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Association between alcohol dehydrogenase 1C gene *1/*2 polymorphism and pancreatitis risk: a meta-analysis

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ABSTRACT. Numerous studies have focused on the relationship between alcohol dehydrogenase 1C gene (*ADH1C*) *1/*2 polymorphism (Ile350Val, rs698, also known as *ADH1C* *1/*2) and pancreatitis risk, but the results have been inconsistent. Thus, we conducted a meta-analysis to more precisely estimate this association. Relevant publications were searched in several widely used databases and 9 eligible studies were included in the meta-analysis. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the association. Significant associations between *ADH1C* *1/*2 polymorphism and pancreatitis risk were observed in both overall meta-analysis for 12 *vs* 22 (OR = 1.53, 95%CI = 1.12-2.10) and 11 + 12 *vs* 22 (OR = 1.44, 95%CI = 1.07-1.95), and the chronic alcoholic pancreatitis subgroup for 12 *vs* 22 (OR = 1.64, 95%CI = 1.17-2.29) and 11 + 12 *vs* 22 (OR = 1.53, 95%CI = 1.11-2.11). Significant pancreatitis risk variation was also detected in Caucasians for 11 + 12 *vs* 22 (OR = 1.45, 95%CI = 1.07-1.98). In conclusion, the *ADH1C* *1/*2 polymorphism

is likely associated with pancreatitis risk, particularly chronic alcoholic pancreatitis risk, with the *1 allele functioning as a risk factor.

Key words: Alcohol dehydrogenase 1C; Meta-analysis; Pancreatitis risk; Polymorphism

INTRODUCTION

The alcohol dehydrogenase 1C gene (*ADH1C*) encodes the class I alcohol dehydrogenase gamma subunit, which functions in the metabolism of various substrates, including ethanol (Li and Zhao, 2012). A single nucleotide polymorphism (Ile350Val, rs698, also known as *ADH1C* *1/*2) has been reported in exon 8 of the *ADH1C* gene, and enzymatic activity of ADH1C was found to be higher in subjects with the *1 allele compared to in those with the *2 allele (Bosron and Li, 1986; Crabb et al., 1993; Day et al., 1991, 1993). This polymorphism has been studied in numerous diseases (Olshan et al., 2001; Nishimoto et al., 2004; Peters et al., 2005; Terry et al., 2007; Visvanathan et al., 2007; Yin et al., 2007; Zhang et al., 2007; Li et al., 2008).

Pancreatitis is a complex disorder with both acute and chronic forms. Chronic pancreatitis is a chronic inflammatory disease that causes pancreatic fibrosis and destroys the exocrine and endocrine pancreas functions (Ammann et al., 1984). Acute pancreatitis is an acute inflammatory disease initiated by pancreatic injury and leads to autodigestion (Isenmann and Beger, 1999; Bhatia et al., 2000). In this study, we investigated the association between the *ADH1C* *1/*2 polymorphism and pancreatitis risk. Several studies have focused on the relationship between the *ADH1C* *1/*2 polymorphism and pancreatitis risk, but the results have been inconsistent (Day et al., 1991; Matsumoto et al., 1996; Chao et al., 1997, 2000; Frenzer et al., 2002; Verlaan et al., 2004; Sun et al., 2005; Cichoz-Lach et al., 2006; Homann et al., 2006). Therefore, we performed a meta-analysis including a relatively large sample size of 9 eligible studies (753 cases and 1093 controls) to determine the relationship between the *ADH1C* *1/*2 polymorphism and pancreatitis risk.

MATERIAL AND METHODS

Literature search, selection, and data collection

In this study, we searched for papers published before Jun 3, 2014 using the keywords "alcohol dehydrogenase 1C (class I), gamma polypeptide" / "ADH1C" / "ADH3", "pancreatitis", and "polymorphism" / "polymorphisms" / "variation" / "variations" / "variant" / "variants" / "genotype" / "genotypes" in PubMed, Web of Science, and OVID. The studies were further selected for the meta-analysis based on the following selection criteria: a) full-text study written in English; b) study providing complete case and control data regarding the relationship between the *ADH1C* *1/*2 polymorphism and pancreatitis risk; c) studies sharing the same sample of cases and controls were compared and the most complete study was included in our meta-analysis; d) studies with control group genotypes in Hardy-Weinberg equilibrium. Hardy-Weinberg equilibrium was tested using the χ^2 test, and when χ^2 test reported a P value of more than 0.05, the control group genotypes were consistent with Hardy-Weinberg equilibrium.

In this study, two investigators independently collected data from each eligible paper, including first author, year of publication, country of origin, ethnicity, pancreatitis type, and

numbers of cases and controls. By comparing the results of the two investigators, final data was collected.

Meta-analysis

According to the data collected from each eligible paper, we performed both the overall meta-analysis and subgroup meta-analysis based on ethnicity and pancreatitis type to evaluate the relationship between the *ADH1C* *1/*2 polymorphism and pancreatitis risk. In the overall as well as subgroup meta-analysis, pooled odds ratios (ORs) and 95% confidence intervals (CIs) for dominant, recessive, and codominant genetic models were calculated using the fixed effects model or random effects model. The model chosen was based on the heterogeneity test. For the heterogeneity test, we performed a χ^2-based *Q*-test in this study (Lau et al., 1997). When the *Q*-test reported a P value of more than 0.10, the fixed effect model was used to calculate the pooled ORs (Mantel and Haenszel, 1959); otherwise, the random effect model was used (DerSimonian and Laird, 1986).

Publication bias was also tested using the Begg's funnel plot and the Egger test (Egger et al., 1997). If the funnel plot was asymmetric and the Egger test showed a P value of less than 0.05, publication bias was considered to exist.

In this study, we used the Stata version 12.0 software (StataCorp, College Station, TX, USA) for data analysis.

RESULTS

Studies and data included in this meta-analysis

Through searching and selection, a total of 9 eligible studies (Day et al., 1991; Matsumoto et al., 1996; Chao et al., 1997, 2000; Frenzer et al., 2002; Verlaan et al., 2004; Sun et al., 2005; Cichoz-Lach et al., 2006; Homann et al., 2006) were collected for the meta-analysis (Figure 1).

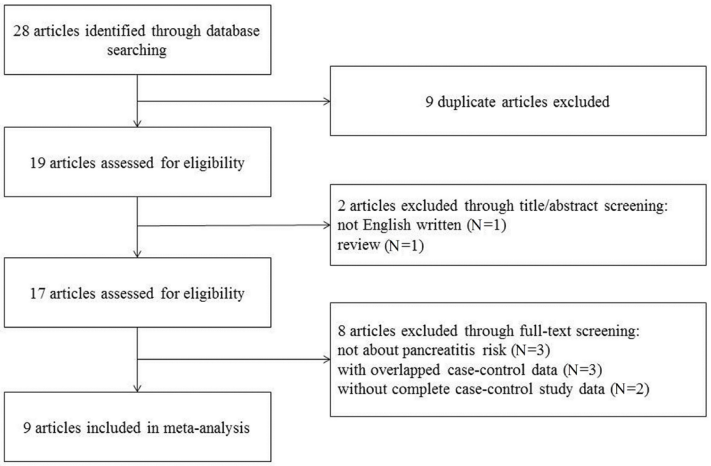

Figure 1. Flow chart of study selection.

All 9 studies collected were case-control studies including various ethnicities (3 studies of Asians and 6 studies of Caucasians), and pancreatitis types (2 studies of acute pancreatitis, and 7 studies of chronic pancreatitis). The control groups of the 9 eligible studies were all in Hardy-Weinberg equilibrium (P > 0.05). The information from these 9 studies and the numbers of cases and controls with different genotypes reported in each study are presented in Table 1. The 9 eligible studies included a total of 753 cases and 1093 controls about the relationship between the *ADH1C* *1/*2 polymorphism and pancreatitis risk.

Table 1. Studies and data included in this meta-analysis.

First author	Published year	Country of origin	Ethnicity	Pancreatitis type	Sample size (case/control)	Cases 11/12/22	Controls 11/12/22	P_{HWE} [a]
Day	1991	UK	Caucasian	Chronic	13/79	5/7/1	25/37/17	0.634
Matsumoto	1996	Japan	Asian	Chronic	52/244	40/12/0	187/54/3	0.683
Chao	1997	China (Taiwan)	Asian	Acute	80/100	63/16/1	88/11/1	0.342
Chao	2000	China (Taiwan)	Asian	Acute	136/105	106/29/1	91/13/1	0.495
Frenzer	2002	Australia	Caucasian	Chronic	71/57	16/49/6	16/28/13	0.911
Verlaan	2004	Netherlands	Caucasian	Chronic	142/128	49/67/26	36/68/24	0.416
Sun	2005	Germany	Caucasian	Chronic	98/163	17/61/20	33/89/41	0.227
Cichoz-Lach	2006	Poland	Caucasian	Chronic	44/43	17/26/1	17/17/9	0.235
Homann	2006	Germany	Caucasian	Chronic	117/174	19/72/26	38/92/44	0.439

[a]P value for Hardy-Weinberg equilibrium test in each control group.

Overall and subgroup meta-analysis results

In this study, we performed both overall meta-analysis and subgroup meta-analysis based on ethnicity and pancreatitis type. The detailed results of our meta-analysis are shown in Table 2. The results of the overall meta-analysis indicated an association between the *ADH1C* *1/*2 polymorphism and pancreatitis risk (OR = 1.53, 95%CI = 1.12-2.10 for 12 *vs* 22; OR = 1.44, 95%CI = 1.07-1.95 for 11 + 12 *vs* 22, Table 2, Figures 2 and 3). The subgroup meta-analysis based on pancreatitis type further indicated that the *ADH1C* *1/*2 polymorphism was significantly associated with chronic pancreatitis risk (OR = 1.52, 95%CI = 1.11-2.10 for 12 *vs* 22; OR = 1.45, 95%CI = 1.07-1.98 for 11 + 12 *vs* 22, see Table 2), particularly with chronic alcoholic pancreatitis (OR = 1.64, 95%CI = 1.17-2.29 for 12 *vs* 22; OR = 1.53, 95%CI = 1.11-2.11 for 11 + 12 *vs* 22, Table 2, Figures 4 and 5), while no significant association was detected in the acute pancreatitis subgroup except for 11 *vs* 12 + 22 (OR = 0.53, 95%CI = 0.31-0.89, Table 2). In stratified meta-analysis based on ethnicity, a significant association between the *ADH1C* *1/*2 polymorphism and pancreatitis risk was observed in Caucasians for 11 + 12 *vs* 22 (OR = 1.45, 95%CI = 1.07-1.98, Table 2), while no clear association was observed in Asians (Table 2). In summary, according to the results of our meta-analysis, the *ADH1C* *1/*2 polymorphism is likely associated with pancreatitis risk, particularly chronic alcoholic pancreatitis risk, with the *1 allele functioning as a risk factor.

Publication bias test results

The results of Begg's funnel plot (Figure 6) and the Egger test revealed no publication bias for 11 *vs* 22 (P = 0.171), for 12 *vs* 22 (P = 0.116), for 11 + 12 *vs* 22 (P = 0.171), and for 11 *vs* 12 + 22 (P = 0.629) in the overall meta-analysis.

Table 2. Detailed results of the meta-analysis.

Meta-analysis groups	No. of studies	Sample size (case/control)	11 *vs* 22		12 *vs* 22		11+12 *vs* 22		11 *vs* 12+22	
			OR (95%CI)	P[a]	OR (95%CI)	P[a]	OR (95%CI)	P[a]	OR (95%CI)	P[a]
Overall analysis	9	753/1093	1.30 (0.90-1.88)	0.619	1.53 (1.12-2.10)[c]	0.262	1.44 (1.07-1.95)[c]	0.393	0.85 (0.67-1.07)	0.469
Ethnicity										
Asian	3	268/449	1.08 (0.22-5.42)	0.935	1.73 (0.32-9.42)	0.977	1.17 (0.23-5.87)	0.948	0.66 (0.44-1.00)	0.343
Caucasian	6	485/644	1.32 (0.90-1.92)	0.298	1.69 (1.00-2.86)[b]	0.077	1.45 (1.07-1.98)[c]	0.142	0.95 (0.72-1.26)	0.606
Pancreatitis subtypes										
Chronic	7	537/888	1.32 (0.91-1.92)	0.412	1.52 (1.11-2.10)[c]	0.126	1.45 (1.07-1.98)[c]	0.218	0.96 (0.74-1.24)	0.725
Chronic alcoholic	7	477/853	1.34 (0.90-1.99)	0.411	1.64 (1.17-2.29)[c]	0.211	1.53 (1.11-2.11)[c]	0.274	0.91 (0.69-1.20)	0.858
Acute	2	216/205	0.91 (0.13-6.57)	0.809	1.79 (0.24-13.58)	0.836	1.02 (0.14-7.30)	0.809	0.53 (0.31-0.89)[c]	0.893

[a]P value for heterogeneity test. If P > 0.1, ORs were calculated using fixed effect model; otherwise, the random effect model was used. [b]ORs calculated using random effect model. [c]Statistically significant results.

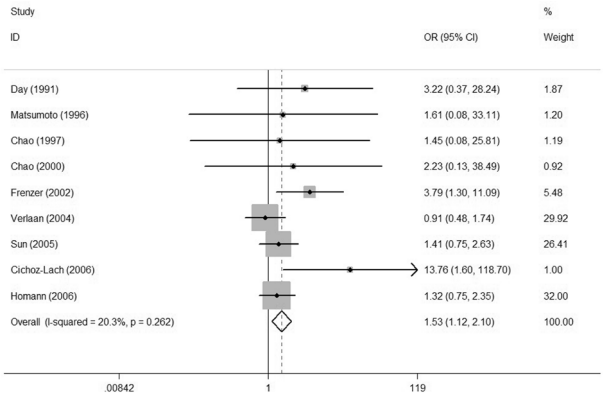

Figure 2. Forest plot for 12 *vs* 22 of the overall meta-analysis using fixed-effect model. OR = odds ratio; CI = confidence interval.

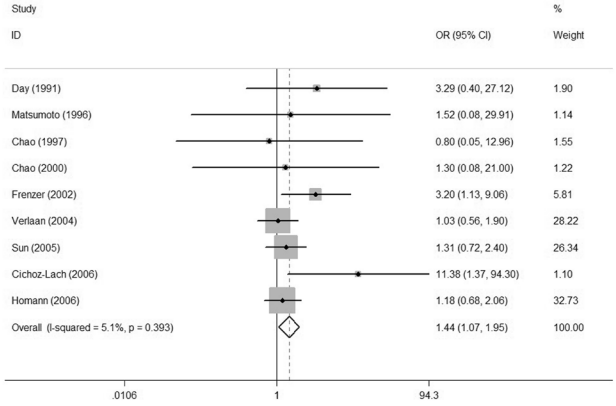

Figure 3. Forest plot for 11 + 12 *vs* 22 of the overall meta-analysis using fixed-effect model. OR = odds ratio; CI = confidence interval.

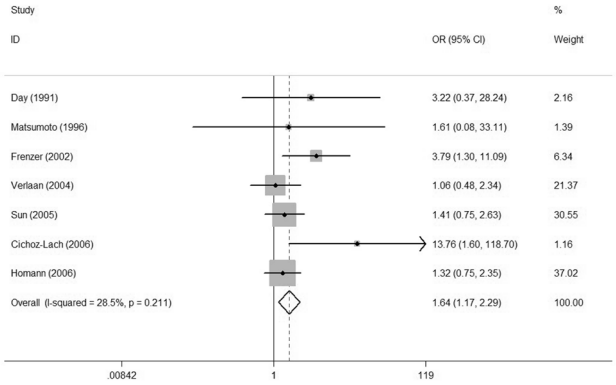

Figure 4. Forest plot for 12 *vs* 22 of the chronic alcoholic pancreatitis subgroup using fixed-effect model. OR = odds ratio; CI = confidence interval.

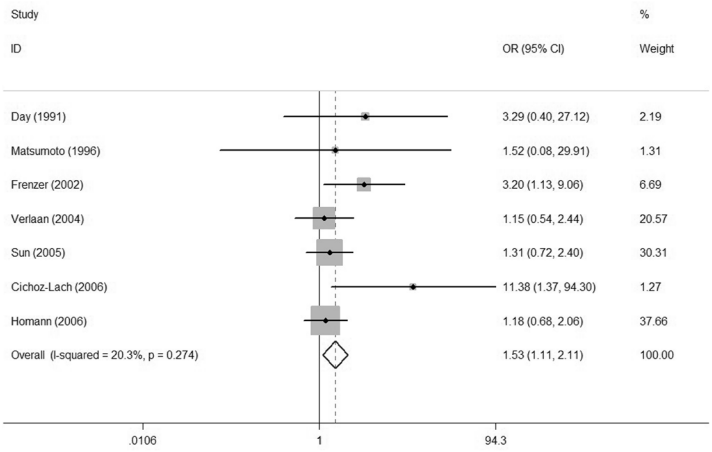

Figure 5. Forest plot for 11 + 12 *vs* 22 of the chronic alcoholic pancreatitis subgroup using fixed-effect model. OR = odds ratio; CI = confidence interval.

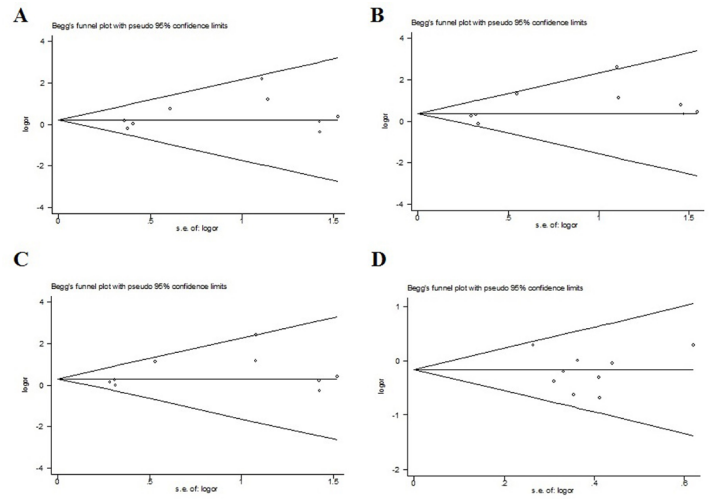

Figure 6. Begg's funnel plots for the *ADH1C* *1/*2 polymorphism and pancreatitis risk (A: 11 *vs* 22, B: 12 *vs* 22, C: 11+12 *vs* 22, D: 11 *vs* 12+22). logor = logarithm of odds ratios; s.e. = standard error.

DISCUSSION

The results of our overall meta-analysis and subgroup meta-analysis based on pancreatitis type suggest that the *ADH1C* *1/*2 polymorphism is likely associated with pancreatitis risk, particularly chronic alcoholic pancreatitis risk, with the *1 allele functioning as a risk factor. This conclusion is supported by the reported potential biological function of the *ADH1C* *1/*2 polymorphism, which was found to influence enzyme activity (Bosron and Li, 1987). Because the enzyme encoded by *ADH1C* *1/*1 showed higher activity and produced larger amounts of acetaldehyde, toxicity can occur and stable DNA adducts can be generated (Bosron

and Li, 1987; Helander and Lindahl-Kiessling, 1991). Thus, the *ADH1C* *1/*2 polymorphism may influence chronic alcoholic pancreatitis risk by affecting the enzyme activity of ADH1C. In addition, there may be combined effects of this polymorphism and other genetic and environmental factors. Further studies examining the detailed molecular mechanism are required.

In the acute pancreatitis subgroup, no significant association was detected, except for 11 *vs* 12 + 22 (OR = 0.53, 95%CI = 0.31-0.89); however, this result may not be reliable because of the limited amount of data available for this subgroup. Future studies including larger sample sizes are necessary to determine the role of the *ADH1C* *1/*2 polymorphism in acute pancreatitis.

In stratified meta-analysis based on ethnicity, a significant association between the *ADH1C* *1/*2 polymorphism and pancreatitis risk was detected in Caucasians, while no clear association was observed in Asians. However, insufficient data was available for each subgroup (Asian subgroup in particular), and the exact roles of the *ADH1C* *1/*2 polymorphism in different ethnicities require further analysis.

In addition, the results of our meta-analysis should be considered with caution because there were several limitations to this study. One limitation was the insufficient sample size used in our meta-analysis, particularly in the subgroup analysis based on ethnicity and pancreatitis type. A second limitation was the lack of case-control data adjustment according to detailed individual information such as age, gender, and lifestyle in our meta-analysis. The third limitation was that the exact molecular basis of the association between the *ADH1C* *1/*2 polymorphism and pancreatitis risk remains unclear and requires further investigation. Henc3e, in order to overcome these limitations, further analysis including a larger sample size and adjusted individual data is required, and further experimental studies on the molecular mechanism should be performed.

In conclusion, based on our meta-analysis that included a total of 9 eligible studies (753 cases and 1093 controls), the *ADH1C* *1/*2 polymorphism is likely associated with pancreatitis risk, particularly chronic alcoholic pancreatitis risk, and the *1 allele functions as a risk factor. Although there were some limitations to this study, our meta-analysis provides valuable information for studying the relationship between the *ADH1C* *1/*2 polymorphism and pancreatitis risk.

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