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Original Article

Aldehyde dehydrogenase 2 (ALDH2) Glu504Lys polymorphism is associated with hypertension risk in Asians: a meta-analysis

Kui Jia, Honglei Wang, Pingshuan Dong

Department of Cardiology, First Affiliated Hospital of Henan University of Science and Technology, Luoyang 471003, Henan Province, China

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Abstract: Background: The association of the aldehyde dehydrogenases-2 (ALDH2) Glu504Lys polymorphism and hypertension in Asians has been investigated. This meta-analysis aims to comprehensively assess the influence of this polymorphism on the hypertension risk. Method: An electronic literature search was conducted using the following database: PubMed, Embase and China National Knowledge Infrastructure (CNKI) till to Mar 25th, 2015. The strength of the association between statins and fractures risk was calculated with the OR and respective 95% CIs. The random effect model was used. Results: Nine studies evaluating the relationship between ALDH2 Glu504Lys polymorphism and hypertension risk in Asians were selected in this meta-analysis. A total of 12161 subjects were included. The data showed that ALDH2 Glu504Lys polymorphism could increase the risk of hypertension of Asians (OR = 1.31; 95% CI, 1.18-1.47; $P < 0.00001$). In the subgroup analysis of race, both Japanese and Chinese with ALDH2 Glu504Lys polymorphism showed increased hypertension risk (OR = 1.23; 95% CI, 1.09-1.38; $P = 0.0006$ and OR = 1.46; 95% CI, 1.21-1.77; $P = 0.0001$), respectively. In the subgroup analysis of gender, males with this polymorphism showed increased hypertension risk (OR = 1.59; 95% CI, 1.40-1.80; $P < 0.00001$). However, females did not showed this result (OR = 0.94; 95% CI, 0.69-1.30; $P = 0.71$). When considered alcohol consumption, we found that drinkers and non-drinkers all had increased hypertension risk, if they carried this polymorphism. Conclusion: This meta-analysis suggested that ALDH2 Glu504Lys polymorphism was a risk factor of hypertension in Asians.

Keywords: ALDH2, hypertension, Asians, association

Introduction

Hypertension is one of the most important preventable causes of death and one of the most common conditions treated in primary healthcare. In addition, hypertension represents an important public health challenge because of its high prevalence and the concomitant increase in the risk of cardiovascular, cerebrovascular and renal diseases [1]. A number of constitutional and environmental factors have been identified that influence blood pressure. These include age, body size, physical activity, salt intake, and alcohol consumption. People who have family history would more likely suffer from hypertension. So it is inferred that genetic factors are also important [2].

Aldehyde dehydrogenase-2 (ALDH2) is expressed in the liver as well as gastrointestinal tract. It belongs to a low-Km mitochondrial ALDH and is the second enzyme to eliminate most of the acetaldehyde generated during alcohol metabolism in vivo [3]. Human ALDH2 gene is located on chromosome 12q24 and the polymorphisms of ALDH2 gene would affect the blood acetaldehyde concentrations after alcohol consumption [4]. The Glu504Lys polymorphism (also named Glu487Lys, or rs671 has been the most commonly studied [5].

One effect of the ALDH2 504Lys mutation is the "Asian flush": the red face, nausea, and rapid heartbeat that many people with East Asian ancestry experience when they drink alcohol. The alcohol flushing response (Asian Glow) is a biomarker for ALDH2 504Lys allele [6]. Some studies suggested that ALDH2 Glu504Lys polymorphism was associated with the risk of hypertension. However, other studies have shown that ALDH2 Glu504Lys polymorphism was unlikely to play a crucial role in hyperten-

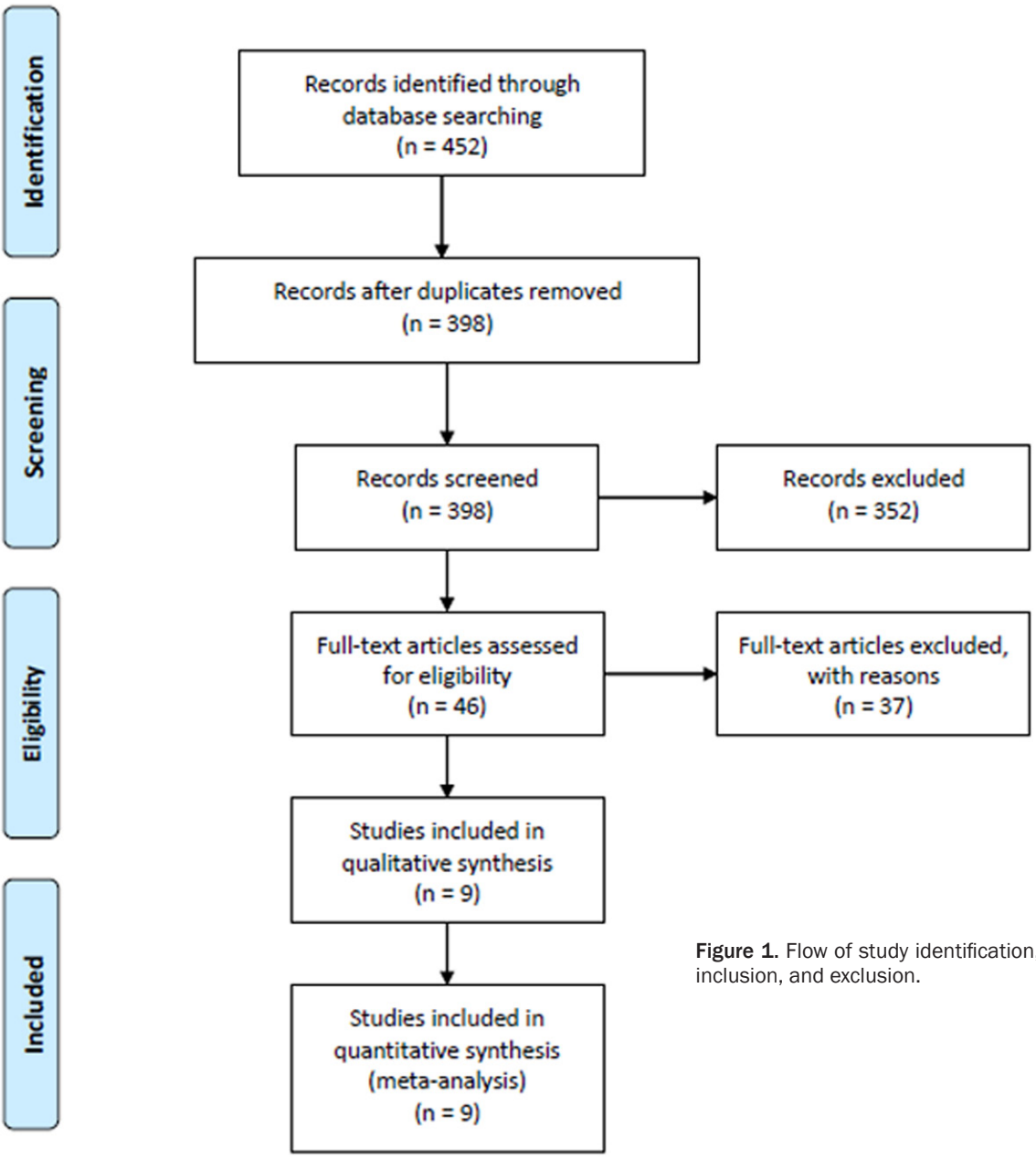

Figure 1. Flow of study identification, inclusion, and exclusion.

sion development [7-16]. The reason for this discrepancy may be due to different sample size and race. Therefore, in order to derive a more comprehensive estimation of the association between ALDH2 Glu504Lys polymorphism and hypertension risk, we conducted a meta-analysis to investigate this relationship in Asians.

Methods

Publication search

An electronic literature search was conducted using the following database: PubMed, Embase and China National Knowledge Infrastructure (CNKI) till to Mar 25th, 2015. The Medical Subject Heading (MeSH) terms "Aldehyde dehydrogenase-2", "ALDH2", "mutation", "hypertension" and the individual corresponding free terms were employed as the searching words. In addition, the citations in the retrieved articles were reviewed to search for relevant studies.

Criteria for article screening

The studies included must meet the following criteria: 1) the paper assessed the association

Table 1. Characteristics of the included studies

First author/Year	Study design	Country	Gender	Alcohol consumption	No. of participants	GG genotype in cases (%)	AG+AA genotype in cases (%)	Quality score
Takagi 2001	Cohort	Japan	Mixed	Mixed	4057	39.7	36.2	8
Amamoto 2002	Cohort	Japan	Mixed	Not available	2395	40.3	37.2	7
Saito 2003	Cohort	Japan	Male	Drinkers	335	43.5	29.7	5
Hui 2007	Case-control	China	Mixed	Not available	532	55.0	41.3	6
Hasi 2011	Case-control	China	Mixed	Not available	161	60.1	34.8	6
Feng 2012	Case-control	China	Mixed	Not available	111	75.7	65.9	4
Nakagawa 2012	Cohort	Japan	Mixed	Mixed	444	30.2	24.6	7
Wang 2013	Case-control	China	Mixed	Not available	2119	54.4	48.3	7
Yokoyama 2013	Cohort	Japan	Male	Drinkers	1902	27.0	20.9	7

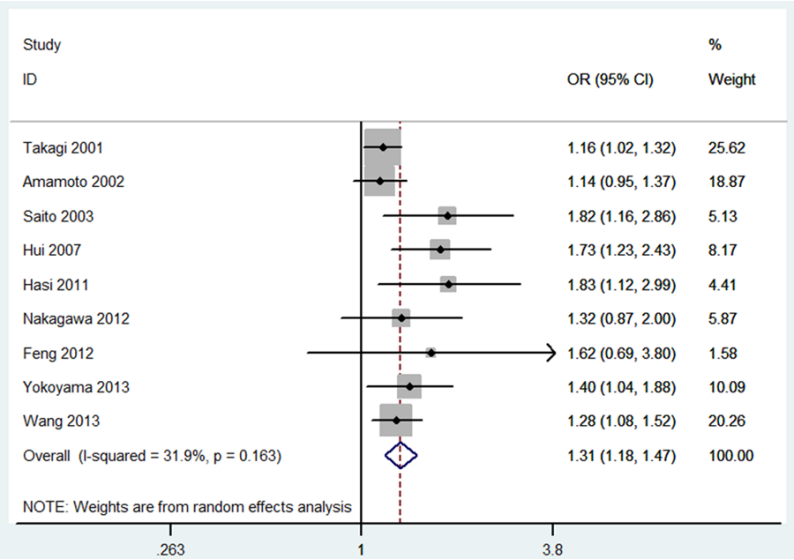

Figure 2. Effect of ALDH2 Glu504Lys polymorphism on risk of hypertension.

between ALDH2 Glu504Lys polymorphism and hypertension risk; 2) the paper should be case-control or cohort study; 3) the diagnosis of hypertension follows the guidelines, and the control should be matched non-hypertension cases; 4) odds ratio (OR) with the 95% confidence interval (CI) was reported or could be figured out through the available data; and 5) the paper should be aimed at Asian population.

Data extraction

Two investigators independently assessed the extracted data from the included study, and reached a final common results. Any disagreement was resolved by discussing with the third expert. The following information was extracted from all obtained publications: first author's name, publication year, country, study design, gender, alcohol consumption, the included subject number and the percent of mutation.

Quality assessment

The included studies were assessed independently by the two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS employs a star rating system to assess quality from 3 broad perspectives of the study: (1) selection of the study groups, (2) comparability of the groups, and (3) identification of the exposure (for case-control studies) or outcome of interest (for cohort studies). Scores ranged from 0 to 9 stars.

Statistical analysis

The strength of the association between ALDH2 Glu504Lys polymorphism and hypertension risk was calculated with the OR and respective 95% CI in recessive genetic model. The significance of the pooled OR was determined by the Z test, and *P*-values of less than 0.05 were considered significant. Statistical heterogeneity among studies was assessed with the I^2 statistics. This value ranges from 0% (complete consistency) to 100% (complete inconsistency). The random-effects model was chosen to calculate the pooled OR. The subgroup analysis was carried out by race, gender, alcohol consumption, and sample size ($n > 1000$ and $n < 1000$). In the sensitivity analysis, we did the meta-analysis when the each study was excluded. The presence of publication bias was assessed by a visual inspection of a funnel plot. All statistical tests were used by the STATA 11.0 software (Stata Corporation, College Station, TX).

Table 2. Meta-analysis of ALDH2 Glu504Lys polymorphism and risk of hypertension

	No. of study	OR (95% CI)	Model	*P* Value	I^2 (%)
Overall	9	1.31 (1.18-1.47)	Random	< 0.00001	32
Ethnicity					
Japanese	5	1.23 (1.09-1.38)	Random	0.0006	21
Chinese	4	1.46 (1.21-1.77)	Random	0.0001	21
Gender					
Male	7	1.59 (1.40-1.80)	Random	< 0.00001	0
Female	5	0.94 (0.69-1.30)	Random	0.71	61
Alcohol					
Drinkers	4	1.50 (1.22-1.88)	Random	< 0.0001	40
Non-drinkers	2	1.22 (1.01-1.47)	Random	0.03	0
Sample size					
Large	4	1.20 (1.10-1.31)	Random	< 0.0001	0
Small	5	1.65 (1.35-2.02)	Random	< 0.00001	0

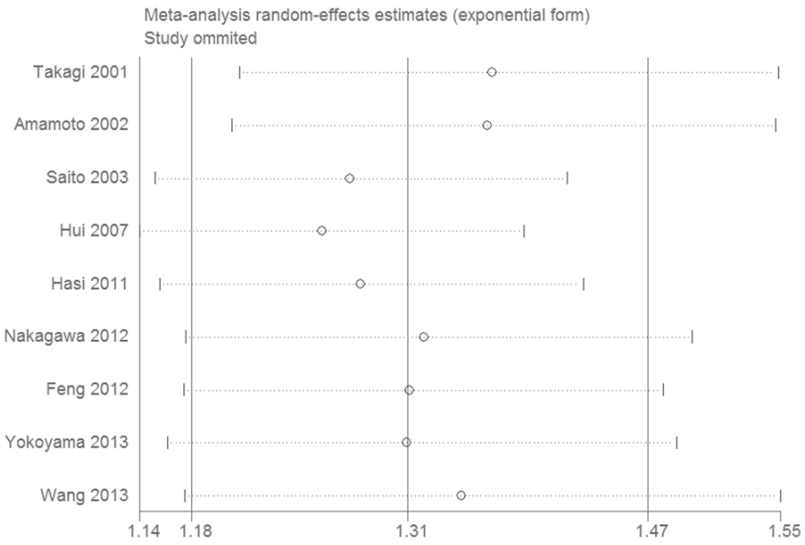

Figure 3. Galbraith plot of ALDH2 Glu504Lys polymorphism on risk of hypertension.

Results

Literature search

According to the searching strategy, 452 papers were found. We reviewed the titles, abstracts and the full texts of all retrieved articles through defined criteria. Finally, nine studies evaluating the relationship between ALDH2 Glu504Lys polymorphism and hypertension risk in Asians were selected in our meta-analysis. **Figure 1** showed the flow diagram. Characteristics of the included studies were shown in **Table 1**. Of the nine included studies, four were from China and five were from Japan. A total of 12161 subjects were included.

Meta-analysis

As shown in **Figure 2**, we observed a statistically significant association between ALDH2 Glu504Lys polymorphism and hypertension risk in Asians. The data showed that ALDH2 Glu504Lys polymorphism could increase the risk of hypertension of Asians (OR = 1.31; 95% CI, 1.18-1.47; *P* < 0.00001). In the subgroup analysis of race, both Japanese and Chinese with ALDH2 Glu504Lys polymorphism showed increased hypertension risk (OR = 1.23; 95% CI, 1.09-1.38; *P* = 0.0006 and OR = 1.46; 95% CI, 1.21-1.77; *P* = 0.0001), respectively. In the subgroup analysis of gender, males with this polymorphism showed increased hypertension risk (OR = 1.59; 95% CI, 1.40-1.80; *P* < 0.00001). However, females did not showed this result (OR = 0.94; 95% CI, 0.69-1.30; *P* = 0.71). When considered alcohol consumption, we found that drinkers and non-drinkers all had increased hypertension risk, if they carried this polymorphism (**Table 2**). Finally, both large and small sample size did not change the result (OR = 1.20; 95% CI, 1.10-1.31; *P* < 0.0001 and OR = 1.65; 95% CI, 1.35-2.02; *P* < 0.00001). In the sensitivity analysis (**Figure 3**), the results were not altered. Publication bias was not found in **Figure 4**.

Discussion

This meta-analysis suggested that ALDH2 Glu504Lys polymorphism was a risk factor of hypertension in Asians. In the general population, the variant 504Lys allele is prevalent in Northeast Asian individuals (approximately 45% of Japanese, 31% of Chinese) [17]. After stratified by race, significantly increased hypertension risk was found in Japanese and

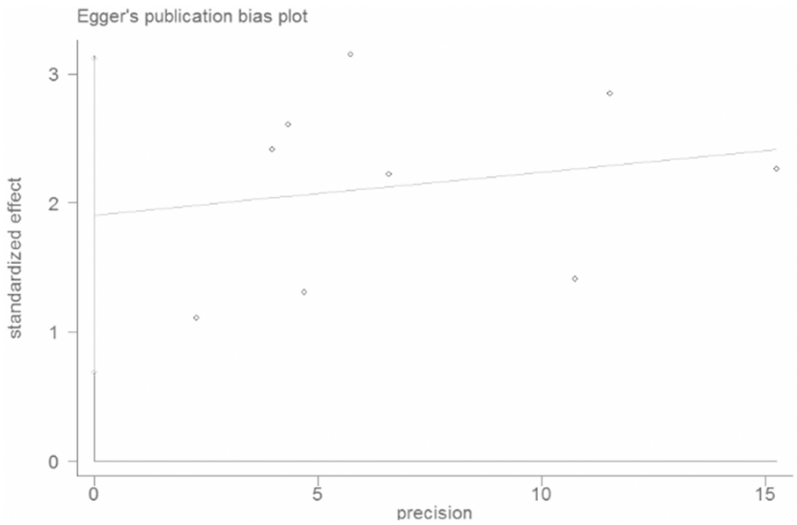

Figure 4. Funnel plot to assess publication bias.

Chinese. Shin et al. showed a significant association between a common ALDH2 polymorphism and stroke risk in Korean men, but not in Korean women [18]. Thus, we also did a subgroup analysis by gender. We also found that ALDH2 Glu504Lys polymorphism was significantly associated with hypertension risk in men, but not in women. Thus, these men may need to make more concerted efforts to control modifiable risk factors of hypertension. In addition, we performed subgroup analysis according to drinkers and non-drinkers to clarify the alcohol-genotype interaction. We observed a significant association between drinkers with ALDH2 Glu504Lys polymorphism and hypertension risk. Finally, the sample size did not altered the overall result. Furthermore, the heterogeneity was decreased in this subgroup analysis, suggesting that sample size was the source of heterogeneity.

The advantages of this study were, first, our meta-analysis included all the clinical studies with this topic. Thus, the statistical power was enough. Second, the results of our meta-analysis can help clinicians to pay more attention to the population with ALDH2 Glu504Lys polymorphism. What is more, the heterogeneity was low in our meta-analysis. However, some potential limitations were existed in this meta-analysis. First, the observed association was substantially based on observational studies. Possible confounding factors might influence the results. Second, the inconsistency of the base line characteristics between the studies, such as age and gender, might increase the selection bias. Finally, the publication biases cannot be completely excluded due to that all of the included studies were mainly relying on observation.

ALDH2 Glu504Lys polymorphism also may contribute to the risk of other diseases. Zhao et al. found that ALDH2 Glu504Lys polymorphism may be associated with the risk of colorectal cancer [19]. Wang et al. found that ALDH2 Glu504Lys polymorphism may increase the risk of both CHD and MI among Asian populations [20]. Fang et al. indicated that ALDH2 genotype increased the risk of esophageal cancer [21].

In conclusion, this meta-analysis provided evidence that ALDH2 Glu504Lys polymorphism was significantly associated with increased risk of hypertension. Gene-alcohol interaction confirmed the contribution of ALDH2 Glu504Lys polymorphism to hypertension susceptibility.

Disclosure of conflict of interest

None.

Address correspondence to: Pingshuan Dong, Department of Cardiology, First Affiliated Hospital of Henan University of Science and Technology, Luoyang 471003, Henan Province, China. E-mail: dongps23882@163.com

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