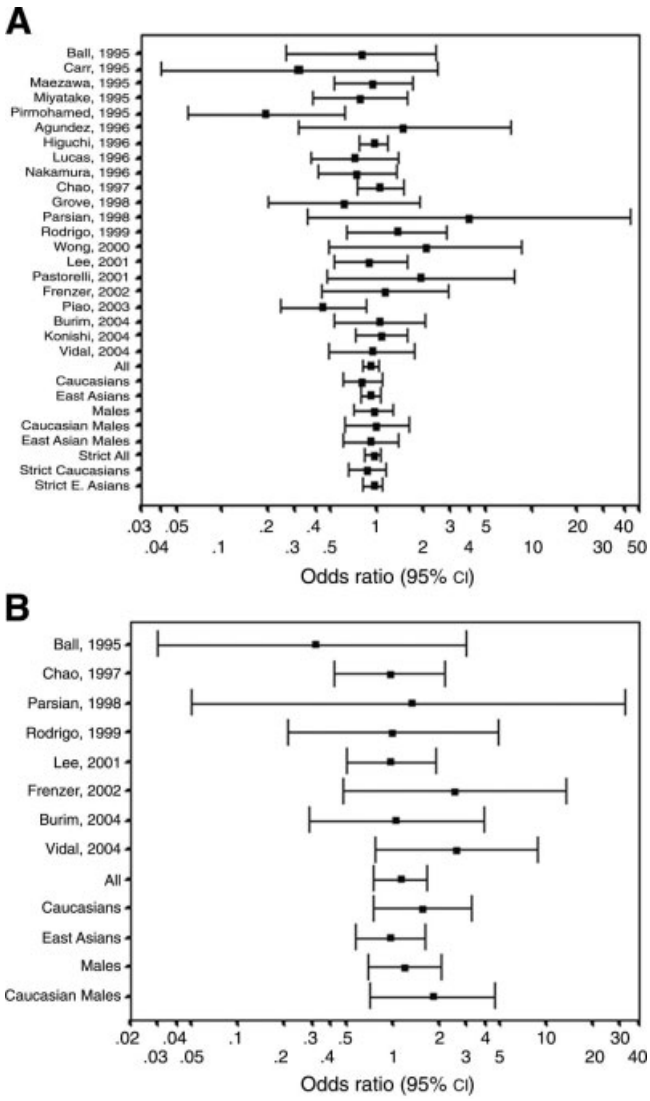

Fig. 4. *CYP2E1* polymorphism and the risk of (A) alcoholism and (B) liver disease: contrasts of allele **1* against **2*. Each study is shown by an OR estimate with the corresponding 95% CI. The horizontal axis is plotted on a log scale.

ing procedures, and number of loci included in the analyses have been used.

Meta-analysis is an invaluable means of shedding some light on these contradictory results, as well as to decrease the uncertainty of the effect size of estimated risk.[13] Two meta-analyses regarding the role of the genetics of alcoholism and alcoholic liver disease have been previously described, but they were restricted to the role of *ADH* and included the relatively scarce information available at the time of the analysis.[14,15] We report the results of a large meta-analysis of individual patient data regarding *ADH2*, *ADH3*, *ALDH2*, and *CYP2E1* polymorphisms and their associations with alcoholism and alcoholic liver disease.

Materials and Methods

Selection of Studies. All studies published before January 2005 were identified by extended computer-based searches of the PubMed database. As a search criterion, the following entries were used: *polymorphism*, *ADH2*, *ADH1B*, *ADH3*, *ADH1C*, *CYP4502E1*, *CYP450IIE1*, *CYP2E1*, or *ALDH2* and *alcoholism*, *alcohol*, *alcoholic liver disease*, or *liver disease*. The retrieved studies were then read in their entirety to assess their appropriateness for inclusion in the meta-analysis. All references cited in the studies were also reviewed to identify additional published work not indexed by PubMed. Case reports, editorials, and review articles were excluded. The search was restricted to articles written in English.

Case–control studies that determined the distribution of *ADH2*, *ADH3*, *CYP2E1*, *Pst-I/Rsa-I*, and *ALDH2* genotypes in cases with alcoholism, or alcohol-induced liver disease, and in a control group, were eligible for inclusion

Table 1. Random Effect ORs (95% CI) for Various Contrasts and Subpopulations

ADH2			**ADH3**		
Alcoholism			**Alcoholism**		
1 vs. 2	All	1.89 (1.56, 2.28)	2 vs. 1	All	1.32 (1.12, 1.57)
	Caucasians	1.29 (0.80, 2.02)		East Asians	1.91 (1.45, 2.53)
	East Asians	2.23 (1.81, 2.74)		Caucasians	1.03 (0.88,1.20)
	All HWE	1.99 (1.68, 2.35)		All HWE	1.40 (1.11, 1.76)
	East Asians HWE	2.18 (1.76, 2.70)		Caucasians HWE	0.99 (0.79, 1.23)
	Caucasians HWE	1.52 (1.22, 1.89)*		Males	1.20 (0.68, 2.13)
	Males	2.15 (1.60, 2.88)		East Asian males	1.69 (1.10, 2.59)*
	Caucasian males	1.68 (0.80, 3.53)		Strict all	1.36 (1.15, 1.62)
	East Asian males	2.21 (1.57, 3.10)		Strict Caucasians	1.06 (0.91, 1.24)
	Caucasian females	1.00 (0.17, 5.78)		Strict East Asians	1.91 (1.45, 2.53)
	Strict all	1.91 (1.57, 2.34)	Recessive model	All	1.35 (1.07, 1.71)
	Strict Caucasians	1.26 (0.77,2.06)		All HWE	1.42 (0.99, 2.02)
	Strict East Asians	2.02 (1.55, 2.64)		East Asians	2.74 (1.33, 5.65)
Recessive model	All	2.62 (1.88, 3.66)		East Asian males	6.99 (0.84, 58.45)*
	East Asians	4.73 (3.14, 7.11)		Strict all	1.39 (1.08, 1.78)
	All HWE	2.74 (2.03, 3.68)		Strict East Asians	3.37 (1.90, 5.99)*
	East Asians HWE	4.33 (2.89, 6.48)	Dominant model	All	1.35 (1.08, 1.67)
	Caucasians HWE	1.55 (1.22, 1.95)		All HWE	1.45 (1.12, 1.86)
	Males	2.98 (1.91, 4.66)		East Asians	1.92 (1.44, 2.55)
	Males East Asians	3.84 (2.08, 7.11)		East Asian males	1.61 (1.01, 2.55)*
	Strict all	2.70 (1.88, 3.88)		Strict all	1.40 (1.13, 1.74)
	Strict East Asians	5.13 (3.38, 7.80)		Strict East Asians	1.92 (1.44, 2.55)
Dominant model	All	1.87 (1.54, 2.28)	**Liver disease**		
	East Asians	1.95 (1.58, 2.40)	1 vs. 2	All	1.04 (0.85, 1.27)*
	All HWE	1.94 (1.63, 2.30)		Caucasians	1.02 (0.83, 1.26)*
	East Asians HWE	1.93 (1.55, 2.40)		East Asians	1.13 (0.57, 3.00)*
	Caucasians HWE	3.80 (1.10, 13.05)		Males	0.89 (0.56, 1.41)*
	Males	1.84 (1.36, 2.48)			
	Males East Asians	1.90 (1.34, 2.69)			
	Strict all	1.93 (1.58, 2.35)	**ALDH2**		
	Strict East Asians	2.02 (1.64, 2.49)	**Alcoholism**		
Liver disease			1 vs. 2	All	4.35 (3.04, 6.23)
1 vs. 2	All	0.70 (0.52, 0.94)*		Males	3.66 (1.68, 7.96)
	Caucasians	0.74 (0.45, 1.19)*		Strict all	5.31 (3.80, 7.43)
	East Asians	0.68 (0.37, 1.25)	Recessive model	All	4.16 (2.94, 5.89)
	All HWE	0.70 (0.52, 0.94)*		Males	4.04 (1.74, 9.38)
	Males	0.66 (0.39, 1.12)*		Strict all	5.00 (3.63, 6.90)
	Caucasian males	0.93 (0.43, 2.02)*	Dominant model	All	39.77 (12.97, 122)
	East Asian males	0.56 (0.26, 1.21)*		Males	5.75 (1.27, 25.93)
Recessive model	All	0.77 (0.51, 1.17)*		Strict all	13.83 (6.28,30.46)
Dominant model	All	0.49 (0.29, 0.84)*	**Liver disease**		
			1 vs. 2	All	0.73 (0.35, 1.53)*
CYP2E1				Males	0.49 (0.19, 1.24)*
Alcoholism			**CYP2E1**		
1 vs. 2	All	0.92 (0.82, 1.04)*	**Liver disease**		
	Caucasians	0.82 (0.62, 1.09)*	1 vs. 2	All	1.13 (0.76, 1.68)*
	East Asians	0.91 (0.79, 1.06)*		Caucasians	1.58 (0.76, 3.28)*
	Males	0.95 (0.70, 1.29)*		East Asians	0.97 (0.58, 1.62)*
	Strict all	0.95 (0.84, 1.07)*		Males	1.19 (0.69, 2.05)*
	Strict Caucasians	0.86 (0.65, 1.14)*		Caucasian males	1.81 (0.72, 4.55)*
	Strict East Asians	0.95(0.81, 1.10)*			

*Lack of heterogeneity ($P > .10$) and FE OR.

in the meta-analysis. Observational studies were excluded. In investigating alcoholism, cases were considered alcoholics, including alcoholics with liver disease, based on valid published criteria (DSM-III-R, DSM-IV, CAGE, SAPS, Feighner, ICD-10) or validated questionnaires; alcohol consumption >40 g/d for at least 5 years; and reported alcohol abuse or dependence. The control group consisted of nonalcoholic subjects. In addition,

strict criteria for defining alcoholism were imposed: diagnosis of cases using valid published criteria and/or alcohol consumption >80 g/d for at least 10 years. Some individuals not fulfilling these criteria were also included if they unequivocally had any type of alcoholic end-organ damage, such as alcoholic cirrhosis or chronic pancreatitis. In investigating alcohol-induced liver disease, cases were considered alcoholics with cirrhosis due to alcoholism. Cirrhosis was diagnosed by histology or clinical, radiological, and endoscopic findings. Studies with cases positive in hepatitis virus were excluded. The controls were alcoholics free of liver disease. In studies with overlapping cases or controls, the most recent and/or largest study with extractable data was included in the meta-analysis. Only studies that used validated genotyping methods were considered, and the distribution of the genotypes in the control group was tested for Hardy-Weinberg equilibrium (HWE) ($P \geq .05$).[16-18] Finally, studies based on pedigree data were excluded because they investigate linkage and not association.[19]

Data Abstraction. From each study, the following information was abstracted: first author, journal, year of publication, racial background of the study population, demographics, matching, validity of the genotyping method, and the number of cases and controls for each ADH2, ADH3, CYP2E1, and ALDH2 genotypes (Appendices A and B, available at the HEPATOLOGY website [http://interscience.wiley.com/jpages/0270-9139/suppmat/index.html]). The frequencies of the alleles and the genotypic distributions were extracted or calculated for both the cases and the controls. In addition, it was recorded whether the genotyping in each study was blinded to clinical status. When studies investigated more than 1 polymorphism, information on linkage disequilibrium and haplotype estimation was recorded.

Meta-analysis. Prior to the main analysis, the significance of the associations between the two alleles of each genotype—namely, ADH2*1 versus ADH2*2, ADH3*2 versus ADH3*1, CYP2E1*1 versus CYP2E1*2, and ALDH2*1 versus ALDH2*2—and risk of alcoholism or risk of developing liver damage were evaluated for each study separately. The main analysis examined the overall association of the allele of interest with the risk of alcoholism, or the risk of developing liver damage, relative to the complementary allele. The dominant and recessive contrasts of the allele of interest were also examined. All associations were indicated as ORs with the corresponding 95% CI. A pooled OR was estimated based on the individual ORs.

The heterogeneity between studies was tested using the *Q*-statistic.[20] A *P* value of less than .10 was considered significant. The pooled OR was estimated using fixed effect (FE) (Mantel-Haenszel) and random effect (RE) (DerSimonian and Laird) models.[17] Random effects modeling assumes a genuine diversity in the results of various studies and incorporates to the calculations a between study variance. Therefore, when there was heterogeneity between studies, the pooled OR was estimated using the RE model. Adjusted estimates of OR were considered whenever possible in a separate analysis. A cumulative meta-analysis and recursive meta-analysis were performed for each polymorphism to evaluate the trend of pooled OR for the allele contrast in time.[21] A differential magnitude of effect in large versus small studies (or publication bias) for the allele contrast was checked using the Egger regression test for funnel plot asymmetry and the Begg-Mazumdar test, which is based on Kendall's tau.[12,22,23]

The main (or overall) analysis included all available data. Subgroup analysis for each racial background was also performed. Racial background was categorized into 2 main groups: Caucasian and East Asian.[24] However, the consistency of genetic effects across these traditionally defined racial groups does not necessarily mean that race-specific genetic effects are exactly the same.[24] In addition, subgroup analyses by male and female cases were performed. A subgroup analysis was applied to those studies that fulfilled strict criteria for alcoholism (>80g/day for at least 10 years). Studies with controls not in HWE were subjected to a sensitivity analysis.[17,18] In sensitivity analysis, the effect of excluding specific studies was examined. Analyses were performed using Meta-Analyst (Lau, Boston, MA), and CVF90.[25]

Results

Eligible Studies

The literature review identified 239 titles that met the search criteria. Data from 50 studies that investigated the association between any of the *ADH2*, *ADH3*, *CYP2E1*, and *ALDH2* polymorphisms and alcoholism, and alcohol-induced liver disease, met the inclusion criteria and were included in the meta-analysis. Thirty-three studies dealt with *ADH2,*[2,3,5-8,26-52] 24 dealt with *ADH3,*[5-8,26,29-32,37-42,45-47,50-55] 23 dealt with *ALDH2,*[2-3,6,8,11,26-32,37,39-44,46,47,51,56] and 21 dealt with *CYP2E1.*[6,11,26,31,32,35,41-43,54,57-67] However, the strict criteria for alcoholism were met by 31 studies in *ADH2,*[2,3,5-8,26,27,29-37,39-52] 23 studies in *ADH3,*[5-8,26,29-32,37,39-42,45-47,50-55] 21 studies in *ALDH2,*[2-3,6,8,11,26-27,29-32,37,39-44,46,47,51] and 20 studies in *CYP2E1.*[6,11,26,31,32,35,41-43,54,57-65,67] To investigate the association between any of the four loci considered and alcohol-induced liver disease, ten studies dealt with *ADH2,*[5,6,31-33,35,44,49,50,57] six dealt with *ADH3,*[5,6,31,32,50,57] three dealt with ALDH2,[32,44,57] and

eight dealt with CYP2E1.[6,31,32,35,57,58,63,67] The studies were published between 1990 and 2004. A list of all the details abstracted from these studies is provided in Supplementary Appendices A and B.

For the determination of the genetic polymorphisms of *ADH2*, *ADH3*, *CYP4502E1*, *Pst-I/Rsa-I*, and *ALDH2*, validated genotyping methods were used in all studies—namely, polymerase chain reaction and restriction of the polymerase chain reaction product with the enzyme corresponding to each polymorphism. In three studies,[45,49,50] the genetic polymorphisms of the two alcohol dehydrogenase loci (*ADH2* and *ADH3*) were determined from the enzymatic phenotypes (*i.e.*, by electrophoretic differentiation of the ADH isozymes and by measurements of the ADH enzymatic activity in homogenized liver biopsy specimens).

Eight studies in alcoholism[28,33,38,39,44,56,65,66] and two studies in liver disease[33,44] reported that the controls were age- or sex-matched. Studies were conducted in various populations of racial background: 24 involved Caucasians,[5,6,31,33,35,36,38,45,47-52,54,55,58-65] 21 involved East Asians,[2,3,7,8,11,26-28,32,39-44,46,53,56,57,66,68] and 5 involved other ethnicities (White and Maori, mixed Brazilians, Mexican Americans, Native Americans, mixed Polynesians).[26,29,30,34,67] In liver disease studies, 12 involved Caucasians,[5,6,31,33,35,49,50,58-61,63] five involved East Asians,[2,4,7,32,57] and one involved another ethnicity (mixed Brazilians).[67] Fourteen studies involved male cases,[2,3,6,26,28,30,32,35,39,40,43,44,56,59] and two studies provided data for males and females.[5,36]

Summary Statistics

The genotype distributions are shown in Appendix B. In studies of alcoholism, the distribution of genotypes in the control group departured from HWE in two studies for *ADH2,*[41,48] in five studies for *ADH3,*[5,26,29,31,45] in nine studies for *ALDH2*,[6,8,26,29-31,47,51,56] and in two studies for *CYP2E1.*[11,60] Because a lack of HWE indicates possible genotyping errors and/or population stratification, a sensitivity analysis was performed excluding studies not in HWE. Although the majority of studies reviewed in this meta-analysis reported on more than two of the investigated polymorphisms, only four of them provided analyses of haplotypes.[7,8,37,40] Seven studies[5-8,31,37,40] investigated the existence of linkage disequilibrium, and six demonstrated linkage disequilibrium between *ADH2* and *ADH3.*[5,7,8,31,37,40] Because all studies provided unadjusted estimates, adjusted pooled OR were not calculated.

Main Results, Subgroup and Sensitivity Analyses

Figures 1 through 4 and Table 1 show the results for the association between the different polymorphisms and the risk of alcoholism or liver disease.

ADH2. For the *ADH2* polymorphism and its relationship to alcoholism, the allele contrast **1* versus **2* showed heterogeneity among studies ($P < .01$), and the RE-pooled OR was significant (OR = 1.89 [95% CI 1.56, 2.28]). In subgroup analysis, the RE-pooled OR for Caucasians was not significant (OR = 1.29 [95% CI 0.82, 2.02]). However, for those studies involving East Asians, the RE-pooled OR was significant (OR = 2.23 [95% CI 1.81, 2.74]). In sensitivity analysis,[41,48] the RE-pooled ORs remained significant in both the main analysis and in East Asians. On the other hand, the result in Caucasians changed, producing a significant association (FE OR = 1.52 [95% CI 1.22, 1.89]). The recessive (**1/*1* vs. **1/*2 + *2/*2*) and dominant (**1/*2 + *1/*1* vs. **2/*2*) models for the effect of allele **1* produced the same overall pattern as the allele contrast (RE OR = 2.62 [95% CI 1.88, 3.66] and 1.87 [95% CI 1.54, 2.28], respectively). However, in Caucasians the association was not significant ($P > .05$), whereas in East Asians the opposite trend was detected for the recessive and dominant models (RE OR = 4.73 [95% CI 3.14, 7.11] and 1.95 [95% CI 1.58, 2.40], respectively). On the other hand, the sensitivity analysis for the recessive and dominant models produced the same pattern of results as the overall allele contrasts, both in East Asians and Caucasians. In the subgroup analysis by sex, males produced a significant association for the allele contrast (RE OR = 2.15 [95% CI 1.60, 2.88]). However, Caucasians showed no association, whereas the East Asians did (RE OR = 2.21 [95% CI 1.57, 3.10]). In East Asians, both recessive and dominant models produced significant association. In Caucasian females, there is no association for the allele contrast. The strict meta-analysis produced results similar to those of the extended one: overall, in Caucasians and in East Asians there is significant association for the allele contrast: RE OR = 1.91 [95% CI 1.57, 2.34], 1.26 [95% CI 0.77, 2.06], and 2.02 [95% CI 1.55, 2.64], respectively. The dominant and recessive models produced significant results overall and for East Asians.

Regarding the relationship between the *ADH2* polymorphisms and liver disease, the heterogeneity between studies was not significant ($P > .10$) and the analysis detected an association for the allele contrast **1* vs. **2* (FE OR = 0.70 [95% CI 0.52, 0.94]). However, the association was not significant in East Asians or Caucasians ($P > .05$). The overall analysis produced significant results because it includes more data than the individual analyses by racial background. On the whole, the recessive model for the effect of allele **1* also produced no significant association; however, the dominant model did (FE OR = 0.49 [95% CI 0.29, 0.84]). In the subgroup analysis for males, overall, in Caucasian males, and in East Asian males there

is no significant association ($P > .05$) for the allele contrast.

ADH3. For the *ADH3* polymorphism and its relationship to alcoholism, the allele contrast **2* versus **1* showed heterogeneity among studies ($P < .01$), and the pooled OR was significant (RE OR = 1.32 [95% CI 1.12, 1.57]). There was, however, a substantial difference between East Asians and Caucasians, because a significant association between allele **2* and the risk of alcoholism was detected for the former (RE OR = 1.91 [95% CI 1.45, 2.53]) but not the latter. In sensitivity analysis,[5,26,29,31,45] the pattern of results was also similar. In a subgroup analysis for the men[6,32,39] (no study provided data for women), there was no association. However, the lack of association was due to the Caucasians,[6] because in East Asians the association is significant (OR = 1.69 [95% CI 1.10, 2.59]).

Overall and for East Asians, the recessive model for allele *ADH3*2* (**2/*2* vs. **1/*2* + **1/*1*) (RE OR = 1.35 [95% CI 1.07, 1.71] and 2.74 [95% CI 1.33, 5.65], respectively) and the dominant model (**1/*2* + **2/*2* vs. **1/*1*) (RE OR = 1.35 [95% CI 1.08, 1.67]) and 1.92 [95% CI 1.44, 2.55], respectively) produced results similar to those of the allele contrast, and the subsequent sensitivity analysis did not alter the results except for the overall recessive model (RE OR = 1.42 [95% CI 0.99, 2.02]). In a strict meta-analysis, the associations were significant overall and for East Asians (RE OR = 1.36 [95% CI 1.15, 1.62] and 1.91 [95% CI 1.45, 2.53], respectively), whereas for the Caucasians the associations were not significant. Both the recessive and dominant models were significant overall and for East Asians.

Concerning the *ADH3* polymorphisms and liver disease, there was no heterogeneity among all studies ($P > .10$) and the association was nonsignificant overall for Caucasians, East Asians, and men. The dominant and recessive models for the allele *ADH3*2* produced nonsignificant associations ($P > .05$) with no heterogeneity ($P > .10$).

ALDH2. For the *ALDH2* polymorphism, all studied individuals but 1 among Mexican Americans[26] in alcoholism and 1 among Caucasians[31] in alcoholic liver disease, were homozygous for the **1/*1* genotype in Caucasians and Americans; therefore, the analysis was restricted to East Asians.[2-4,8,11,27,28,32,35,37,39-44,46,56,57] There was heterogeneity among studies ($P < .01$), and the allele contrast was highly significant (RE OR = 4.35 [95% CI 3.04, 6.23]). The recessive and dominant models for the effect of allele *ALDH2*1* showed highly significant associations. The sensitivity analysis[8,56] did not change the pattern of results. In subgroup analysis for men, the allele contrast and the recessive and dominant models were significant. The analysis based on the strict criteria for alcoholism produced significant results for the allele contrast (RE OR = 5.31 [95% CI 3.80, 7.43]), the dominant contrast, and the recessive contrast.

Regarding liver disease, the allele contrast showed that there was no heterogeneity among studies ($P > .10$), and the association was not significant overall and in men.

CYP2E1. Finally, in no case (*i.e.*, overall, Caucasians, East Asians, men, or strict criteria) was a statistically significant association found between the *CYP2E1* polymorphism and the risk of developing alcoholism or liver disease for the contrasts under investigation. In addition, there was no significant heterogeneity among studies ($P > .10$).

Potential Bias

None of the studies included in the meta-analysis reported that genotyping was performed blinded to clinical status.

For the *ADH2* polymorphism in alcoholism, the cumulative meta-analysis and recursive meta-analysis for the allelic contrast showed that RE OR fluctuated from 0.58 in 1990 (the first study) to 2.1 in 1996 and then remained fairly constant until 2004 (OR = 1.89). Between-study heterogeneity appeared very early, in 1993. Whereas studies published between 1990 and 1995 showed no association (RE OR = 1.54 [95% CI 0.84, 2.84]), a significant association was reported in studies published between 1996 and 2004 (RE OR = 1.84 [95% CI 1.48, 2.27]). In liver disease, RE OR increased from 0.40 in 1992 (the first study) to 0.68 in 1999, then was relatively stable until 2004 (OR = 1.43).

For the *ADH3* polymorphism in alcoholism, the magnitude of RE OR increased from 1.05 in 1990 to 1.57 in 1996, then exhibited a downward trend until 2004 (OR = 1.32). Heterogeneity appeared in 1996. Whereas studies published between 1990 and 1995 showed no association (RE OR = 1.03 [95% CI 0.77, 1.37]), significant association was seen in studies published between 1996 and 2004 (RE OR = 1.42 [95% CI 1.17, 1.73]). In liver disease, the RE OR increased from 0.80 in 1992 (the first study) to 1.13 in 2002, then declined to 1.04 in 2004.

For the *ALDH2* polymorphism in alcoholism, the RE OR experienced a sharp decline from 1994 (the first study) (OR = 41.93) to 1995 (OR = 6.35) and thereafter exhibited a downward trend until 2003 (OR = 4.35). Heterogeneity appeared in 1995 and remained throughout the entire period. In liver disease, the RE OR was not significant in 1995 (OR = 0.48) and then became significant in 1996 (OR = 0.34); it increased in 2001 (OR = 0.95), but it was not significant.

For the *CYP2E1* polymorphism in alcoholism, the RE OR was nonsignificant in the studied period; however, it exhibited an upward trend between 1995 (the first study) (OR = 0.75) and 1999 (OR = 0.93) and then was stabilized throughout the remaining period (OR = 0.93 in 2004). For liver disease, there was an upward trend from 1995 (OR = 0.49) to 2004 (OR = 0.98), with the association being nonsignificant.

The Egger test and the Begg-Mazumdar test indicated that there is no differential magnitude of effect in large versus small studies (*i.e.*, no publication bias) for each polymorphism investigating alcoholism or liver disease ($P > .05$).

Discussion

Why some individuals become alcohol-dependent is an unresolved question. Why some alcoholic individuals develop cirrhosis, while others do not, is also unknown. Because environmental factors do not fully explain this, researchers have sought the answer at the host genetic background. Most research performed so far deals with those genes that codify for ADH, ALDH, and CYP2E1, given their critical role in alcohol and acetaldehyde metabolism and the fact that single-point mutations in each of these genes are known to alter protein activity. To partly cover the main limitation of case-control studies (*i.e.*, the low sample sizes in single studies, because usually thousands of individuals are needed to provide convincing information), a meta-analysis offers a robust tool.

The first meta-analysis[14] focused on the *ADH2* and *ADH3* polymorphisms (8 and 5 studies, respectively) in association with alcoholism and on the *ADH2* polymorphism in liver disease (3 studies). An update review[15] for *ADH2* in alcoholism involved 17 studies. A total of 50 different case-control association studies have been analyzed here for the *ADH2*, *ADH3*, *ALDH2,* and *CYP2E1* polymorphisms. Virtually all of the studies were performed in Caucasians and East Asians. Overall, our results indicate that carriers of the *ADH2*1* and *ADH3*2* less active coding enzymatic alleles, and the highly active *ALDH2*1* coding allele (only in East Asians, and probably according to a dominant model), incur an increased risk of alcoholism. In any case, a subset analysis showed that the role of these allelic variants presents some differences between Caucasians and East Asians, with the strongest effect in the latter. Caucasians lack allele *ALDH2*2* and, hence, the role of ALDH cannot be assessed. To conclude, the meta-analysis and the subsequent subgroup and sensitivity analyses supported an association between the *ADH2* polymorphism and alcoholism (which is stronger in East Asians, and in East Asian men, than in Caucasians), and an association for *ADH3* and *ALDH2* which is basically due to East Asians. The meta-analysis based on strict criteria for alcoholism, produced the same pattern of results as the extended criteria. In liver disease, there is association with *ALDH2*1* as a protective factor under a dominant model. Neither the ADH2 polymorphism nor the ADH3 polymorphism have been implicated in the development of liver disease. Allelic variants of *CYP2E1* do not seem to be involved in alcoholism or in alcoholic liver disease.

The results of the meta-analysis were affected by population origin and/or sensitivity analysis for the *ADH2, ADH3*, and *ALDH2* polymorphisms, so any conclusion should be interpreted with caution. Our meta-analysis was based on unadjusted estimates. However, a more precise analysis could be performed if adjusted (by sex, age, age at onset) estimates were provided in all studies. In addition, the results depend on the study design and the inclusion criteria of the cases and the controls in each study. One of the difficulties of the present meta-analysis is the extremely heterogeneous definitions of alcoholic cases; thus, the meta-analysis based on strict criteria for alcoholism may overshadow the possible weaknesses of the extended criteria. However, the controls had a relatively low diversity. The genotyping method was not similar across studies.

In conclusion, although this meta-analysis was based on a large amount of subjects, the investigation of genetic associations should be based on large population studies with similar study designs providing subgroup data (*e.g.*, sex). In addition, other probable genetic risk factors interacting with the above polymorphisms should be investigated. Therefore, this meta-analysis could be a guide for future case-control studies investigating the genetic basis of alcoholism and alcohol-induced liver disease.

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