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Original Article

Genetic polymorphism in alcohol dehydrogenase 2 (ADH2) gene and alcoholic liver cirrhosis risk

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Abstract: The alcohol dehydrogenase 2 (ADH2) gene has been implicated in the development of alcoholic liver cirrhosis (ALC). However, the results are inconsistent. In this study, a meta-analysis was performed to assess the associations between the ADH2 polymorphism and the risk of ALC. Relevant studies were retrieved by searching PubMed, Web of Science, CNKI, Wanfang and VIP databases up to January 10, 2015. The pooled odds ratio (OR) with a 95% confidence interval (CI) was calculated using the fixed- or random effects model. A total of 21 case-control studies included 1812 cases and 3468 controls were included. Overall, the ADH2 polymorphism was associated with a decreased risk of ALC in all four genetic models (dominant model: OR=0.56, 95% CI: 0.38-0.83; recessive model: OR=0.59, 95% CI: 0.39-0.91; *1/*2 vs. *1/*1: OR=0.58, 95% CI: 0.40-0.85; *2/*2 vs *1/*1: OR=0.35, 95% CI: 0.16-0.75). Besides, in stratification analysis by ethnicity, similar results were observed in Asian populations, however, we detected no association in Caucasian populations under recessive and homozygote comparison model. The pooled evidence suggests that ADH2 polymorphism may be an important protective factor for alcoholic liver cirrhosis, especially for Asians.

Keywords: ADH2, 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]. 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 [3, 4].

The ADH2 (also named ADH1B) gene is located on chromosome 4q21-q23. There are several polymorphism sites in the ADH2 gene, and the Arg47His polymorphism (rs1229984, with the Arg corresponding to *1 allele, and His corresponding to *2 allele) has been the most frequently studied. The $\beta_2\beta_2$ enzyme encoded by ADH2 2*2 is approximately 20-fold more active in ethanol oxidation than the $\beta_1\beta_1$ enzyme [5]. Individuals who inherit the ADH2*2 allele have homodimeric and heterodimeric β_2-containing isozymes and could be expected to have faster rates of alcohol metabolism and possibly higher concentrations of acetaldehyde production after alcohol consumption [6]. Furthermore, the variant ADH2*2 allele is prevalent in East Asian individuals, but is rare in non-Asians [7]. To date, many studies have investigated the association between the ADH2 polymorphism and the risk of alcoholic liver cirrhosis [8-30]. 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

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	2000	Mixed	Caucasian	PCR-RFLP	180/224	175/214	5/10	0/0	0.733
Chao	1994	China	Asian	PCR-RFLP	27/47	4/3	15/19	8/25	0.808
Chao	1997	China	Asian	PCR-RFLP	75/100	17/6	39/41	19/53	0.600
Chao	2000	China	Asian	PCR-RFLP	116/105	20/7	62/43	34/55	0.717
Chao	2003	China	Asian	PCR-RFLP	159/100	33/7	74/38	52/55	0.901
Cichoz-Lach	2007	Poland	Caucasian	PCR-RFLP	57/54	56/48	1/6	0/0	0.666
Couzigou	1990	France	Caucasian	PCR	46/39	44/38	2/1	0/0	0.935
Day	1991	England	Caucasian	PCR	59/79	59/78	0/1	0/0	0.955
Frenzer	2002	Australia	Caucasian	PCR-RFLP	57/200	57/184	0/16	0/0	0.556
Garcia-Banuelos	2012	Mexico	Caucasian	PCR-RFLP	32/66	31/58	1/8	0/0	0.600
Kee	2003	Korea	Asian	PCR-RFLP	27/39	11/18	14/18	2/3	0.603
Khan	2010	India	Asian	PCR-RFLP	175/255	141/222	34/33[&]		NA
Kim	2004	Korea	Asian	PCR-RFLP	20/77	13/36	5/23	2/18	0.001
Lee	2001	Korea	Asian	PCR-RFLP	56/64	7/6	11/18	38/40	0.084
Ogurtsov	2001	Russia	Caucasian	PCR	37/50	13/15	23/29	1/6	0.160
Poupon	1992	France	Caucasian	Starch-Gel Electrophoresis	23/42	23/41	0/1	0/0	0.938
Rodrigo	1999	Spain	Caucasian	PCR-RFLP	120/200	108/173	12/27	0/0	0.306
Vidal	2004	Spain	Caucasian	PCR-RFLP	99/64	85/54	13/10	1/0	0.498
Yamauchi	1995a	Japan	Asian	PCR-RFLP	46/60	8/2	12/22	26/36	0.534
Yamauchi	1995b	Japan	Asian	PCR-RFLP	42/60	8/2	12/22	22/36	0.534
Yokoyama	2013	Japan	Asian	PCR-RFLP	359/1543	75/441	128/497	156/605	0.000

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

VIP databases using the following terms: "alcohol dehydrogenase 2 or ADH2 or alcohol dehydrogenase 1B or ADH1B" 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 ADH2 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

HWE was evaluated for each study using an internet-based HWE calculator (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The risk of alcoholic liver cirrhosis associated with the ADH2 polymorphism was estimated for each study by odds ratio (OR) and 95% confidence interval (95%CI). Four different ORs were calculated: the dominant model (*1/*2+*2/*2 vs. *1/*1), the recessive model (*2/*2 vs. *1/*2+*1/*1), heterozygote comparison (*1/*2 vs. *1/*1), and homozygote comparison (*2/*2 vs. *1/*1). A χ^2-test-based Q statistic test was performed to assess the between-study heterogeneity [31]. We also quantified the effect of heterogeneity by I^2 test. When a significant Q test (P>0.1) or I^2<50% indicated homogeneity across studies, the fixed effects model was used [32], or else the random effects model

Table 2. Summary of OR of the ADH2 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	21	0.56 (0.38, 0.83)	<0.0001	66	0.59 (0.39, 0.91)	<0.0001	73	0.58 (0.40, 0.85)	0.006	50	0.35 (0.16, 0.75)	<0.00001	81
Ethnicity													
Asian	11	0.53 (0.30, 0.93)	<0.00001	80	0.60 (0.39, 0.93)	<0.00001	77	0.54 (0.30, 0.95)	0.0005	70	0.34 (0.15, 0.77)	<0.00001	84
Caucasian	10	0.60 (0.41, 0.88)	0.72	0	0.39 (0.08, 1.85)	0.25	24	0.60 (0.41, 0.89)	0.71	0	0.40 (0.08, 1.94)	0.25	24

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

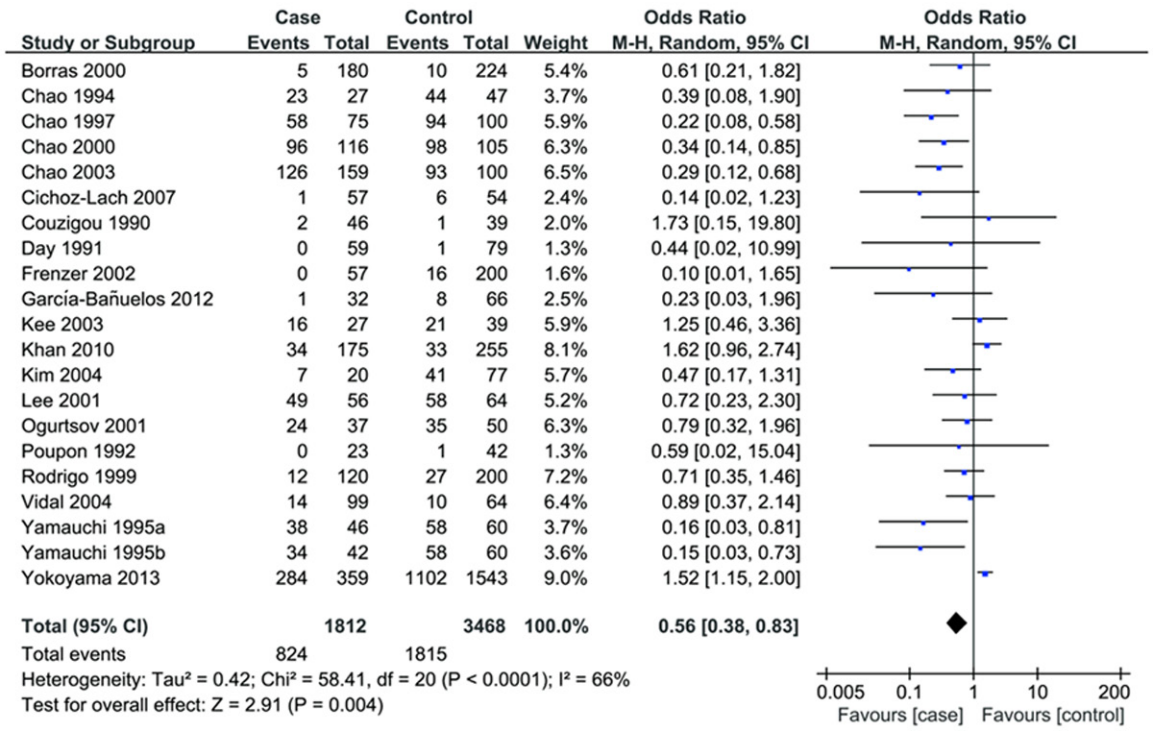

Figure 1. Forest plots for the association of ADH2 polymorphism and ALC risk. (dominant model).

was used [33]. Then, we performed stratification analyses on ethnicity. Analysis of sensitivity was performed to evaluate the stability of the results. Finally, potential publication bias was investigated using Begg's funnel plot and Egger's regression test [34, 35]. $P<0.05$ was considered statistically significant.

All analyses were performed using the Cochrane Collaboration RevMan 5.2 and STATA package version 12.0 (Stata Corporation, College Station, Texas).

Results

Study characteristics

The search strategy retrieved 73 potentially relevant studies. According to the inclusion criteria, 23 studies [8-30] with full-text were included in this meta-analysis and 50 studies were excluded. Because two studies [29, 30] did not present detailed genotyping information, we excluded them. Therefore, as shown in **Table 1**, there were 21 case-control studies with 1812 cases and 3468 controls concerning ADH2 polymorphism. Of the 21 eligible studies, two ethnicities were addressed: eleven studies [9-12, 18-21, 26-28] were conducted on Asian populations and ten studies [8, 13-17, 22-25] on Caucasian populations. The distribution of genotypes in the controls was consistent with the HWE for all selected studies, except for two studies [20, 28].

Quantitative data synthesis

Overall, the ADH2 polymorphism was associated with a decreased risk of ALC in all four genetic models (dominant model: OR=0.56, 95% CI: 0.38-0.83; recessive model: OR=0.59, 95% CI: 0.39-0.91; *1/*2 vs. *1/*1: OR=0.58, 95% CI: 0.40-0.85; *2/*2 vs *1/*1: OR=0.35, 95% CI: 0.16-0.75) (**Table 2**; **Figure 1**).

In stratification analysis by ethnicity, similar results were observed in Asian population, however, we detected no association in Caucasian populations under recessive and homozygote comparison model (**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

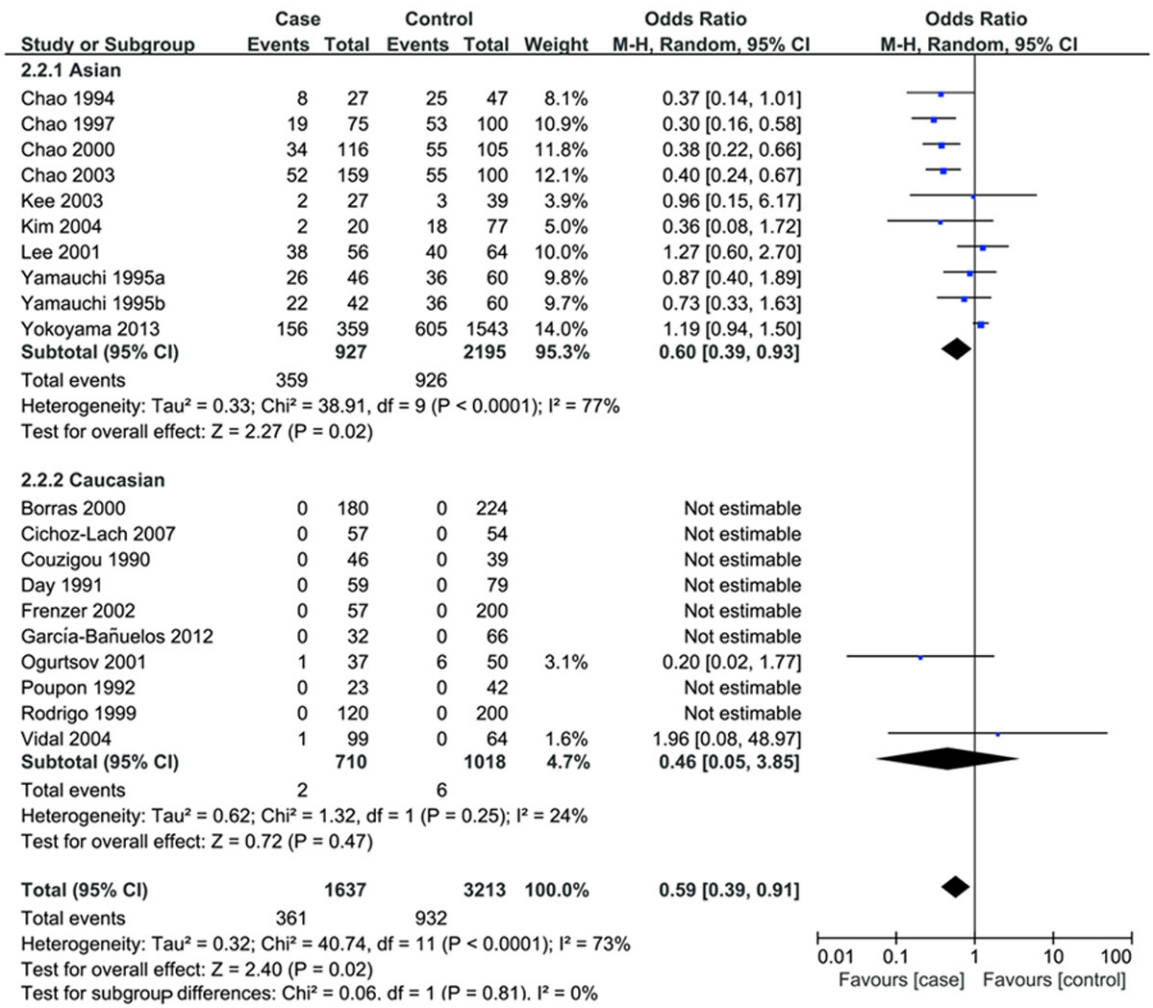

Figure 2. Forest plots for subgroup analysis by ethnicity for the association of ADH2 polymorphism and ALC risk. (recessive model).

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<0.0001, I^2=66%; recessive model: P<0.0001, I^2=73%; *1/*2 vs. *1/*1: P=0.006, I^2=50%; *2/*2 vs. *1/*1: P<0.00001, I^2=81%). In the subgroup analysis by ethnicity, results were similar in the Asian population. However, there was no significant heterogeneity in the Caucasian population.

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 (Figure not shown). Egger's test also showed that there was no statistical significance for the evaluation of publication bias (dominant model: P=0.432; recessive model: P=0.117; *1/*2 vs. *1/*1: P=0.381; *2/*2 vs. *1/*1: P=0.217).

Discussion

Alcohol dependence (AD), which is multifactorial and chronic relapsing disorders, is a major public health problem. Among the patients with AD, ALC occurs in around 10% [36]. The enzyme encoded by ADH2 is a member of the alcohol dehydrogenase family, which metabolizes alcohol into acetaldehyde. ADH2 was hypothesized to be an important ethanol oxidizing enzyme that may alter genetic susceptibility to ALD [37].

Recently, a previous meta-analysis conducted by Li et al [38] has evaluated the association between ADH2 polymorphism and the risk of alcohol dependence and alcohol-induced medical diseases and the results of that provide confirmation of the involvement of the human ADH2 gene in the pathogenesis of alcohol dependence and abuse as well as alcohol-induced medical illnesses in the multiple ethnic populations-in particular, certain Asian populations. However, only 12 studies focusing on ALC were included in the above meta-analysis, due to the limited studies, further analyses was not conducted. Compared with it, we conducted a comprehensive literature search in different databases (i.e. Web of science, CNKI, Wanfang and VIP) and added 9 studies, which allowed for a larger number of subjects and more precise risk estimation. In this study, 21 case-control studies included 1812 cases and 3468 controls were included. We found that the ADH2*2 allele is associated with ALC. Individuals with the ADH2*2/*2 and/or *1/*2 genotype had a lower risk of developing ALC when compared to individuals with the ADH2*/1*1 genotype. They might be explained that ALDH2*2 allele encodes a superactive allozyme, which oxidize ethanol into acetaldehyde fast. The accumulation of acetaldehyde could develop intense facial flushing responses with nausea, headache, drowsiness and other unpleasant symptoms resulting from high blood acetaldehyde levels after alcohol consumption [39]. This unpleasant discomfort may prevent people from consuming alcohol and may keep them from developing alcoholism thus they have much lower chance to expose to the acetaldehyde [40], which may decrease the risk of developing ALC. In addition, in stratification analysis by ethnicity, significant associations were observed in Asian populations. However, we detected no association in Caucasian populations under recessive and homozygote comparison models. There are some possible explanations for the discrepant results. Due to Linkage disequilibrium (LD), the ADH2*2 allele could be coinherited with other ADH (such ADH3) variants that might affect the risk of alcoholism and that could differ between Caucasians and Asians [41]. Another reason may be found in the population genetics of alcohol metabolizing enzyme variants.

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 Caucasian populations. However, heterogeneity still existed in Asian 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 Asian. 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 ADH2 polymorphism may be an important protective factor for alcoholic liver cirrhosis, especially for Asians. Since potential confounders could not be ruled out completely, further studies are needed to confirm these results.

Disclosure of conflict of interest

None.

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