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Strong Association of The Alcohol Dehydrogenase 1B Gene (*ADH1B*) With Alcohol Dependence And Alcohol-induced Medical Diseases

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Abstract

Background—The alcohol dehydrogenase 1B gene (*ADH1B*) is hypothesized to affect predisposition to alcohol dependence (AD) and abuse. A variant of the *ADH1B* gene (rs1229984 or Arg48His; previously referred to as Arg (*1) and His (*2)) has been reported to be associated with reduced rates of alcohol and drug dependence. Different studies have produced inconclusive results regarding association between rs1229984 (or rs2066702) and substance dependence.

Methods—Using the cumulative association study literature from the past 21 years from both English and Chinese-language publications, this meta-analysis seeks to clarify the contradictory findings and to examine whether the aggregate data provide new evidence of significant association.

Results—The results, based on a large sample size (9,638 cases and 9,517 controls), suggested strong associations with alcohol dependence and abuse as well as alcohol-induced liver diseases, with an allelic (Arg vs. His) *P* value being 1×10^{-36} and odds ratio (OR) 2.06 (1.84, 2.31) under the random effects model. The dominant and recessive models produced larger ORs of 2.17 and 3.05, respectively. When more stringent criteria and sub-group analyses were imposed, the associations remained consistent, and were strongest in various Asian groups (allelic $P = 7\times10^{-42}$

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Conflict of Interest
The authors reported no biomedical financial interests or potential conflicts of interest.

Electronic-database information
Accession Numbers and URLs for data in this article are as follows:
GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ for genomic structure of *ADH1B*;
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim for *ADH1B*;
Genotype data, http://www.hapmap.org/ for *ADH1B*;
Genome data, http://genome.ucsc.edu/ for *ADH1B*.

and OR = 2.24 (1.99, 2.51) with ORs of 2.16 and 4.11 for dominant and recessive models, respectively).

Conclusions—Our findings provide further strong evidence for the involvement of the *ADH1B* gene in the pathogenesis of alcohol dependence and abuse as well as for some alcohol-induced medical diseases in the multiple ethnic populations, in particular, in certain Asian populations.

Keywords

Meta-analysis; Addiction; Ethanol Metabolism; Drinking; Liver Disease

Introduction

Alcohol and drug dependence, which are multifactorial and chronic relapsing disorders, constitute major public health problems. The isoenzymes coded by the alcohol dehydrogenase 1B and 1C genes (*ADH1B* and *ADH1C*) and aldehyde dehydrogenase 2 gene (*ALDH2*) metabolize alcohol into acetaldehyde and acetaldehyde into acetate, respectively. The enzyme encoded by *ADH1B* is a member of the alcohol dehydrogenase family, which metabolize a wide variety of substrates, including ethanol, retinol, other aliphatic alcohols, hydroxysteroids, and lipid peroxidation products. Among the patients with alcohol dependence (AD), alcoholic cirrhosis occurs in around 10%, hepatitis in 10-35%(1), and alcohol-induced pancreatitis in approximately 5%(2). Alcohol dehydrogenase 1B was hypothesized to be an important ethanol-oxidizing enzyme that may alter genetic susceptibility to AD as well as alcoholic liver disease, cirrhosis, and pancreatitis (the latter two are often alcohol-induced diseases)(3).

The *ADH1B* gene is located on chromosome 4q21–q23. Naturally occurring single nucleotide polymorphisms (SNPs) may be capable of altering ethanol metabolism(4). One common form of a SNP (rs1229984 or Arg48His in exon 3) is *ADH1B* Arg (previously referred to as *1). The *ADH1B* His (*2) allele encodes a super-active allozyme, which has been reported to be associated with lower rates of AD in numerous association studies. *ADH1B* His is common among Asian populations and moderately common in Russian and Jewish populations, but rare in western and central Europeans(5). In some African and Mexican populations rs2066702 (Arg370Cys, previously designated *ADH1B* *3) is observed. On the other hand, some individuals with a high daily intake of alcohol develop alcohol-induced diseases, and a proposed mechanism is that the His allele (or Cys allele) can increase the level of acetaldehyde after a certain dose of ethanol, and then result in enhanced objective and subjective negative reactions to alcohol, which would in turn reduce the likelihood of habitual alcohol use, AD, and alcohol-induced liver diseases.

Several issues prompted us to carry out an updated meta-analysis to seek further evidence regarding the proposed association with *ADH1B*. First, the findings of case-control studies have been controversial and nonconclusive. Second, rates of AD differ across the ethnic populations, even among Asian populations. Third, the low prevalence of *ADH1B* His/His individuals in subjects of European ancestry makes it particularly difficult to determine the effect of homozygous His/His in that population due to the need for very large sample size. The previous meta-analyses(3, 6, 7) regarding the role of *ADH1B* His in alcoholism, however, involved relatively small numbers of subjects available at the time of the analyses and thus the results were limited or incomplete. Therefore, a new meta-analysis with systematic statistical approaches is required.

There have been many published genetic association studies in recent years from multiple populations. We performed a comprehensive and systematic meta-analysis with AD and alcohol abuse as well as alcohol-induced medical diseases, based on both English and

Chinese-language publications, to clarify the potential association and to compare the results with those in previous studies.

Methods

Inclusion criteria

Eligible studies had to meet the following criteria: they (a) were published in peer-reviewed journals; (b) contained original and independent data; (c) presented sufficient data to calculate the odds ratio (OR) with confidence interval (CI) and *P* value; (d) were association studies investigating *ADH1B* Arg/His and (or) *ADH1B* Arg/Cys; (e) described or referenced appropriate genotyping methods; (f) investigated alcohol, heroin, cocaine, or methamphetamine dependence (or abuse) diagnosed by valid published criteria (tobacco and cannabis were not included due to lack of sufficient relevant publications). For the studies investigating alcoholic liver disease, cirrhosis, or chronic pancreatitis, the cases were considered as alcoholics with the induced diseases due to alcoholism. The patients with cirrhosis were diagnosed by histological, clinical, radiological, and (or) endoscopic findings; (g) had no description of other major psychiatric disorders for patients in the studies (this information was not available in all the studies); and (h) used unrelated individuals in case-control studies. Authors were contacted in cases where we determined it would be useful to have additional information regarding their studies.

Statistical analyses

Association studies were divided among those dealing with samples with Asian ancestries, those with European ancestries, those with African ancestries, and those with Mexican (or Native American) ancestries. For studies that contained data from multiple populations, each was considered effectively as an independent study. Data from the case-control studies were summarized by two-by-two tables. From each table a log-odds ratio and its sampling variance were calculated(8). The Cochran s χ^2-based Q statistic test was performed in order to assess heterogeneity to ensure that each group of studies was suitable for meta-analysis. Where heterogeneity was found, the random effects model, which yields a wider CI, was adopted; otherwise, both the fixed and random effects models were adopted. A test for funnel plot asymmetry, described by Egger et al.(9), was used to assess evidence for publication bias. The test used a linear regression approach to measure funnel plot asymmetry on the natural logarithm of the OR. The larger the deviation of each study from the funnel curve, the more pronounced the asymmetry. Results from small studies will scatter widely at the bottom of the graph, with the spread narrowing among larger studies. The significance of the intercept was evaluated using the T test.

For datasets with evidence for publication bias, the “Duval and Tweedie's Trim and Fill” procedure(10) was used to impute the number of potentially-missing studies. In the absence of bias, the funnel plot would be symmetric with respect to the summary effect. If there are more small studies on the right than on the left, some studies may be missing from the left. The Trim and Fill procedure imputes these missing studies, adds them to the analysis, and then re-computes the adjusted overall effect size.

ORs were pooled using the method of DerSimonian and Laird(11), and 95% CIs were constructed using Woolf s method(12). The significance of the overall OR was determined using the Z-test. To measure sensitivity of our analysis results, each study was removed in turn from the total, and the remainder then reanalyzed. This procedure was used to ensure that no individual study was entirely responsible for the combined results. In addition, different combinations of the ethnic populations and different combinations of the alcohol-induced medical conditions (e.g., alcoholic liver disease, cirrhosis, and pancreatitis) were

also analyzed. Genotypic analyses were carried out under both dominant and recessive models. Retrospective analysis was performed to better understand the potential effect of year of publication upon the results. The type I error rate was set at 0.05. The tests were two-tailed. The methods for literature search and those for linkage disequilibrium (LD) and haplotype structure analyses are shown in Supplement 1.

Results

The combined search yielded 1024 references. After discarding the overlapping references and those which clearly did not meet the criteria, 91 studies remained. These studies were then filtered to ensure conformity with the inclusion criteria (13 studies(13–26) were excluded (Supplement 1)). In the end, 78 case-control studies (Table S1 in Supplement 1) met our criteria for inclusion. These studies included 48 studies (5, 14, 27–61) of Asian populations; 21 studies(43, 62–78) of European populations; four studies(79–82) of Mexican Americans; one(76) of African Americans; and four studies(76, 79, 83) investigating the Cys allele (Native Americans, African Americans, and Trinidadians). Among these studies, two(48, 68) investigated heroin dependence or abuse; three(76) investigated multi-drug dependence, and the other 73 studies investigated AD or AD and alcohol abuse. These 73 studies included 18 studies(28, 32, 35, 36, 44, 46, 50, 62, 63, 65, 66, 70–72, 74, 75, 77) in which the alcoholic patients were affected by alcoholic liver disease, cirrhosis, and (or) pancreatitis (10 of the 18 studies also included data for the patients without any alcohol-induced diseases). These studies included 9,638 cases and 9,517 controls. The results are detailed below.

Based on all these samples, the frequency of the protective *ADH1B* His allele varied widely across the populations: high in the Asian normal populations 69% (19% – 91%) and affected subjects, 51% (9% – 93%); low in the European normal populations 5.5% (1% – 43%) and affecteds, 6.9% (0% – 51%); and rare in the Mexican normal populations 3% (2% – 7%) and affecteds, 4% (2% – 8%). On average, the frequencies of the His allele were 34% and 45% in the combined patients and controls, respectively. The *ADH1B* Cys allele was found in African Americans, native Americans, and Trinidadians with frequencies of 11% (1% – 30%) in controls and 7% (0% – 18%) in affecteds. In the 48 Asian studies, 45 studies showed lower frequency in cases than in controls; in the 21 European studies, 16 showed lower frequency in cases than in controls; in the four Mexican American studies, two showed lower frequency; and all the four studies of the Cys allele, that allele showed lower frequency in cases than in controls. Only the studies of AD and alcohol abuse were included in the following meta-analysis.

All the combined studies of AD and alcohol abuse, in particular, the Asian studies, showed strong association, with allelic (Arg vs. His) P values of 1×10^{-36} (OR = 2.06 (1.84, 2.31)) and 7×10^{-42} (OR = 2.24 (1.99, 2.51)), respectively (Table 1). The strong association was also found under both dominant (ArgArg + ArgHis vs. HisHis) and recessive (ArgArg vs. ArgHis + HisHis) models ($P < 9\times10^{-23}$ in all the populations and $P < 2\times10^{-31}$ in Asians) with much lower heterogeneity under the dominant model ($P > 0.01$). Strong association was also revealed in the combined Asian and European-ancestry studies (allelic $P = 2\times10^{-36}$), however, it was moderate in the European ($P = 0.0002$) and non-Asian studies ($P = 2\times10^{-5}$). The strict random effects model was applied when evidence for significant heterogeneity between studies was found throughout this meta-analysis.

In some studies the AD subjects had alcoholic liver disease, cirrhosis, or pancreatitis (designated as “induced diseases” in Table 1). Meta-analysis of these studies showed significant evidence of association ($P = 4\times10^{-12}$ and OR = 1.76 (1.5, 2.07)). The association was stronger in the Asian populations ($P = 3\times10^{-12}$ and OR = 1.97 (1.54, 2.52)) but was not

significant in the European populations (Table 1). The patients with only alcoholic liver disease also produced significant association ($P = 0.005$). For the subjects only with cirrhosis, the significant association was found with $P = 9\times10^{-8}$, which was also significant in Asians ($P = 4\times10^{-8}$) but not in Europeans.

In order to understand whether these strong associations were due only to the alcohol-induced medical diseases, we also analyzed the samples without any of these diseases. The results showed that there was not any decrease on the level of significance compared with the results with these induced diseases (e.g., $P = 9\times10^{-33}$ and OR = 2.1 (1.86, 2.37), Table 1).

Two studies investigated both AD and alcohol abuse; seven studies had no explicit description of the patients as alcohol dependent (the possibility that subjects with a diagnosis of alcohol abuse could not be excluded); the other studies clearly described the patients as alcohol dependent (these “definite” alcohol dependent patients without any alcohol-induced diseases were designated as “AD” in Table 1). The meta-analysis based on these “definite” alcohol dependent subjects also showed that there was no major change on the significance level of the association. Strong association was still detected in all the combined populations, in particular, in the Asian populations and in the combined Asians and Europeans for both allelic and genotypic analyses. For instance, the allelic *P* values were 2×10^{-29} (OR = 2.12 (1.86, 2.42)) and 1×10^{-33} (OR = 2.28 (1.99, 2.6)) in the combined populations and the Asian populations, respectively (Table 1).

For the Cys allele, evidence of significant association was detected with *P* value of 7×10^{-5} and OR of 2.74 (1.67, 4.51) under the recessive model (ArgArg vs. ArgCys + CysCys). Statistical significance was also identified in allelic analysis (Table 1). The studies of AD and alcohol abuse combined with those from the Cys allele showed stronger association with allelic *P* value of 1×10^{-38} (OR = 2.08 (1.86, 2.32)).

The four studies with the Cys allele, two studies of heroin dependence and abuse, and three studies of multi-drug dependence were analyzed separately. However, they were also combined with AD and alcohol abuse considering that alcohol and drug dependence have been reported to share common genetic risk(84-86). The results showed that there was still strong evidence of association with *ADH1B* His and Cys in both allelic (Arg vs. His and Cys) and genotypic analyses (Table 1). The overall *P* value was 4×10^{-31} and OR was 1.98 (1.76, 2.22) for the allelic analysis, which was stronger under the dominant model. The Asian studies produced an allelic *P* value of 6×10^{-32} (OR = 2.17 (1.9, 2.46)), and significant results were found consistently under the dominant and recessive models ($P = 9\times10^{-32}$ and 2×10^{-31}, respectively). Significant association was further detected in the combined Asian and European studies and non-Asian studies ($P = 1\times10^{-28}$ and 1×10^{-6}, respectively). In contrast, the European studies showed moderate evidence of association with an allelic *P* value of 0.0007. The Mexican studies showed weak association ($P = 0.034$) possibly due to limited sample size. In addition, significant association was also revealed in the combined Mexican Americans and African Americans (including the studies investigating the Cys allele), and the *P* values were 0.0001 and 4×10^{-15} for the allelic analysis and recessive model, respectively.

The demography of the association studies are shown in Table S1 (see Supplement 1). The results of overall and sub-grouped meta-analyses are shown for both allelic and genotypic analyses in Table 1. Other sub-grouped analyses are shown in Table S2 in Supplement 1. The forest plots of the allelic and genotypic analyses are shown in Figure 1, and Figures S1 and S2 in Supplement 1.

Other Heterogeneity Analyses

Heterogeneity Q tests were also performed for differences in OR between the studies using the World Health Organization s International Statistical Classification ofDiseases and Related Health Problems (ICD)(87), the American Psychiatric Association s Diagnostic and Statistical Manual of Mental Disorders (DSM)(88) system, or other identified criteria and studies with no description of diagnosis criteria; between the English-language publications and Chinese-language publications; and between the studies of China-mainland and Taiwan and those of other countries or regions. The results showed that there was only evidence of marginal heterogeneity regarding diagnosis criteria using the recessive model ($P(Q) = 0.04$), but no heterogeneity using the allelic analysis and dominant model; and weak heterogeneity regarding publication languages using the allelic analysis ($P(Q) = 0.01$), but no heterogeneity under the dominant and recessive models. The weak heterogeneity between the languages may be due to the heterogeneity between the Asian studies because all the Chinese-language publications were investigating Chinese populations. The results are shown in Table S3 in Supplement 1.

Publication Bias Analyses

Publication bias is an important issue in meta-analysis. In the present study, no evidence of significant publication bias was found in the studies of AD and alcohol abuse with European samples ($P(T) > 0.05$) for either allelic or genotypic analysis. However, evidence of publication bias was found in those studies with Asian samples as well as when all the populations were combined as described below. For the allelic analysis, in the studies of AD and alcohol abuse with Asian samples, the Egger's regression *P* value (1-tailed) was 0.0002, and Kendall's tau (Begg and Mazumdar rank correlation)(89) *P* value (1-tailed) was 0.005; the analysis of Duval and Tweedie's trim and fill showed that there might potentially be eight missing studies, and the adjusted overall effect size was 2.50(2.21, 2.83) under the random effects model; in all the populations the Egger's regression *P* value was 0.0001, and Kendall's tau *P* value was 0.04; the trim and fill analysis showed that there might be six potential missing studies, and the adjusted effect size was 2.17(1.93, 2.43) under the random effects model. For the dominant model, in the Asian samples the $P(T)$ was 0.032, there might be four potential missing studies, and the adjusted effect size was 2.24(1.96, 2.57). However, it should be noted that all the three adjusted values of effect size were *larger* than the corresponding observed values, which implied stronger associations in the adjusted studies compared with the observed studies. That is, the imputed missing studies were positive.

The classic fail-safe analysis showed that for the allelic analysis at least 8,512 assumed non-significant studies could bring the overall $P(Z)$ value to > 0.05 for all the studies of AD and alcohol abuse (6,606 for the Asian studies and 62 for the European studies); for the dominant model at least 2,839 assumed non-significant studies could bring the *P* value to > 0.05 (2,466 for the Asian studies); and for the recessive model it needed at least 5,882 assumed non-significant studies (4,337 for the Asian studies and 64 for the European studies). The results further supported the strong associations detected in this meta-analysis. The funnel plots are shown for the allelic and genotypic analyses of all the studies of AD and alcohol abuse in Figures S3-S5 in Supplement 1. Figure S3 in Supplement 1 indicates the increase of effect size from the observed to adjusted values.

Sensitivity and Retrospective Analyses

The sensitivity analyses showed that no individual study among the 78 that were included biased the findings to the extent that it could account for the strong observed associations. For example, the studies of AD and alcohol abuse showed strong consistency, regardless of the data set removed, with the allelic *P* values always between 3×10^{-39} and 2×10^{-33} among

the 70 studies; For the dominant and recessive models, the results were also strong and consistent, regardless of the data set removed, with the *P* values never > 3×10^{-31} among the 57 studies and never > 3×10^{-21} among the 66 studies, respectively. The results are shown for the allelic analysis, dominant model, and recessive model in Tables S4–S6 (see Supplement 1), respectively.

The asymptote lines of the analyses in retrospect based on 21 publication years showed that the cumulative synthesis tended towards stability in recent years, in line with the overall results of this meta-analysis. The results of the allelic analysis are shown in Figure 2; and the results of the genotypic analyses are shown in Figures S6 and S7 in Supplement 1. The *P*(Z) and *P*(Q) values are shown in Tables S7-S9 in Supplement 1.

LD and Haplotype Structure Analyses

The genes encoding alcohol dehydrogenase alpha, beta, and gamma subunits are organized as a gene cluster on chromosome 4q. Strong LD was found in the region of the gene cluster of the *ADH6*, *ADH1A*, *ADH1B*, *ADH1C*, and *ADH7* genes (Figure S8 in Supplement 1), which were consistent with the studies by colleagues(76, 90). The first four genes were in a strong LD structure (large triangle in dark red and blue that was composed of multiple haplotype blocks), and *ADH1A* and *ADH1B* were in a same haplotype block, which indicated that the contribution of the gene cluster to the association effect on alcohol and drug dependence was not independent. Since *ADH1B* haplotypes have not been fully evaluated, it will be necessary for subsequent studies to investigate the roles of other polymorphisms in the same haplotype block (e.g., the nonsynonymous SNPs shown on the LD plot or in Table S10 in Supplement 1) or the polymorphisms on other genes within the strong LD structure. The LD plots are shown for the Asian and European populations in Figures S8 and S9 (see Supplement 1), respectively.

Discussion

Strong evidence of association was found between the *ADH1B* Arg48His and alcohol abuse and dependence, as well as alcohol-induced medical diseases, in multiple populations, in particular, in Asians, in this meta-analysis. The His allele was highly prevalent in the Asian ethnic populations, particularly in northeast Asians. It was slightly lower in some Chinese aboriginal groups (e.g., Elunchan) but was higher in others (e.g., Atayal and Paiwan). Figure 3 and Table S11 in Supplement 1 show the His48 allele frequencies of by location.These aboriginal groups (e.g., Atayal and Bunun) may to some extent contribute to the significant heterogeneity between the Asian studies. However, the allele frequency was very low in Europeans, Native Americans, and Africans, and thus, the homozygous His/His was not observed at all in some studies of these populations. This constitutes one of the reasons that the association studies, reported by different research groups, produced discrepant or contradictory results. There are some other possible explanations: for example, the His48 allele could (because of LD) be co-inherited with other ADH variants that might affect the risk of alcoholism and which could differ between Europeans and Asians(91). Another reason may be found in the population genetics of alcohol metabolizing enzyme variants (Supplement 1).

Most published genome-wide association studies (GWAS) of addictions have focused on smoking behavior or AD. Four GWAS of AD with a range of 1,100 to 1,897 patients have been published thus far, and only two SNPs have received modest support of replication in a subsequent study(92). One GWAS(93) has identified nine SNPs located in genes, for example, the *CDH13* and *ADH1C* genes, to be nominally associated with AD, including rs1614972 on the *ADH1C* gene ($P = 0.0001$). Another study (94) reported that fifteen SNPs yielded $P < 10^{-5}$, but in two independent replication series, no SNP passed a replication

threshold of 0.05. Edenberg et al.(95) found that 15 SNPs in the ADH gene cluster were nominally significant. However, no single SNP met genome-wide significance. Other studies(96, 97) also failed to report genome-wide significance in the ADH gene cluster. Another study(98) compared six published association studies between AD and the seven *ADH* genes and only a few SNPs reached the *P* value < 0.001 across this region.

Compared with previous meta-analyses(3, 6, 7) that applied different statistical methods(99–104) from those in our studies(105–109), the present study identified much stronger evidence of association for *ADH1B*. The differences included: the study by Zintzaras et al. (3), in which the latest dataset was published in 2004, included 33 studies (no more than one third of our sample size); only included English publications; provided OR without specific *P* values; and found no association between liver disease and *ADH1B* His. The meta-analysis by Luczak et al.(6), in which the latest dataset was also published in 2004, only included Asian samples; of there, there were 685 cases and 890 controls from 12 studies (less than 9% of our sample size); performed genotypic analysis without allelic analysis and specific *P* values; and no association was found for the analysis of His/His vs. Arg/His by this meta-analysis. The older study by Whitfield et al.(7) published in 2002, included 22 studies (17 publications) between *ADH1B* His and alcoholism. In contrast, our meta-analysis included the largest sample size up to the present (9,638 cases and 9,517 controls) from both 72 English and six Chinese-language publications (it was important to include Chinese-language publications as well); used both strict and extended criteria to measure the effect estimates; performed both allelic and genotypic analyses under the strict random effects model; applied systematic analysis procedure, as shown in the results, to study additional questions not answered in those previous meta-analyses; and found consistently stronger evidence of associations for *ADH1B* His with both AD and alcohol-induced diseases (our results have the same direction as a recent study(110) showing that Arg48/Arg48 can increase the risk of esophageal cancer among drinkers). Our results also provided significant evidence of association of this polymorphism (also Cys) with drug dependence although those studies were excluded from meta-analyses of AD. In addition, the procedure of extended-quality score suggested in our previous study(8) was also applied to assist the assessment of quality of the individual association studies.

To conclude, using the cumulative data from 78 English and Chinese publications, this meta-analysis found strong associations of *ADH1B* Arg48His in the combined populations, in particular, in Asians, using both the allelic and genotypic analyses. When both strict and extended criteria as well as the sub-group analyses were imposed, the strong associations remained consistent. Our findings support that the His allele can greatly lower the risk against AD and alcohol abuse as well as alcohol-induced medical diseases, and thus, provide strong evidence for the involvement of the human *ADH1B* gene in the pathogenesis of AD and alcohol-induced diseases in multiple populations, in particular, in the Asian populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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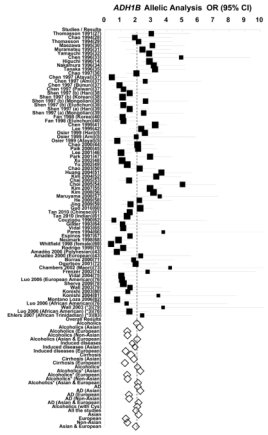

Figure 1.

Forest plots of ln(OR) with 95% CI for the allelic analysis. Black squares indicate the ln(OR) (ln(OR) can be better fitted than OR), with the size of the square inversely proportional to its variance, and horizontal lines represent the 95% CIs. The pooled results are indicated by the unshaded black diamond. Two studies, including Day 1991 and Ehlers 2007 (East Indian Trinidadian) (Cys), are not shown on the forest plots because the scale of the wide CIs can not fit into the current plot.

*, alcoholic patients without alcoholic liver disease, cirrhosis or pancreatitis.

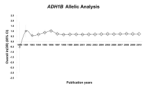

Figure 2.
Retrospective analysis for the allelic analysis. Analysis in retrospect was based on publication year since 1990.

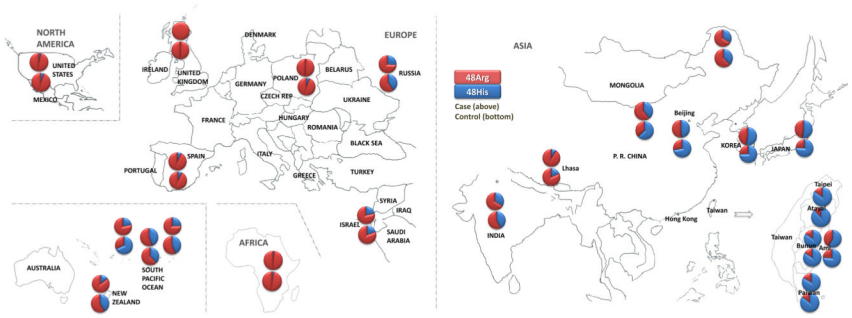

Figure 3.

His48 allele frequencies among different populations. Blue and red represent His48 and Arg48, respectively. Upper graphs are based on the patients and , lower graphs on controls. Only those 57 studies that described their geographic origins specifically are shown on the map. The geographical borders(111) of Taiwan aboriginals were based on a previous study.

Table 1

Results of the overall and sub-grouped studies

Groups	N*	OR (95% CI) Allelic (Arg vs. His)	P(Z)	P(Q)	OR (95% CI) (ArgArg +ArgHis) vs. HisHis	P(Z)	P(Q)	OR (95% CI) ArgArg vs. (ArgHis+HisHis)	P(Z)	P(Q)
Alcoholics[a]	70	2.06 (1.84,2.31)	**1×10^{-36}**	2×10^{-13}	2.17 (1.92,2.45)	**5×10^{-36}**	0.0425	3.05 (2.44,3.81)	**9×10^{-23}**	1×10^{-20}
Alcoholics[a] (Asian)	47	2.24 (1.99,2.51)	**7×10^{-42}**	6×10^{-10}	2.16 (1.9,2.46)	**9×10^{-32}**	0.0105	4.11 (3.24,5.21)	**2×10^{-31}**	8×10^{-9}
Alcoholics[a] (European)	19	1.44 (1.19,1.74)	**0.0002**	0.1396	2.1 (0.95,4.64)	0.0700	0.7113	1.45 (1.18,1.79)	**0.0004**	0.0900
Alcoholics[a] (Non-Asian)	23	1.46 (1.23,1.75)	**2×10^{-5}**	0.1275	2.01 (0.98,4.15)	0.0600	0.8462	1.47 (1.22,1.79)	**0.0001**	0.0800
Alcoholics[a] (Asian & European)	66	2.08 (1.86,2.33)	**2×10^{-36}**	2×10^{-13}	2.17 (1.92,2.45)	**1×10^{-34}**	0.0281	3.19 (2.54,4.02)	**4×10^{-23}**	1×10^{-19}
Induced diseases[b]	18	1.76 (1.5,2.07)	**4×10^{-12}**	0.3626	2.05 (1.6,2.64)	**2×10^{-8}**	0.2554	1.91 (1.47,2.49)	**2×10^{-6}**	0.2607
Induced diseases[b] (Asian)	7	1.95 (1.61,2.35)	**3×10^{-12}**	0.3421	2.04 (1.59,2.62)	**3×10^{-8}**	0.2570	3.13 (2.06,4.76)	**8×10^{-8}**	0.7493
Induced diseases[b] (European)	11	1.34 (0.99,1.83)	0.0621	0.6659	3.39 (0.44,26.4)	0.2438	0.3256	1.37 (0.97,1.93)	0.0703	0.6466
Cirrhosis	12	1.68 (1.39,2.03)	**9×10^{-8}**	0.3994	1.98 (1.47,2.66)	**6×10^{-6}**	0.1303	1.75 (1.28,2.38)	**0.0004**	0.4458
Cirrhosis (Asian)	5	1.87 (1.5,2.34)	**4×10^{-8}**	0.1854	1.96 (1.45,2.64)	**1×10^{-5}**	0.0710	2.86 (1.74,4.7)	**4×10^{-5}**	0.5671
Cirrhosis (European)	7	1.29 (0.89,1.88)	0.1743	0.8731	3.39 (0.44,26.4)	0.2438	0.3256	1.28 (0.86,1.9)	0.2230	0.9263
Alcoholic liver disease	3	1.92 (1.21,3.03)	**0.0053**	0.0980				1.97 (1.07,3.6)	**0.0283**	0.0523
Alcoholics[c]	63	2.1 (1.86,2.37)	**9×10^{-33}**	1×10^{-13}	2.17 (1.9,2.49)	**8×10^{-29}**	0.0193	3.11 (2.44,3.96)	**4×10^{-20}**	1×10^{-20}
Alcoholics[c] (Asian)	43	2.28 (2.01,2.59)	**4×10^{-37}**	2×10^{-10}	2.17 (1.88,2.51)	**9×10^{-26}**	0.0042	4.27 (3.29,5.55)	**1×10^{-27}**	9×10^{-10}
Alcoholics[c] (European)	16	1.43 (1.16,1.78)	**0.0010**	0.1560	1.97 (0.85,4.57)	0.1156	0.6883	1.45 (1.14,1.83)	**0.0020**	0.0800
Alcoholics[c] (Non-Asian)	20	1.47 (1.21,1.78)	**0.0001**	0.1424	1.9 (0.89,4.07)	0.0968	0.8406	1.47 (1.19,1.82)	**0.0003**	0.0700
Alcoholics[c] (Asian & European)	59	2.12 (1.87,2.4)	**1×10^{-32}**	2×10^{-13}	2.17 (1.89,2.5)	**9×10^{-28}**	0.0118	3.28 (2.55,4.22)	**2×10^{-20}**	1×10^{-19}
AD[d]	56	2.12 (1.86,2.42)	**2×10^{-29}**	2×10^{-14}	2.15 (1.86,2.47)	**2×10^{-26}**	0.0128	3.31 (2.53,4.33)	**4×10^{-18}**	2×10^{-19}
AD[d] (Asian)	41	2.28 (1.99,2.6)	**1×10^{-33}**	8×10^{-11}	2.15 (1.85,2.49)	**7×10^{-24}**	0.0031	4.31 (3.3,5.63)	**1×10^{-26}**	6×10^{-8}
AD[d] (European)	11	1.55 (1.02,2.37)	**0.0421**	0.0332	1.91 (0.82,4.48)	0.1348	0.5984	1.73 (1.02,2.94)	**0.0410**	0.0136
AD[d] (Non-Asian)	15	1.57 (1.12,2.19)	**0.0082**	0.0370	1.86 (0.87,4)	0.1119	0.7922	1.67 (1.12,2.5)	**0.0117**	0.0151
AD[d] (Asian & European)	52	2.16 (1.89,2.46)	**2×10^{-29}**	3×10^{-14}	2.15 (1.86,2.48)	**2×10^{-25}**	0.0074	3.55 (2.68,4.7)	**9×10^{-19}**	8×10^{-18}
Cys allele (*3)	4	2.05 (1.34,3.13)	**0.0010**	0.4610	0.79 (0.16,3.95)	0.7789	0.3449	2.74 (1.67,4.51)	**7×10^{-5}**	0.7533
Alcoholics[a] (with Cys)	73	2.08 (1.86,2.32)	**1×10^{-38}**	6×10^{-13}	2.27 (2.08,2.49)	**7×10^{-70}**	0.0512	3.07 (2.47,3.8)	**3×10^{-24}**	8×10^{-20}

Groups	N*	OR (95% CI) Allelic (Arg vs. His)	P(Z)	P(Q)	OR (95% CI) (ArgArg +ArgHis) vs. HisHis	P(Z)	P(Q)	OR (95% CI) ArgArg vs. (ArgHis+HisHis)	P(Z)	P(Q)
All the studies	78	1.98 (1.76,2.22)	**4×10^{-31}**	3×10^{-20}	2.12 (1.87,2.4)	**2×10^{-32}**	0.0235	2.91 (2.36,3.59)	**2×10^{-23}**	9×10^{-22}
Asian	48	2.17 (1.9,2.46)	**6×10^{-32}**	4×10^{-17}	2.16 (1.9,2.46)	**9×10^{-32}**	0.0105	4.11 (3.24,5.21)	**2×10^{-31}**	8×10^{-9}
European	21	1.35 (1.13,1.6)	**0.0007**	0.1251	1.39 (0.73,2.66)	0.3120	0.5223	1.39 (1.15,1.68)	**0.0008**	0.1000
Non-Asian	30	1.45 (1.25,1.69)	**1×10^{-6}**	0.1154	1.32 (0.75,2.33)	0.2932	0.7277	1.52 (1.29,1.8)	**8×10^{-7}**	0.0800
Asian & European	69	1.99 (1.76,2.24)	**1×10^{-28}**	3×10^{-21}	2.13 (1.88,2.42)	**8×10^{-32}**	0.0154	3.05 (2.43,3.84)	**1×10^{-21}**	4×10^{-22}
Mexican	4	1.64 (1.04,2.61)	**0.0345**	0.1819	1.65 (0.29,9.5)	0.5756	0.6122	1.59 (0.97,2.61)	0.0650	0.1466
Mexican & African (with Cys)	9	1.83 (1.35,2.49)	**0.0001**	0.4331	1.11 (0.34,3.62)	0.8641	0.6924	2.06 (1.46,2.9)	**4×10^{-5}**	0.3385

*number of studies included in the analyses.

*a*alcoholic patients with and without alcoholic liver disease, cirrhosis or pancreatitis (only one study described that the patients had both alcohol dependence and abuse).

*b*alcoholic patients with alcoholic liver disease, cirrhosis or pancreatitis.

*c*alcoholic patients without any alcoholic liver disease, cirrhosis or pancreatitis and those without liver disease status described.

d"definite" alcohol dependence patients without any alcoholic liver disease, cirrhosis or pancreatitis (i.e., including only patients clearly described as alcohol dependent).

Key: AD: alcohol dependence; Mexican: Mexican American or Native American; African: African American; Induced diseases: alcohol-induced diseases.

The Cys (*3) allele was only detected in some populations including the African and Mexican populations.

P(Z): Z test used to determine significance of the overall OR. The *P* values < 0.05 are indicated in boldfaces.

P(Q): Cochran s X^2-based Q statistic test used to assess heterogeneity.

P(T): T test used to evaluate significance of publication bias (not shown).

#The recessive model (ArgArg vs. ArgHis + HisHis) produced less significant *P* values but a greater odds ratio, presumably reflecting the sample size in each genotype class and the relative risks between genotypes.