ALDH2 Gene rs671 Polymorphism May Decrease the Risk of Essential Hypertension

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Summary

Aldehyde dehydrogenase-2 (ALDH2) rs671 G>A polymorphism can influence the activity of ALDH2 and may be associated with the risk of essential hypertension (EH). Although many previous studies have explored such a relationship, the conclusion is still controversial.

The PubMed, Embase, and China National Knowledge Infrastructure databases were searched on the ALDH2 gene and EH. We used the Newcastle-Ottawa Scale to evaluate the quality of the study. Then we calculated the strength of relationship between ALDH2 rs671 mutation and EH by utilizing odds ratios and 95% confidence intervals. Besides, subgroup analysis and sensitivity analysis were performed and the publication bias was assessed.

There were 12 studies containing 8153 cases and 10,162 controls. Our meta-analysis showed significant association between ALDH2 rs671 polymorphism and EH in four genetic models (the allele model, the homozygote model, the heterozygote model, and the dominant model), whereas it did not indicate this connection in the recessive model. However, a trend of decreased risk still could be seen. Furthermore, we also found an obvious association between rs671 mutation and the risk of EH in the male group than in the female group in all five genetic models.

We concluded that ALDH2 rs671 G>A polymorphism may decrease the risk of EH. Furthermore, susceptibility to EH reduced in males but not in females. As a variant in ALDH2, rs671 G>A could be an attractive candidate for genetic therapy of EH. In addition, more case-control studies should be conducted to strengthen our conclusion and evaluate the gene-gene and gene-environment interactions between the ALDH2 gene and EH.

Key words: Single nucleotide polymorphism, Association, Meta-analysis

Hypertension is the most common chronic disease at present, and it is characterized by elevated systemic arterial pressure. It can be accompanied with clinical syndromes of functional or organic damage of organs such as heart, brain, and kidney. Hypertension is also the most important risk factor for cardiovascular and cerebrovascular diseases, mainly affected by genetic and environmental effects, seriously affecting human physical and mental health. A related research showed that approximately 25% to 65% of blood pressure variation is affected by genetic factors.1 Hypertension can be classified into two types: essential hypertension (EH) and secondary hypertension. Quantitatively, EH composes more than 95% of hypertensive cases.2 Genetic variation in ethanol-metabolizing enzymes has been reported to influence the progression of hypertension by regulating the behavior of alcohol consumption or alcohol sensitivity.3

Aldehyde dehydrogenase-2 (ALDH2) is the principal enzyme in the process of ethanol metabolism.4 In addition, ALDH2 is a protective factor against oxidative stress, so deficiency in ALDH2 increases oxidative stress in the body, which is a risk factor of hypertension.5 Human ALDH2 gene, which contains 13 exons, is located on chromosome 12q24. There is a G-to-A point mutation in which glutamate at position 504 is replaced by lysine on exon 12 of the ALDH2 gene (rs671 polymorphism), and then three patterns are formed: GG, GA, and AA.6,7 In addition, the rs671 polymorphism reduces enzyme activity and biological function significantly.8

One genome-wide association study on ALDH2 has shown that ALDH2 rs671 polymorphism might be associated with EH.9 Some studies are consistent with this re-
and EH by combining various contradictory results. So we conducted this meta-analysis to further confirm the association between ALDH2 rs671 polymorphism and EH by combining various contradictory results.

Methods

Our meta-analysis was performed by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search strategy: The terms “alcohol dehydrogenase 2” or “ALDH2,” “polymorphism” or “mutation” or “variation,” and “hypertension” were used to search on the PubMed, Embase, and China National Knowledge Infrastructure databases up to April 2019, and there were no language restrictions. The references of relevant articles were also searched and reviewed to discover other potential eligible studies.

Selection and exclusion criteria: In order to make eligible studies included in this meta-analysis, we have established criteria before the search strategy. The criteria for inclusion were as follows: (1) case-control or cohort studies; (2) publications that explored the relationship between ALDH2 gene rs671 mutation and EH; (3) the diagnosis of EH was defined as either having a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg or taking antihypertensive medication; and (4) sufficient data should be available to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). The exclusion criteria were as follows: (1) case-control or cohort studies that are not about the association between ALDH2 rs671 polymorphism and EH; (2) duplicate publications; (3) insufficient data for extraction; and (4) studies with genotype frequencies in the controls’ departure from Hardy-Weinberg equilibrium (HWE).

Data extraction: Two authors extracted significant data in all included studies independently. Disagreement was resolved by a third investigator, and common results were finally reached. We extracted the following information: first author, publication year, country where the subjects come from, ethnicity, number of cases and controls, allele and genotype frequencies, and source of controls. We have tried to contact the original author if the data of the study were incomplete. The quality of the study was assessed by the method of the 9-point Newcastle-Ottawa Scale (NOS).

Statistical analysis: We performed HWE tests with a significance level set at \( P < 0.05 \). The strength of correlation between the ALDH2 gene rs671 mutant and EH was evaluated by combining ORs and 95% CIs via a fixed- or random-effects model. We demonstrated the extent of heterogeneity between studies by using \( I^2 \) ranging from 0% (complete consistency) to 100% (complete inconsistency). We adopted a random-effects model (the DerSimonian and Laird method) for pooled analysis with \( I^2 \geq 50\% \) indicating heterogeneity among studies. Otherwise, a fixed-effects model (the Mantel-Haenszel method) should be used. We also performed subgroup analysis to recognize the possible heterogeneity: gender, source of controls, and sample size. All analyses were conducted in five genetic models: the allele model (A versus G), the homozygote model (AA versus GG), the heterozygote model (GA versus GG), the dominant model (GA + AA versus GG), and the recessive model (AA versus GA + GG). Sensitivity analysis was conducted to assess each study’s effect on the combined ORs by omitting each study. We also conducted an Egger test and drew a Begg funnel plot to identify publication bias and considered that there was no statistically significant publication bias when \( P > 0.05 \). All statistical tests were performed by using Stata version 15.0 (StataCorp, College Station, TX, USA).

Results

Study characteristics: In total, 155 potential articles relevant to the searched keywords were identified, and we excluded 38 duplicate studies. Then we screened the remaining 117 articles, and 85 of these records were excluded. Thirty-two articles were read by full text, and 20 of them were excluded because of not being related to ALDH2 rs671 polymorphism and EH. There were 12 studies containing 8153 cases and 10,162 controls. All the characteristics of the studies are shown in Table I. The score of NOS for each included study is more than 6 points, which indicates a good quality, and the results are shown in Table II.

Quantitative synthesis: All statistical results of our meta-analysis are shown in Table III. Our meta-analysis showed significant association between ALDH2 gene rs671 polymorphism and EH in four genetic models: allele (A versus G): \( OR = 0.86, 95\% CI = 0.76-0.97, P = 0.017 \); homozygote (AA versus GG): \( OR = 0.73, 95\% CI = 0.55-0.96, P = 0.027 \); heterozygote (GA versus GG): \( OR = 0.85, 95\% CI = 0.75-0.96, P = 0.007 \); and dominant (GA + AA versus GG): \( OR = 0.84, 95\% CI = 0.74-0.96, P = 0.010 \). Differently, the recessive (AA versus GA + GG): \( OR = 0.77, 95\% CI = 0.59-1.00, P = 0.051 \) analysis indicated that rs671 mutation was not relevant to EH. However, a trend of decreased risk still could be seen. The results of the forest plot are shown in Figure 2.

As shown in Table III, all five genetic models have considerable heterogeneity (allele model: \( I^2 = 73.3\% \); homozygote model: \( I^2 = 60.1\% \); heterozygote model: \( I^2 = 56.6\% \); dominant model: \( I^2 = 66.9\% \); recessive model: \( I^2 = 56.0\% \)). We tried to identify more reliable results and explore sources of heterogeneity by conducting subgroup analysis in gender, different sources of controls, and sample size. In the subgroup analysis of gender, an obvious association between rs671 mutation and the risk of EH was discovered in the male group in five genetic models (allele: \( OR = 0.77, 95\% CI = 0.70-0.85, P = 0.000 \); homozygote: \( OR = 0.65, 95\% CI = 0.52-0.82, P = 0.000 \); heterozygote: \( OR = 0.73, 95\% CI = 0.65-0.82, P = 0.000 \); dominant: \( OR = 0.72, 95\% CI = 0.64-0.80, P = 0.000 \);
and recessive: OR = 0.75, 95% CI = 0.60-0.94, P = 0.013). But in the female group, no significant association was shown (allele: OR = 0.93, 95% CI = 0.78-1.12, P = 0.442; homozygote: OR = 0.88, 95% CI = 0.68-1.15, P = 0.355; heterozygote: OR = 0.97, 95% CI = 0.77-1.21, P = 0.773; dominant: OR = 0.94, 95% CI = 0.75-1.18, P = 0.579; and recessive: OR = 0.89, 95% CI = 0.71-1.11, P = 0.294). In addition, heterogeneity was decreased apparently in the gender subgroup analysis. We found that hospital-based controls showed a significant relationship between rs671 mutation and the risk of EH in all five genetic models (allele: OR = 0.66, 95% CI = 0.54-0.81, P = 0.000; homozygote: OR = 0.39, 95% CI = 0.20-0.78, P = 0.007; heterozygote: OR = 0.66, 95% CI = 0.52-0.84, P = 0.001; dominant: OR = 0.63, 95% CI = 0.50-0.80, P = 0.000; and recessive: OR = 0.45, 95% CI = 0.23-0.88, P = 0.020), whereas there is no relevant influence in population-based controls (allele: OR = 0.91, 95% CI = 0.80-1.04, P = 0.179; homozygote: OR = 0.79, 95% CI = 0.59-1.07, P = 0.124; heterozygote: OR = 0.89, 95% CI = 0.78-1.01, P = 0.074; dominant: OR = 0.89, 95% CI = 0.77-1.03, P = 0.111; and recessive: OR = 0.83, 95% CI = 0.63-1.09, P = 0.176). The result of subgroup analysis in terms of the sample size being ≥300 indicated obvious association between ALDH2 rs671 polymorphism and the risk of EH in the five models (allele: OR = 0.84, 95% CI = 0.75-0.95, P = 0.003; homozygote: OR = 0.69, 95% CI = 0.54-0.89, P = 0.004; heterozygote: OR = 0.84, 95% CI = 0.75-0.95, P = 0.005; dominant: OR = 0.83, 95% CI = 0.73-0.94, P = 0.003; and recessive: OR = 0.74, 95% CI = 0.59-0.94, P = 0.013), but the relationship disappeared in the group with a sample size of ≤300 (allele: OR = 0.85, 95% CI = 0.43-1.68, P = 0.647; homozygote: OR = 0.72, 95% CI = 0.08-3.63, P = 0.771; heterozygote: OR = 0.84, 95% CI = 0.48-1.49, P = 0.562; dominant: OR = 0.85, 95% CI = 0.44-1.64, P = 0.621; and recessive: OR = 0.75, 95% CI = 0.10-5.75, P = 0.783).

Sensitivity analysis: We conducted sensitivity analysis to explore whether the ORs would change by omitting each study. As shown in Figure 3, no single study could change
### Table 1. The Characteristics of the Included Studies and rs671 Polymorphism Genotype Distribution and Allele Frequency in Cases and Controls

| Author (Year) | Country   | Ethnicity | Source of controls | Cases (male/female) | Genotype (n) | Controls (male/female) | Allele Frequency (n, %) | NOS HWE score test |
|---------------|-----------|-----------|--------------------|---------------------|--------------|------------------------|-------------------------|---------------------|
| Takagi (2001)| Japan     | Asian     | PB                 | GG (289/309)        | 809          | 598                    | 1427                    | (1542/1777) 0.758    |
| Hasi (2011)  | China     | Asian     | PB                 | GG (289/309)        | 809          | 598                    | 1427                    | (1542/1777) 0.758    |
| Feng (2012)  | China     | Asian     | HB                 | GG (289/309)        | 809          | 598                    | 1427                    | (1542/1777) 0.758    |
| Wang (2013)  | China     | Asian     | PB                 | GG (289/309)        | 809          | 598                    | 1427                    | (1542/1777) 0.758    |
| Li (2017)    | China     | Asian     | PB                 | GG (289/309)        | 809          | 598                    | 1427                    | (1542/1777) 0.758    |
| Ma (2018)    | China     | Asian     | PB                 | GG (289/309)        | 809          | 598                    | 1427                    | (1542/1777) 0.758    |
| Zhang (2018) | China     | Asian     | PB                 | GG (289/309)        | 809          | 598                    | 1427                    | (1542/1777) 0.758    |

NOS indicates Newcastle-Ottawa Scale; HWE, Hardy-Weinberg equilibrium; PB, population-based; HB, hospital-based; and MAF, minor allele frequency.
the results of our meta-analysis, which indicated that our results were extremely reliable.  

**Publication bias:** We conducted an Egger test and drew a Begg funnel plot to assess publication bias. Figure 4 indicates no publication bias in our meta-analysis (allele model: $P = 0.975$; homozygote model: $P = 0.752$; heterozygote model: $P = 0.918$; dominant model: $P = 0.940$; and recessive model: $P = 0.717$).

**Discussion**

Presently, many studies about exploring the relationship between ALDH2 gene mutation and EH have been published, but the results are still controversial. Eight$^{10,11,13,14,16,19-21}$ of the 12 included studies reported the relationship between rs671 mutation and susceptibility to EH, whereas the other four$^{12,15,17,18}$ publications showed no obvious relationship. What is more surprising is the fact that two meta-analyses,$^{18,20}$ both published in 2017, concluded completely different results. So we conducted this meta-analysis to make a more eligible result about the association between ALDH2 gene rs671 polymorphism and EH. Compared with previous studies, we formulated rigorous criteria of selection and exclusion to include eligible publications such as not considering articles with genotype frequencies in controls’ departure from HWE. Moreover, some latest published articles have also been included.

The precise functional mechanism of ALDH2 gene rs671 polymorphism is still uncertain. ALDH2 is a key enzyme that is responsible for metabolizing toxic aldehydes and plays a significant role in alcohol metabolism. In addition, it has been found that a genetic mutant in ethanol-metabolizing enzymes could influence the occurrence of hypertension by regulating the behavior of alcohol consumption or alcohol sensitivity.$^{3}$ ALDH2 gene rs671 mutation forms three patterns: GG, GA, and AA. This polymorphism makes the ALDH2 miss enzyme activity because it loses its ability to combine coenzymes.$^{7}$ The individual enzyme activity of heterozygous ALDH2 mutant GA is 10% to 45%, whereas homozygous mutant AA has only 1% to 5% enzyme activity.$^{23}$ Persons with inactive ALDH2 seem to be less susceptible to hypertension induced by alcohol than are those who consume more alcohol without suffering from alcoholism and alcohol flush-

| Author   | Selection | Comparability | Exposure |
|----------|-----------|---------------|----------|
| Takagi   | ***       | *             | **       |
| Hasi     | ***       | *             | ***      |
| Feng     | ***       | *             | **       |
| Wang     | ***       | *             | **       |
| Lv       | ***       | *             | ***      |
| Wu       | ***       | *             | ***      |
| Jing     | ***       | *             | **       |
| Zhang    | ***       | *             | **       |
| Li       | ***       | *             | **       |
| Ma       | ***       | *             | **       |
| Wu       | ***       | *             | **       |
| Zhang    | ***       | *             | **       |

NOS indicates Newcastle-Ottawa Scale; HWE, Hardy-Weinberg equilibrium; HB, hospital-based; OR, odds ratio; and CI: confidence interval.
Figure 2. Forest plot from the meta-analysis on the association of ALDH2 rs671 polymorphism and EH risk. A: allele; B: homozygote; C: heterozygote; D: dominant; and E: recessive.

These previous findings well confirmed our result that ALDH2 rs671 G>A polymorphism may decrease the risk of EH.

Our subgroup analysis revealed that ALDH2 rs671 mutation decreased EH risk in males but not in females (Table III), and this finding was confirmed in a previous study. We thought that this finding can be explained by touching more alcohol in males and then weakening the role of ALDH2. Besides, it has been found that females could detoxify more aldehyde adducts produced by reactive oxygen species via increasing phosphorylation and ALDH2 activity. Furthermore, it is suggested that gender may be the source of heterogeneity, because the heterogeneity was decreased in the gender subgroup analysis. In the other subgroup analysis, similar relationship still
could be confirmed when it comes to the groups of hospital-based controls and sample size of ≥300. However, we thought that larger sample sizes of studies are demanded to approve this result. In the subanalysis of source of control, we found that hospital-based controls showed much significant risk reduction of EH associated with ALDH2 gene polymorphism compared with the population-based group. We thought this difference was mainly caused by selection bias. The hospital-based group is more likely to merge with other diseases, which is also associated with ALDH2 gene mutation. We did not perform subgroup analysis in ethnicity because all included studies are from Asia. No single study could change the results of our meta-analysis in sensitivity analysis (Figure 3). No publication bias was found in our study (Figure 4).

Some limitations exist in our study. First, we only included articles published in English and Chinese, although we performed publication bias tests and found no publication bias. Second, all combined populations were from Asia, which may make our study localized. Third, the data were not further stratified into subgroups such as alcohol consumption, age, smoking, and other lifestyle factors, be-
cause the included studies in this research lacked consistent baseline data.

Conclusion

In conclusion, ALDH2 rs671 G>A polymorphism may decrease the risk of EH. Furthermore, susceptibility to EH reduced in males but not in females. As a variant in ALDH2, rs671 G>A could be an attractive candidate for genetic therapy of EH. In addition, more case-control studies should be conducted to strengthen our conclusion and evaluate the gene-gene and gene-environment interactions between the ALDH2 gene and EH.

Disclosure

Conflicts of interest: None.

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