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Original Article

Alcohol dehydrogenase 1C (ADH1C) gene polymorphism and alcoholic liver cirrhosis risk: a meta analysis

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Abstract: The association between alcohol dehydrogenase 1C (ADH1C) gene polymorphism and alcoholic liver cirrhosis (ALC) has been analyzed in several studies, but results have been conflicting. In this study, a meta-analysis was performed to assess the associations between the ADH1C polymorphism and risk of ALC. Relevant studies were identified using PubMed, Web of Science, CNKI and Wanfang databases up to January 10, 2015. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the association using the fixed or random effect model. A total of 16 case-control studies, including 1375 cases and 1802 controls, were included. Overall, no significant association between the ADH1C polymorphism and ALC risk was found (dominant model: OR=0.87, 95% CI: 0.62-1.23; recessive model: OR=1.30, 95% CI: 0.84-1.99; *1/*2 vs. *1/*1: OR=0.87, 95% CI: 0.63-1.21; *2/*2 vs. *1/*1: OR=1.10, 95% CI: 0.71-1.70). In the subgroup analysis by ethnicity, we observed a significant association in Asian descent (*1/*2 vs. *1/*1: OR=1.63, 95% CI: 1.07-2.49), while a decreased risk was found among Caucasians (dominant model: OR=0.81, 95% CI: 0.66-0.99; *1/*2 vs. *1/*1: OR=0.76, 95% CI: 0.61-0.95). This meta-analysis demonstrated that the ADH1C polymorphism might increase the risk of ALC in Asians, while it may be a protective factor for ALC among Caucasians.

Keywords: ADH1C, polymorphism, alcoholic liver cirrhosis, meta-analysis

Introduction

Alcoholic liver disease (ALD) refers to a wide spectrum of liver abnormalities, ranging from fatty liver to acute alcoholic hepatitis, and alcoholic liver cirrhosis (ALC). The most severe of these, ALC, causes an estimated 373, 000 deaths per year [1]. The burden of ALD is highest in the developed world, where it may account for as much as 9.2% of all disability-adjusted life years [2]. For example, the annual costs of hospitalization for ALD in the United States are estimated to be between $600 million and $1.8 billion [3]. It has been demonstrated that a clear correlation exists between cumulative alcohol intake and ALD; however, only a small portion of the alcohol abusers develop signs of liver disease, which suggests some of the genetic variations are involved in the etiology of ALD [4].

Alcohol dehydrogenase (ADH) is a dimeric protein consisting of two 40-kDa enzyme subunits. There are at least five different classes of human ADH isoenzymes based on differences at the molecular level [5]. The class I ADH enzymes, encoded by ADH1A, ADH1B, and ADH1C (previously known as ADH1, ADH2, and ADH3, respectively) are mainly involved in the oxidation of ethanol. Polymorphic variants exist among the class I ADH genes, specifically ADH1B and ADH1C, and are known to produce enzymes with distinct kinetic properties [6]. As for ADH1C, the polymorphic sites are Arg272Gln (rs1693482) and Ile350Val (rs698) [7], the 272Arg and 350Ile carriers have the ADH1C*1 allele, whereas 272Gln and 350 Val carriers have the ADH1C*2 allele. Individuals with ADH1C*1 allele have an ethanol oxidizing capacity 2.5-times higher when compared to ADH1C*2 allele [8] and therefore produces more acetaldehyde. Thus, it has been hypothesized that individuals with homozygosity for the allele ADH1C*1 carry an increased risk for alcohol-induced organ damage, such as liver cirrhosis, than patients with heterozygosity or those homozygous for ADH1C*2 [9].

To date, many studies have investigated the association between the ADH1C polymorphism and the risk of alcoholic liver cirrhosis [10-28]. However, the results remain controversial. In this study, we conduct a meta-analysis to evaluate the association between the polymorphism and alcoholic liver cirrhosis risk.

Materials and methods

Search strategy

Relevant articles published before January 10, 2015 were identified through a search of PubMed, Web of Science, CNKI, Wanfang and VIP databases using the following terms: "alcohol dehydrogenase 3 or ADH3 or alcohol dehydrogenase 1C or ADH1C" and "genetic polymorphism or polymorphisms or variant" and "alcoholic liver disease or ALD or alcoholic liver cirrhosis or ALC or cirrhosis". The search was restricted to humans without language restrictions. Additional studies were identified by a hand search of references of original or review articles on this topic.

Inclusion criteria and exclusion criteria

Studies included in this meta-analysis have to meet the following criteria: (1) studies that evaluated the association between the ADH1C polymorphism and alcoholic liver cirrhosis, (2) in a case-control study design, (3) had detailed genotype frequency of cases and controls or could be calculated from the article text. Studies were excluded when they were: (1) case-only study, case reports, and review articles, (2) based on incomplete data, (3) duplicate of previous publication.

Data extraction

For each study, the following data were extracted independently by two investigators: the first author's name, year of publication, country of origin, ethnicity, genotyping methods, number of cases and controls, and Hardy-Weinberg equilibrium (HWE) in controls (*P* value). The results were compared, and disagreements were discussed among all authors and resolved with consensus.

Statistical analysis

The strength of the association between the ADH1C polymorphism and alcoholic liver cirrhosis risk was estimated by odds ratio (ORs) and 95% confidence interval (CIs). Four different ORs were calculated: dominant model (*1/*2+*2/*2 vs. *1/*1), recessive model (*2/*2 vs. *1/*2+*1/*1), heterozygote comparison (*1/*2 vs. *1/*1), and homozygote comparison (*2/*2 vs. *1/*1). Genotype frequencies of the controls were tested for the HWE using the χ^2 test. Heterogeneity among studies was assessed by χ^2-based Q test as well as the I^2 statistic [29]. When a significant Q test ($P>0.1$) or $I^2<50\%$ indicated homogeneity across studies, the fixed effects model was used [30], or else the random effects model was used [31]. Then, we performed stratification analyses on ethnicity. Sensitivity analysis was performed by removing one individual study each time to evaluate the stability of the results. Begg's funnel plot and Egger's regression test were used to investigate potential publication bias [32, 33]. $P<0.05$ was considered statistically significant. All statistical analyses were performed using the Cochrane Collaboration RevMan 5.2 and STATA package version 12.0 (Stata Corporation, College Station, Texas).

Results

Study characteristics

Initially, the searched keywords identified 52 articles. According to the inclusion criteria, 19 studies [10-28] with full-text were included in this meta-analysis and 33 studies were excluded. Because one study [28] did not present detailed genotyping information, we excluded it. We also excluded two studies [26, 27] because they included the overlapped data with those included in the analysis [14]. Therefore, as shown in **Table 1**, there were 16 case-control studies with 1375 cases and 1802 controls concerning ADH1C polymorphism. Of the 16 eligible studies, two ethnicities were addressed: six studies [10-13, 19-21] were conducted on Asian populations and ten studies [10, 14-18, 22-25] on Caucasian populations. The distribution of genotypes in the controls was consistent with the HWE for all selected studies, except for three studies [17, 22, 25].

Quantitative data synthesis

Overall, no significant association between the ADH1C polymorphism and ALC risk was found (dominant model: OR=0.87, 95% CI: 0.62-1.23;

Table 1. Characteristics of studies included in the meta-analysis

Author	Year	Country	Ethnicity	Genotyping methods	Genotype (case/control)				HWE
					Total	*1/*1	*1/*2	*2/*2	
Borras [10]	2000	Mixed	Caucasian	PCR-RFLP	180/224	62/66	82/117	36/41	0.387
Chao [11]	1994	China	Asian	PCR-RFLP	27/47	17/42	8/5	2/0	0.700
Chao [12]	1997	China	Asian	PCR-RFLP	75/100	57/88	16/11	2/1	0.342
Chao [13]	2000	China	Asian	PCR-RFLP	116/105	88/91	25/13	3/1	0.495
Cichoz-Lach [14]	2007	Poland	Caucasian	PCR-RFLP	57/54	26/10	19/24	12/20	0.559
Couzigou [15]	1990	France	Caucasian	PCR	46/39	13/14	26/17	7/8	0.504
Day [16]	1991	England	Caucasian	PCR	59/79	26/25	22/37	11/17	0.634
Frenzer [17]	2002	Australia	Caucasian	PCR-RFLP	57/200	13/56	21/120	23/24	0.001
Homann [18]	2006	German	Caucasian	PCR-RFLP	217/174	43/38	122/92	52/44	0.439
Khan [19]	2010	India	Asian	PCR-RFLP	175/255	99/84	76/171[&]		NA
Kim [20]	2004	Korea	Asian	PCR-RFLP	22/100	20/76	2/21	0/3	0.313
Lee [21]	2001	Korea	Asian	PCR-RFLP	56/64	50/57	5/7	1/0	0.644
Monzoni [22]	2001	Italy	Caucasian	PCR	15/92	6/31	4/53	5/8	0.028
Poupon [23]	1992	France	Caucasian	Starch-Gel Electrophoresis	23/42	12/12	8/23	3/7	0.472
Sun [24]	2005	German	Caucasian	PCR-RFLP	151/163	30/33	92/89	29/41	0.227
Vidal [25]	2004	Spain	Caucasian	PCR-RFLP	99/64	35/15	45/42	19/7	0.008

HWE: Hardy-Weinberg equilibrium; [&]Numbers of *1/*2+*2/*2; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; NA: not available.

recessive model: OR=1.30, 95% CI: 0.84-1.99; *1/*2 vs. *1/*1: OR=0.87, 95% CI: 0.63-1.21; *2/*2 vs. *1/*1: OR=1.10, 95% CI: 0.71-1.70) (**Table 2**; **Figure 1**).

In the subgroup analysis by ethnicity, we observed a significant association in Asian descent (*1/*2 vs. *1/*1: OR=1.63, 95% CI: 1.07-2.49), while a decreased risk was found among Caucasians (dominant model: OR=0.81, 95% CI: 0.66-0.99; *1/*2 vs. *1/*1: OR=0.76, 95% CI: 0.61-0.95) (**Table 2**; **Figure 2**).

Sensitivity analyses were conducted to determine whether modification of the inclusion criteria of the meta-analysis affected the final results. We examined the influence of these studies on the pooled OR by repeating the meta-analysis while excluding one study at a time. The estimated pooled ORs change quite little, indicating that our results were statistically robust.

Test of heterogeneity

There was significant heterogeneity for overall comparisons (dominant model: $P<0.00001$, $I^2=72\%$; recessive model: $P=0.0005$, $I^2=63\%$; *1/*2 vs. *1/*1: $P=0.002$, $I^2=58\%$; *2/*2 vs. *1/*1: P=0.009, $I^2=52\%$). In the subgroup analysis by ethnicity, the heterogeneity was partially decreased or removed in Asian population. However, significant heterogeneity remain exist in the Caucasian population under recessive and homozygote comparison models.

Publication bias

The Begg's funnel plot and Egger's test was used to address potential publication bias in the available literature. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry (data not shown). Egger's test also showed that there was no statistical significance for the evaluation of publication bias (dominant model: $P=0.395$; recessive model: $P=0.325$; *1/*2 vs. *1/*1: $P=0.645$; *2/*2 vs. *1/*1: $P=0.403$).

Discussion

Pharmacokinetic difference in ethanol metabolism is a plausible determinant of susceptibility to the many diseases associated with alcohol. ADH is a zinc-containing cytosolic enzyme that oxidizes short-chain alcohols to aldehydes, mainly formaldehyde and acetaldehyde. Epidemiological studies have examined the association between the ADH1C*1 allele and risk of ALC with conflicting results. Some investigations demonstrated that the ADH1C*1/*1 genotype exhibited significant association with alcohol liver cirrhosis [14, 19]; on the contrary, Frenzer et al [17] suggest the ADH1C*2*2 is

Table 2. Summary of OR of the ADH1C polymorphism and alcoholic cirrhosis risk

Variables	N[a]	Dominant model			Recessive model			*1/*2 vs. *1/*1			*2/*2 vs. *1/*1		
		OR (95% CI)	*P*[b]	I^2	OR (95% CI)	*P*[b]	I^2	OR (95% CI)	*P*[b]	I^2	OR (95% CI)	*P*[b]	I^2
Total	16	0.87 (0.62, 1.23)	<0.00001	72	1.30 (0.84, 1.99)	0.0005	63	0.87 (0.63, 1.21)	0.002	58	1.10 (0.71, 1.70)	0.009	52
Ethnicity													
Asian	6	1.19 (0.47, 3.04)	<0.00001	87	2.70 (0.90, 8.13)	0.81	0	1.63 (1.07, 2.49)	0.10	48	2.84 (0.96, 8.39)	0.72	0
Caucasian	10	0.81 (0.66, 0.99)	0.07	44	1.19 (0.75, 1.91)	<0.0001	74	0.76 (0.61, 0.95)	0.07	43	0.97 (0.61, 1.56)	0.004	63

[a]Number of comparisons. [b]Test for heterogeneity.

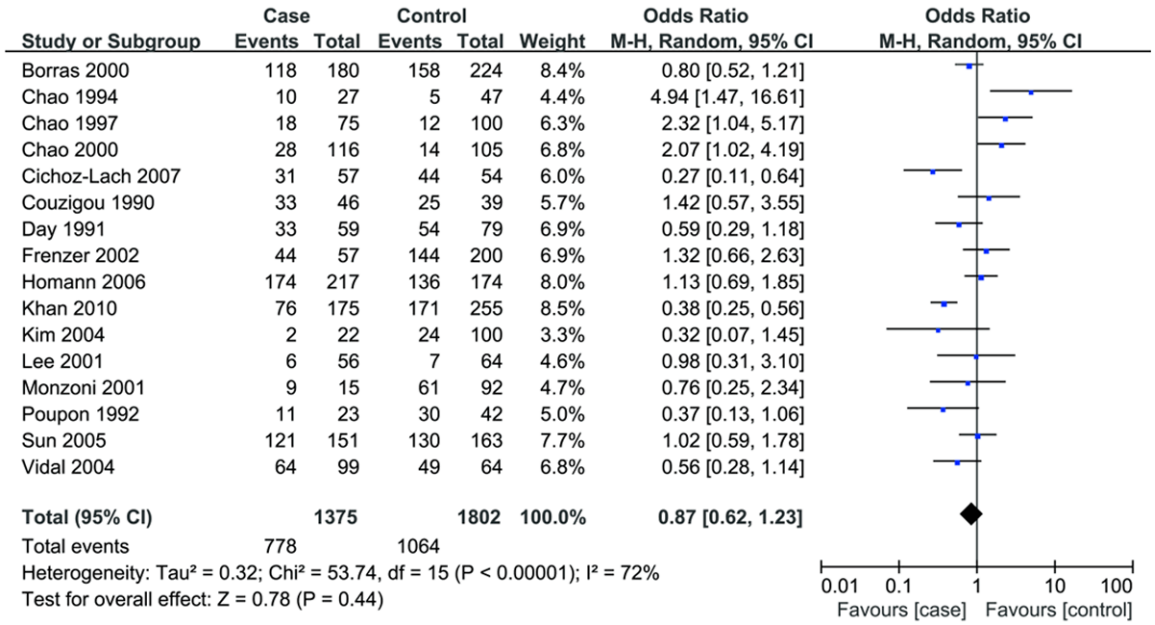

Figure 1. Forest plots for the association of ADH1C polymorphism and ALC risk (dominant model).

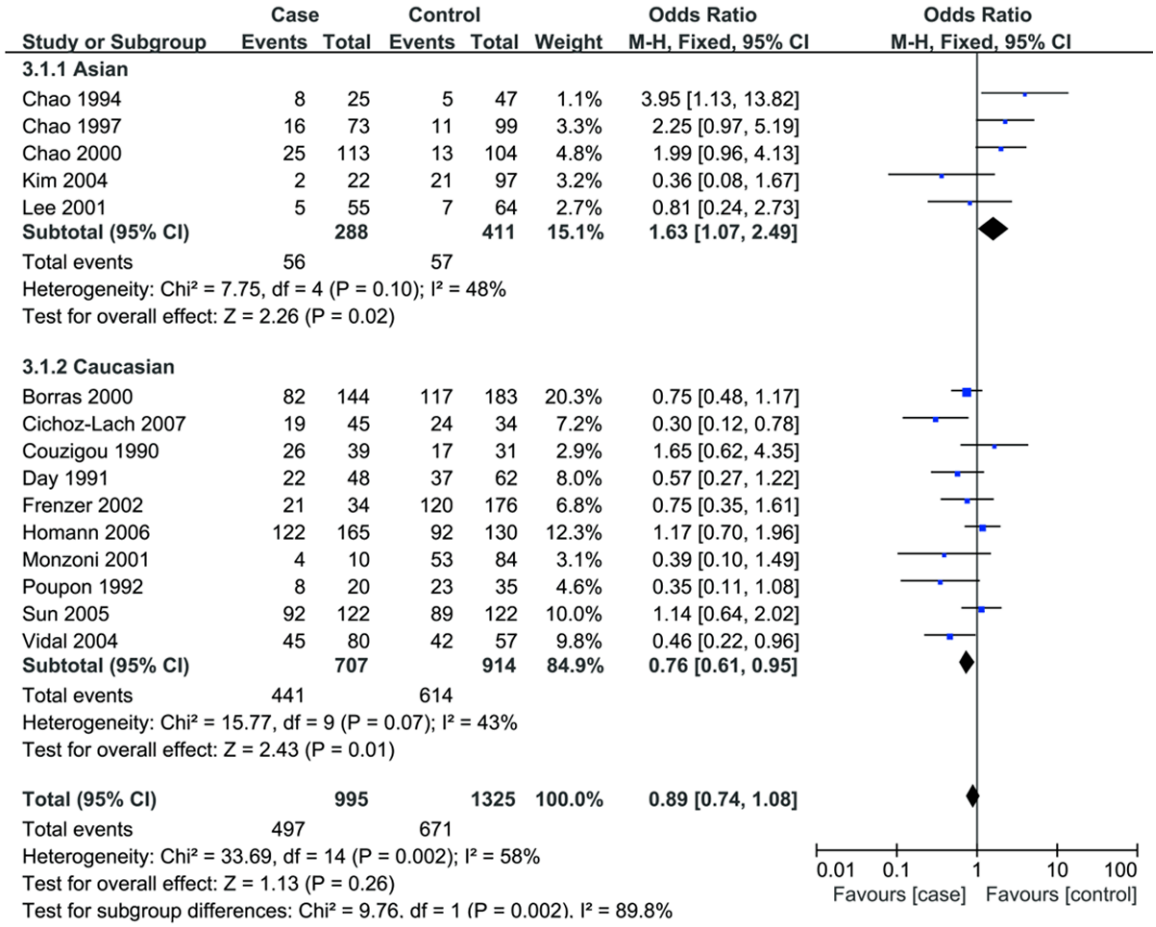

Figure 2. Forest plots for subgroup analysis by ethnicity for the association of ADH1C polymorphism and ALC risk (*1/*2 vs. *1/*1).

associated with alcoholic cirrhosis. Additionally, the association of ADH1C variants and ALC risk was not validated by others [15, 20, 21, 23, 25]. In order to resolve this conflict, we performed a meta-analysis to derive a more precise estimation of the association.

In this study, 16 case-control studies included 1375 cases and 1802 controls were included. We found that the ADH1C*2 allele is not associated with ALC. That is, the ADH1C genotype distribution between ALC and control group was no significant difference. Interestingly, when the analysis was stratified by ethnicity, we observed a significant association in Asian descent, while a decreased risk was found among Caucasians. There are some possible explanations for the discrepant results. First, significant linkage disequilibrium has been detected between the ADH1B and ADH1C polymorphisms as well as the two variants in ADH1C [34]. These functional variants result in the production of enzymes with different kinetic properties [7] and subsequently the generation of different quantities of acetaldehyde, which might affect the risk of ALC and that could differ between Caucasians and Asians. Another reason may be found in the population genetics of alcohol metabolizing enzyme variants. In addition, the prevalence of the variant ADH1C allele is high in Caucasian population (40-50%) and lower in Asians (5%) [9], which may also contribute to the results.

Two significant issues should be addressed in this study, that is, heterogeneity and publication bias, which may influence the results of meta-analysis. We don't detect a significant publication bias in this meta-analysis, suggesting the reliability of our results. With regard to heterogeneity, in this meta-analysis, heterogeneity was found in overall comparison under all four genetic models, when stratified by ethnicity, the heterogeneity was partly decreased or removed in Asian populations. However, heterogeneity still existed among Caucasian population. The results above suggest that the ethnic background might be the source of heterogeneity. Then sensitivity analyses were conducted by successively excluding one study, the estimated pooled odd ratio changed quite little, strengthening the results from this meta-analysis.

This meta-analysis has limitations that must be acknowledged. First, because of incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Second, moderate to higher heterogeneity existed for the analyses especially for the subgroup of Caucasian. Third, our results were based on unadjusted estimates, which may cause serious confounding bias. In addition, all of the studies were conducted in Asian and Caucasians, which may generate selective bias. More studies focused on Africans are needed.

In summary, this meta-analysis suggests that the ADH1C polymorphism might increase the risk of ALC in Asians, while it may be a protective factor for ALC among Caucasians. However, due to the limitations mentioned above, more researches with larger sample size are still required to provide a more reliable and representative statistical analysis precisely.

Disclosure of conflict of interest

None.

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