Association Between ALDH-2 rs671 and Essential Hypertension Risk or Blood Pressure Levels: A Systematic Review and Meta-Analysis

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Background: The association between Aldehyde dehydrogenase II (ALDH-2) rs671 polymorphism and essential hypertension (EH) risk or blood pressure (BP) levels remains unclear.

Objective: To systematically review the influence of the aldehyde dehydrogenase II rs671 polymorphism on essential hypertension risk and blood pressure levels.

Methods: The PubMed, EMBase, Web of Science, Cochrane Library, CNKI and CBM databases were electronically searched to identify case-control or cohort studies published prior to July 2019 that examined the association between the rs671 polymorphism and the risk of essential hypertension or blood pressure levels. A meta-analysis was conducted with Stata 15.1 software.

Results: Twenty-two articles were included. Among these articles, 20 incorporated 30 individual studies evaluating the association between the rs671 polymorphism and EH (11,051 hypertensive patients and 15,926 normotensive controls), and 8 incorporated 12 individual studies evaluating the association between the rs671 polymorphism and BP (20,512 subjects). The results of the meta-analysis showed that the mutation of the rs671 polymorphism was associated with a significantly decreased risk of EH in all models: allelic model (OR = 0.80, 95% CI: 0.73–0.87), homozygous model (OR = 0.71, 95% CI: 0.63–0.80), heterozygous model (OR = 0.79, 95% CI: 0.72–0.87), dominant model (OR = 0.79, 95% CI: 0.71–0.87), and recessive model (OR = 0.76, 95% CI: 0.68–0.85). In the stratified analyses, significant associations were found for males, drinkers and population-based studies. Simultaneously, the A carriers had lower SBP (WMD = −1.78, 95% CI: −3.02 to −0.53) and DBP (WMD = −1.09, 95% CI: −1.58 to −0.61) levels than individuals with the GG homozygote.
Conclusion: The collective findings of this meta-analysis suggested that the ALDH-2 rs671 polymorphism represented an important genetic marker in the development of hypertension. Considering the overall quality of evidence and the relatively small pooled sample size, more well-conducted high-quality studies are required to verify the above conclusion.

Systematic Review Registration Number: PROSPERO (CRD42019129746).

Keywords: ALDH-2, rs671, essential hypertension, blood pressure, meta-analysis, polymorphism
## TABLE 1 | The baseline characteristics of all included articles (for EH).

| Study            | Ethnicity | Genotyping method | Source design | Study size | Alcohol consumption | Gender Case | Control | HWE | NOS |
|------------------|-----------|-------------------|---------------|------------|---------------------|-------------|---------|-----|-----|
| Amamoto et al. (2002) | Japan      | PCR-RFLP          | P Cohort study | 2035      | Overall             | Male 161 134 17 | Male 174 217 46 | 584 564 99 | 0.2020 7 |
| (Du, 2018) | China     | PCR-RFLP          | H Case-control | 337       | Overall             | Male 93 62 6   | Male 93 62 6   | 93 62 6   | 0.0048 8 |
| Feng et al. (2012) | China      | PCR-RFLP          | H Case-control | 111       | Overall             | Male 45 22 0   | Male 13 9 2   | 13 9 2   | 0.9517 7 |
| Hasi et al. (2011) | China      | TaqMan PCR         | P Case-control | 161       | Overall             | Male 83 8 0   | Male 55 15 0   | 55 15 0   | 0.3154 6 |
| Hui et al. (2007) | Japan      | TaqMan PCR         | P Case-control | 532       | Overall             | Male 118 45 7 | Male 90 78 14 | 90 78 14 | 0.6674 6 |
| Iwai et al. (2004) | Japan      | TaqMan PCR         | P Cohort study | 1852      | Overall             | Male 413 300 51 | Male 550 429 109 | 550 429 109 | 0.0630 8 |
| Jing et al. (2015) | China      | TaqMan PCR         | P Case-control | 832       | Overall             | Male 338 126 10 | Male 220 122 16 | 220 122 16 | 0.8605 7 |
| Li et al. (2017)  | China      | TaqMan PCR         | P Case-control | 3038      | Overall             | Male 1136 691 94 | Male 653 390 72 | 653 390 72 | 0.1848 8 |
| Lv et al. (2013)  | China      | PCR-RFLP          | H Case-control | 465       | Overall             | Male 73 30 2   | Male 209 139 12 | 209 139 12 | 0.0522 8 |
| Ma et al. (2017)  | China      | PCR                | H Case-control | 4018      | Overall             | Male 871 295 15 | Male 1888 857 92 | 1888 857 92 | 0.6613 6 |
| Nakagawa et al. (2013) | Japan      | PCR-RFLP          | H Case-control | 444       | Overall             | Male 74 49 17 | Male 171 150 7 | 171 150 7 | N 7 |
| Ota et al. (2016) | Japan      | PCR-RFLP          | P Case-control | 1225      | Overall             | Male 137 62 6  | Male 630 396 97 | 630 396 97 | N 7 |
| Saito et al. (2003) | Japan      | PCR-RFLP          | P Cohort study | 335       | Overall             | Male 77 44 3   | Male 100 93 18 | 100 93 18 | 0.5776 8 |
| Takagi et al. (2001) | Japan      | TaqMan PCR         | P Cohort study | 4057      | Overall             | Male 809 598 133 | Male 1227 1065 225 | 1227 1065 225 | 0.7782 8 |
| Wang et al. (2013) | China      | PCR-LDR            | P Case-control | 2119      | Overall             | Male 668 373 57 | Male 560 396 65 | 560 396 65 | 0.6531 7 |
| Wu et al. (2013)  | China      | PCR-RFLP          | H Case-control | 737       | Overall             | Male 254 59 8   | Male 353 58 5   | 353 58 5   | 0.1468 6 |
| Wu et al. (2017)  | China      | PCR-LDR            | P Case-control | 2326      | Overall             | Male 586 440 65 | Male 606 531 98 | 606 531 98 | 0.2181 8 |
| Yokoyama et al. (2013) | Japan      | PCR-RFLP          | P Case-control | 1902      | Overall             | Male 433 62 0   | Male 1172 235 0 | 1172 235 0 | 0.0006 7 |
| Zhang et al. (2016) | China      | PCR                | P Case-control | 212       | Overall             | Male 95 17 0   | Male 86 13 1   | 86 13 1   | 0.5283 7 |
| Zhang et al. (2018) | China      | PCR-RFLP          | H Case-control | 239       | Overall             | Male 80 39 18  | Male 71 26 5   | 71 26 5   | 0.2141 7 |
HIGHLIGHTS

- The rs671 polymorphism was associated with essential hypertension risk.

- The rs671 polymorphism represents an important genetic marker of hypertension.

INTRODUCTION

Hypertension is a disease whose pathophysiological mechanism involves hundreds of genes (Zheng et al., 2017). Several studies have investigated the association between the ALDH-2 rs671 polymorphism and essential hypertension, but evidence is conflicting (Du, 2018). Furthermore, we not only estimate the association between the ALDH-2 rs671 polymorphism and essential hypertension risk, but also estimate the association between the ALDH-2 rs671 polymorphism and hypertension. In Japan, hypertension alone accounted for 6.61% of the 3.1869 trillion medical expenses spent on health care in Japan (Ota et al., 2003). In Japan, mean blood pressure has steadily declined over the last 50 years, but hypertension remains one of the biggest risk factors for cardiovascular diseases. Elevated blood pressure is the leading cause of death worldwide, and the burden of hypertension is expected to increase globally. In 2012, hypertension affected 270 million individuals in China and had prevalence of 25.2% (Chen et al., 2017). The ALDH-2 rs671 polymorphism is associated with blood pressure levels. Non-drinkers represent more susceptible for hypertension.

Numerous epidemiological studies have elucidated some risk factors, such as sex, age, and drinking alcohol (Zheng et al., 2017). Wu et al. (2013) and Zhang et al. (2017) showed that ALDH-2 deletion is a susceptibility factor for blood pressure. Previously, numerous published studies have confirmed that the ALDH-2 superfamily includes key enzymes in the major pathway of alcohol metabolism. Alcohol dehydrogenase (ADH) is a disease whose pathophysiological mechanism is a disease whose pathophysiological mechanism involves hundreds of genes (Zheng et al., 2017). Several studies have investigated the association between the ALDH-2 rs671 polymorphism and essential hypertension, but evidence is conflicting (Du, 2018). Furthermore, we not only estimate the association between the ALDH-2 rs671 polymorphism and essential hypertension risk, but also estimate the association between the ALDH-2 rs671 polymorphism and hypertension. In Japan, hypertension alone accounted for 6.61% of the 3.1869 trillion medical expenses spent on health care in Japan (Ota et al., 2003). In Japan, mean blood pressure has steadily declined over the last 50 years, but hypertension remains one of the biggest risk factors for cardiovascular diseases. Elevated blood pressure is the leading cause of death worldwide, and the burden of hypertension is expected to increase globally. In 2012, hypertension affected 270 million individuals in China and had prevalence of 25.2% (Chen et al., 2017). The ALDH-2 rs671 polymorphism is associated with blood pressure levels. Non-drinkers represent more susceptible for hypertension.

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|                  | Allelic | Homozygous | Heterozygous | Dominant | Recessive |
|------------------|---------|------------|--------------|----------|-----------|
|                  | N       | Sample (E/C) | OR (95%CI) | I²       | N         | Sample (E/C) | OR (95%CI) | I² |
| Overall          | 18      | 10729/14579 | 0.81 (0.74, 0.89) | 69%      | 18        | 10729/14579 | 0.81 (0.73, 0.89) | 60% |
| Ethnicity        |         |            |              |          |           |            |              |     |
| Chinese          | 12      | 6757/7838 | 0.83 (0.72, 0.96) | 55%      | 12        | 6757/7838 | 0.81 (0.69, 0.98) | 96% |
| Japanese         | 6       | 3972/6741 | 0.70 (0.53, 0.92) | 49%      | 6         | 3972/6741 | 0.81 (0.72, 0.92) | 95% |
| Gender           |         |            |              |          |           |            |              |     |
| Male             | 10      | 3170/4706 | 0.72 (0.66, 0.78) | 19%      | 10        | 3170/4706 | 0.68 (0.62, 0.76) | 76% |
| Female           | 8       | 2538/3729 | 0.93 (0.77, 1.14) | 5%       | 8         | 2538/3729 | 1.02 (0.92, 1.14) | 15% |
| Alcohol consumption |     |         |              |          |           |            |              |     |
| Drinkers         | 4       | 2368/3430 | 0.71 (0.55, 0.92) | 58%      | 4         | 2368/3430 | 0.70 (0.55, 0.96) | 58% |
| No-drinkers      | 2       | 1026/918  | 1.19 (0.59, 2.40) | 85%      | 2         | 1026/918  | 0.98 (0.66, 1.52) | 14% |
| Source           |         |            |              |          |           |            |              |     |
| Population       | 12      | 8761/10640 | 0.83 (0.77, 0.89) | 14%      | 12        | 8761/10640 | 0.82 (0.75, 0.91) | 47% |
| Hospital         | 6       | 1968/3939 | 0.86 (0.59, 1.25) | 75%      | 6         | 1968/3939 | 0.79 (0.56, 1.13) | 7%  |
| Study design     |         |            |              |          |           |            |              |     |
| Case-control     | 13      | 7018/8109 | 0.81 (0.71, 0.93) | 51%      | 13        | 7018/8109 | 0.79 (0.68, 0.92) | 92% |
| Cohort           | 5       | 3711/6470 | 0.84 (0.76, 0.93) | 57%      | 5         | 3711/6470 | 0.85 (0.78, 0.94) | 7%  |
| Size             |         |            |              |          |           |            |              |     |
| ≥1000            | 8       | 8880/10477 | 0.85 (0.79, 0.90) | 44%      | 8         | 8880/10477 | 0.86 (0.79, 0.92) | 35% |
| <1000            | 10      | 1849/2112 | 0.76 (0.58, 1.01) | 59%      | 10        | 1849/2112 | 0.72 (0.54, 0.96) | 67% |
rs671 polymorphism and blood pressure levels. At the same time, we carried out a series of subgroup analysis to make the result more practical. This study was registered with PROSPERO (CRD42019129746) and performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines (Liberati et al., 2009).

**MATERIALS AND METHODS**

**Literature Search**

To be as comprehensive as possible, two authors independently performed a systematic search of six available electronic databases, including PubMed, EMBase, Web of Science (WOS), the Cochrane Library, Chinese Biomedical Literature Database (CBM) and China National Knowledge Infrastructure (CNKI), for studies published prior to July 2019. The keywords included “hypertension,” “essential hypertension,” “EH,” “blood pressure,” “aldehyde dehydrogenase 2,” “ALDH 2,” “ALDH-2,” “rs671,” “genotype,” “alleles,” “polymorphism,” “mutation,” and “variation.” We used both MeSH terms and Title/Abstract search. Languages were not restricted during the searching process. Published articles listed in the references of the keyword index results were also screened carefully to avoid possible omissions.

**Inclusion and Exclusion Criteria**

Studies were included if they fulfilled all of the following criteria: (i) case-control design or cohort study design; (ii) studies that examined the association between the ALDH-2 rs671 polymorphism and the risk of essential hypertension or blood pressure levels; (iii) diagnosis of hypertension defined as either systolic blood pressure $\geq 140$ mmHg or diastolic blood pressure $\geq 90$ mmHg (continuously or more than 3 times in a sitting position, on three different days), or taking antihypertensive medication. The exclusive criteria were as follows: (i) repeated publication of literature or reported duplicate data; (ii) research that is not available in full text; and (iii) reports with incomplete data or no usable data.

**Data Extraction**

A data-extraction table was designed in Excel 2016 by all the researchers. The following information was included: name of the study, year, OR (95% CI), and weight. The forest graphs for the association between the ALDH-2 rs671 polymorphism and essential hypertension risk under the allelic model are shown in Figure 2.

![Figure 2](image-url)
first author, year of publication, ethnicity of study population, study design, source of population, genotyping methodology, sample size, average age, gender, alcohol consumption, SBP and DBP. Two researchers independently extracted the necessary data, and all disagreements were resolved through discussion with a third researcher.

Quality Assessment
Two researchers evaluated the quality of each included study using the Newcastle-Ottawa Scale (NOS) (Stang, 2010) independently. Three major aspects of study quality were scored: (i) selection of the study groups (0–4 scores); (ii) determination of the exposure of interest in the studies (0–3 scores); and (iii) the quality of the adjustment for confounding variables (0–2 scores). Scores ranged from zero to nine stars, and a score of six or above was considered a high-quality study.

Statistical Analysis
The $\chi^2$ test was used to assess whether the genotype distributions in the control group of each study were in Hardy-Weinberg Equilibrium (HWE). Heterogeneity among the same category was evaluated using the $\chi^2$ test and Cochran’s Q statistic, and the $I^2$ statistic was used to quantify the percentage variability of the heterogeneity (Higgins et al., 2003). If $P > 0.1$ and $I^2 \leq 50\%$, the fixed-effect model was selected; otherwise, the random-effect model was adopted (DerSimonian and Laird, 1986). The risk of EH was estimated by the pooled odds ratio (OR) along with the 95% confidence interval (CI), and the levels of BP was signified as the weighted mean difference (WMD) with its 95% CI. The pooled ORs and WMDs were measured using the $Z$-test, and a $P$-value of $< 0.05$ was considered statistically significant. A sensitivity analysis was performed to detect the individual effect of each study on the pooled ORs or WMDs by omitting one individual inter-study at a time. Publication bias was evaluated with Begg’s test, Egger’s test and the trim-and-fill method. All statistical analyses were performed with Stata 15.1 software.

RESULTS

Characteristics of Included Studies
Two researchers independently sifted through the literature, extracted the data and cross-checked them. In case of
disagreement, the decision was made through discussion or arbitration by the third researcher. A total of 353 articles were found after searching the existing literature electronic databases. After removing duplicates, 281 articles were retained. A total of 212 articles with irrelevant data were excluded after a further review of titles and abstracts. The full texts of the remaining articles were screened carefully, and another 47 articles were excluded. Finally, 22 articles were included. The selection process for the qualified publications is presented in Figure 1.

Finally, 22 articles (Takagi et al., 2001; Amamoto et al., 2002; Saito et al., 2003; Iwai et al., 2004; Hui et al., 2007; Hasi et al., 2011; Feng et al., 2012; Lv et al., 2013; Nakagawa et al., 2013; Wang et al., 2013; Wu et al., 2013, 2017; Yokoyama et al., 2013; Zhang et al., 2013, 2016, 2018; Isomura et al., 2015; Jing et al., 2015; Ota et al., 2016; Li et al., 2017; Ma et al., 2017; Du, 2018) met the preset inclusion criteria. Among these articles, 20 (Takagi et al., 2001; Amamoto et al., 2002; Saito et al., 2003; Iwai et al., 2004; Hui et al., 2007; Hasi et al., 2011; Feng et al., 2012; Lv et al., 2013; Nakagawa et al., 2013; Wang et al., 2013; Wu et al., 2013, 2017; Yokoyama et al., 2013; Zhang et al., 2013, 2016, 2018; Isomura et al., 2015; Jing et al., 2015; Ota et al., 2016; Li et al., 2017) assessed the association between the rs671 polymorphism and EH risk in 30 individual studies (11,051 hypertensive patients and 15,926 normotensive controls), and 8 (Takagi et al., 2001; Amamoto et al., 2002; Saito et al., 2003; Wang et al., 2013; Zhang et al., 2013, 2016; Ota et al., 2016; Li et al., 2017) assessed the association between the rs671 polymorphism and BP levels in 12 individual studies (20,512 subjects). The baseline characteristics of all included articles are summarized in Table 1 (for EH) and Table 2 (for BP). For the EH association articles, the genotype distribution in the control groups was not in line with HWE in two articles (Yokoyama et al., 2013; Du, 2018), and in another two articles (Nakagawa et al., 2013; Ota et al., 2016) HWE could not be tested. The NOS scores of all studies were six or higher, indicating that they were high-quality studies. For the BP association articles, we extracted the

| Study ID | OR (95% CI) | % | Weight |
|----------|-------------|---|--------|
| Amamoto (2002) | 0.90 (0.74, 1.08) | 8.54 |        |
| Du (2018) | 0.40 (0.24, 0.65) | 3.17 |        |
| Feng (2012) | 0.69 (0.29, 1.67) | 1.24 |        |
| Hasi (2011) | 0.35 (0.14, 0.89) | 1.13 |        |
| Hui (2007) | 0.58 (0.40, 0.84) | 4.78 |        |
| Iwai (2004) | 0.93 (0.77, 1.13) | 8.29 |        |
| Jing (2015) | 0.67 (0.50, 0.91) | 5.88 |        |
| Li (2017) | 1.02 (0.87, 1.19) | 9.25 |        |
| Lv (2013) | 0.62 (0.38, 0.99) | 3.36 |        |
| Ma (2017) | 0.75 (0.64, 0.87) | 9.31 |        |
| Saito (2003) | 0.61 (0.39, 0.98) | 3.47 |        |
| Takagi (2001) | 0.85 (0.74, 0.97) | 9.83 |        |
| Wang (2013) | 0.79 (0.66, 0.95) | 8.66 |        |
| Wu (2013) | 1.41 (0.95, 2.10) | 4.30 |        |
| Wu (2017) | 0.86 (0.72, 1.02) | 8.93 |        |
| Yokoyama (2013) | 0.71 (0.53, 0.96) | 5.89 |        |
| Zhang (2016) | 1.18 (0.54, 2.58) | 1.53 |        |
| Zhang (2018) | 1.33 (0.74, 2.40) | 2.43 |        |
| Overall (I-squared = 60.0%, p = 0.001) | 0.81 (0.73, 0.89) | 100.00 |        |

NOTE: Weights are from random effects analysis

FIGURE 4 | Forest graphs for the association between the ALDH-2 rs671 polymorphism with essential hypertension risk under the heterozygous model.
blood pressure data of rs671A variant carriers. The NOS scores of all studies were higher than six, indicating that they were high-quality studies.

**Meta-Analysis for the Risk of Essential Hypertension: Integral Analyses**

The risk prediction of the rs671 polymorphism for essential hypertension was investigated separately under the allelic, homozygous, heterozygous, dominant and recessive models. The detailed results of the ORs and 95% CIs for different comparisons are shown in Table 3.

The integral analysis of 20 articles (Takagi et al., 2001; Amamoto et al., 2002; Saito et al., 2003; Iwai et al., 2004; Hui et al., 2007; Hasi et al., 2011; Feng et al., 2012; Lv et al., 2013; Nakagawa et al., 2013; Wang et al., 2013; Wu et al., 2013, 2017; Jing et al., 2015; Zhang et al., 2016, 2018; Li et al., 2017; Ma et al., 2017; Du, 2018) revealed that a statistically significant association between the rs671 polymorphism and the risk of essential hypertension was observed under all models (Figures 2–6): allelic model (OR = 0.81, 95% CI: 0.74–0.90), homozygous model (OR = 0.69, 95% CI: 0.56–0.85), heterozygous model (OR = 0.81, 95% CI: 0.73–0.89), dominant model (OR = 0.79, 95% CI: 0.71–0.87), and recessive model (OR = 0.77, 95% CI: 0.68–0.86). In addition, an analysis of 16 articles (Takagi et al., 2001; Amamoto et al., 2002; Saito et al., 2003; Iwai et al., 2004; Hui et al., 2007; Hasi et al., 2011; Feng et al., 2012; Lv et al., 2013; Wang et al., 2013; Wu et al., 2013, 2017; Jing et al., 2015; Zhang et al., 2016, 2018; Li et al., 2017; Ma et al., 2017) in which the genotype distribution in the control group was in line with HWE revealed that the mutation of the rs671 polymorphism was associated with a significantly decreased risk of essential hypertension under all models: allelic model (OR = 0.83, 95% CI: 0.76–0.92), homozygous model (OR = 0.69, 95% CI: 0.56–0.85), heterozygous model (OR = 0.84, 95% CI: 0.76–0.92), dominant model (OR = 0.82, 95% CI: 0.73–0.91), and recessive model (OR = 0.77, 95% CI: 0.68–0.86).
Meta-Analysis for the Risk of Essential Hypertension: Stratified Analyses

Because the heterogeneity in the integral analyses was significant, a string of stratified analyses were implemented to determine the potential reasons for the between-study heterogeneity from other methodological aspects. In the stratified analyses, 20 articles were stratified by ethnicity, gender, alcohol consumption, source of control, study design, sample size, and genotyping methodology under the allelic, homozygous, heterozygous, dominant and recessive models (Table 3).

When all studies were stratified by ethnicity, there was a significant association between the rs671 polymorphism and EH risk in populations of Japanese descent under all models, and the same result was found in populations of Chinese descent. When stratified by gender, there was a significant association between the rs671 polymorphism and EH risk in men under all models; however, there was no significant association in women. When stratified by alcohol consumption, there was a significant association between the rs671 polymorphism and EH risk in drinkers under the allelic, heterozygous and dominant models; however, there was no significant association in non-drinkers. In the subgroup analysis stratified by the source of control, the EH risk prediction was significant in population-based studies for all models; however, the EH risk prediction was not significant in hospital-based studies for all models. When stratified by study design, the EH risk prediction was significant in case-control studies for all models; the EH risk prediction was only not significant in cohort studies for the recessive model. When stratified by sample size, the EH risk prediction was significant in studies with a sample size \( \geq 1,000 \) for all models, and the EH risk prediction was significant in studies with a sample size \(< 1,000\) for the heterozygous and dominant models.

Meta-Analysis for Blood Pressure Levels

Because of the low frequency of AA homozygotes and to avoid deviations from sample size, the association between the rs671 polymorphism and blood pressure levels was only investigated under the dominant model (A carriers vs. GG carriers). The detailed results of the WMDs and 95% CIs for different comparisons are shown in Table 4.
An integral analysis of 12 individual studies (Takagi et al., 2001; Amamoto et al., 2002; Saito et al., 2003; Wang et al., 2013; Zhang et al., 2013; Isomura et al., 2015; Ota et al., 2016; Li et al., 2017) revealed significant variations in blood pressure between A carriers and GG homozygote carriers (Figures 7, 8).

TABLE 4 | The results of the Meta-analysis (for BP).

|        | SBP                                      |           | DBP                                      |           |
|--------|------------------------------------------|-----------|------------------------------------------|-----------|
|        | N | WMD (95%CI) | $\chi^2$ | I²  | N | WMD (95%CI) | $\chi^2$ | I²  |
| Overall| 12 | −1.78 (−3.02,−0.53) | 100% | 12 | −1.09 (−1.58,−0.61) | 100% |
| Ethnicity | | | | | | | |
| Chinese | 5 | −0.57 (−1.17,0.04) | 89% | 5 | −0.50 (−1.05,0.05) | 97% |
| Japanese | 7 | −2.15 (−3.91,−0.39) | 100% | 7 | −1.52 (−2.12,−0.93) | 100% |
| Gender | | | | | | | |
| Male | 4 | −4.08 (−4.16,−3.99) | 0% | 4 | −2.27 (−2.32,−2.22) | 0% |
| Female | 2 | 1.08 (1.01,1.15) | 0% | 2 | −0.26 (−1.51,1.00) | 76% |
| Alcohol consumption | | | | | | | |
| Drinkers | 2 | −2.71 (−7.51,2.09) | 87% | 2 | −0.86 (−0.97,−0.75) | 0% |
| Nodrinkers | 2 | −0.24 (−1.26,0.79) | 45% | 2 | −0.13 (−0.20,−0.06) | 19% |

The A carriers had lower SBP (WMD = −1.78, 95% CI: −3.02 to −0.53) and DBP (WMD = −1.09, 95% CI: −1.58 to −0.61) levels than GG homozygote carriers. In the subgroup analysis stratified by gender, the significant variation in blood pressure between A carriers and GG homozygote carriers remained in men (SBP: WMD = −4.08, 95% CI: −4.16 to −3.99; DBP: WMD = −2.27, 95% CI: −2.32 to −2.22) but not in women (SBP: WMD = 1.08, 95% CI: 1.01–1.15; DBP: WMD = −0.26, 95% CI: −1.51–1.00). In the subgroup analysis stratified by alcohol consumption, the significant variation in DBP between A carriers and GG homozygote carriers remained in both drinkers (WMD=−0.86, 95% CI: −0.97 to −0.75) and non-drinkers (WMD = −0.13, 95% CI: −0.20 to −0.06); there was no significant variation in SBP in either drinkers (WMD=−2.71, 95% CI: −7.51–2.09) or non-drinkers (WMD=−0.24, 95% CI: −1.26–0.79).

Sensitivity Analysis

The sensitivity analysis was performed by sequentially dropping one inter-study at a time to detect the influence of each inter-study on the summary OR and WMD. The outcomes of our meta-analysis were not altered greatly when each individual study was omitted, suggesting that the overall results were stable and robust.

FIGURE 7 | Forest graphs for the association between the ALDH-2 rs671 polymorphism and systolic blood pressure levels.
Publication Bias
Publication bias of the included studies was assessed using Begg's test, Egger's test and the trim-and-fill method. First, we applied Begg's test and Egger's test to evaluate publication bias. All p-values more than 0.05 was considered to have no evidence of publication bias (Table 5). The results of the trim-and-fill method were k = 0. The shape of the funnel plots of the trim-and-fill method in all comparisons did not show any obvious asymmetrical evidence (Figures 9–15), which revealed that there was little evidence of publication bias in the overall analysis.

DISCUSSION
Previous studies exploring the association between the ALDH-2 rs671 polymorphism and hypertension risk and blood pressure levels have provided controversial results, and the sample sizes in most of these studies were relatively small; thus, it was difficult to obtain credible genetic effects. Meta-analyses have been considered as one of the most important tools to precisely define the association between selected genetic polymorphisms and the risk for a morbid state. Based on this situation, we performed this study.

Our meta-analysis indicated that the ALDH-2 rs671 polymorphism is not only a major protective factor against the development of hypertension, particularly in males and drinkers, but it is also a critical factor in decreasing blood pressure. Based on the following aspects, we believe that our findings are more comprehensive and convincing. First, our meta-analysis incorporated more eligible studies, thus providing sufficient statistical power. Second, the association between the rs671 polymorphism and essential hypertension was investigated extensively with five genetic models. Third, we performed a series of more comprehensive subgroup analyses by factors addressed across different studies, which may influence the reliability.
Fourth, the sensitivity analysis indicated that the results are stable and reliable. Finally, little evidence of publication bias was found in the overall analysis.

For essential hypertension association studies, a statistically significant association between the rs671 polymorphism and EH risk was observed under all models. Li et al. did a case-control study and meta-analysis, and shown that ALDH2 rs671 polymorphism may not associate with EH (Li et al., 2017). We have made a more comprehensive systematic analysis, and included the latest studies that they did not include. Therefore, we endorse our result even more. There was a common polymorphism of ALDH2 (rs671 G→A) in East Asians. When stratified by ethnicity, significant associations were observed in both the Japanese and Chinese subgroups, suggesting that the association between the ALDH-2 rs671 polymorphism and the risk of essential hypertension did not differ between Chinese and Japanese populations. In the stratification analysis by gender, significant associations were found in males, although no significant associations were found in females. This may be due to physiological differences between males and females. Studies found that the female heart has elevated phosphorylation and ALDH2 activity (Lagranha et al., 2010). In the stratification analysis by alcohol consumption, significant associations were found in drinkers, although no significant associations were found in non-drinkers. This finding was not consistent with previous meta-analysis results (Fan et al., 2018). Zhang et al. concluded that the rs671 polymorphism may influence the risk of EH independent of alcohol consumption (Zhang et al., 2014). Compared with him, we added a 2018 study on the association between ALDH2 rs671 gene polymorphism and essential hypertension in non-drinkers (Zhang et al., 2018). We concluded that the rs671 polymorphism may affect the risk of essential hypertension in drinkers. Zhang et al. found that the hypertensive effect of alcohol was attributed to ethanol rather than acetaldehyde (Zhang et al., 2013). The rs671 polymorphism, G→A, decreases the activity of alcohol-metabolizing enzymes. As a result, the rs671 polymorphism drinkers had less ethanol, which protected them from hypertension. In the subgroup analysis stratified by the source of control, the EH risk prediction was significant in population-based studies for all models, whereas the EH risk prediction was not significant in hospital-based studies for all models. We trusted that studies whose control groups were from populations accurately reflected the relationship between the rs671 polymorphism and EH risk.
Finally, the study design and sample size did not alter the overall result.

For blood pressure association studies, a significant variation in blood pressure between A carriers and GG homozygote carriers was observed. This result was consistent with the results of the association between the rs671 polymorphism and EH risk. In the stratification analysis by gender, signification associations were found in the male subgroup for SBP and DBP levels, although no significant associations were found in females. In the stratification analysis by alcohol consumption, signification associations were found in both drinkers and non-drinkers’ DBP levels, although no significant associations were found in SBP levels. Notably, there were relatively few studies based on gender differences and alcohol consumption differences; thus, it was difficult to obtain credible genetic effects.
However, there were several limitations in our study. First, only articles published in English and Chinese were incorporated, which led to a potential selection bias. Second, because of the lack of uniform background data for studies in meta-analyses, the data were not further stratified by other factors that may affect blood pressure such as salt consumption and smoking. Third, The ALDH2 polymorphism is observed to be associated with increased risk for diseases such as coronary artery disease and diabetics. However, due to the limitation of included articles, further stratification of the subjects according to these accompanied diseases could not be implemented in this study. Forth, As medications could affect the BP levels. However, due to the limitation of included articles, we were unable to analyze the use of drugs. Fifth, significant heterogeneity was detected even we performed subgroup analyses. Finally, the meta-analysis was limited by the
CONCLUSIONS

The collective findings of this meta-analysis demonstrated that the mutation of the ALDH-2 rs671 polymorphism was significantly associated not only with a decreased predisposition toward essential hypertension but also with lowering blood pressure, suggesting that the ALDH-2 rs671 polymorphism might represent an important genetic marker of hypertension. These findings potentially further our understanding of the contributing role of the ALDH-2 rs671 polymorphism in blood pressure regulation and in the pathogenesis of hypertension.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

AUTHOR CONTRIBUTIONS

YZhe, CN, and ZF conceived and designed the experiments. YZhe, XZ, and YL performed the experiments. YZhe, XZ, and LQ analyzed the data. YZhe and YZha contributed materials and analytical tools. YZhe, XZ, and CN wrote the manuscript. YZhe, JL, and ZF revised the manuscript. All authors reviewed and approved the manuscript prior to submission.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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