The dominant models of KCNJ11 E23K and KCNMB1 E65K are associated with essential hypertension (EH) in Asian
Evidence from a meta-analysis
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Abstract

Background: The K+ channel, subfamily J, member-11 (KCNJ11) E23K and β1 subunit of large-conductance Ca2+-activated K+ channel (KCNMB1) E65K polymorphisms were shown to be associated with the risk of essential hypertension (EH). However, the results were inconclusive with relatively small sample size. Thus, we carried out a meta-analysis to investigate the genetic association between KCNJ11 E23K and KCNMB1 E65K polymorphisms and essential hypertension risk.

Methods: Relative studies were collected using PubMed, Web of Science, the Cochrane Library databases, Chinese National Knowledge Infrastructure and Embase databases. Pooled odds ratios with 95% confidence intervals were used to assess the strength of associations.

Results: The dominant models of KCNJ11 E23K (OR = 0.91 [0.83, 1.00]) and KCNMB1 E65K (OR = 0.95 [0.89, 1.02]) were significantly associated with essential hypertension risk. No significant association was detected between the allelic and recessive models of KCNJ11 E23K and KCNMB1 E65K polymorphisms and the susceptibility of EH. Subgroup analysis stratified by ethnicity showed that the dominant model of KCNMB1 E65K was associated with EH risk in Asian population (OR = 0.83 [0.74, 0.94]), but not in Caucasian (OR = 1.02 [0.89, 1.18]).

Conclusions: The dominant model of KCNJ11 E23K and KCNMB1 E65K might be susceptible factors for essential hypertension. To confirm this result, large-scale case-control studies with more subjects are necessary.

Abbreviations: BMI = body mass index, CI = confidence interval, CNKI = Chinese National Knowledge Infrastructure, DBP = diastolic blood pressure, EH = essential hypertension, HDL-C = high-density lipoprotein cholesterol, HWE = Hardy-Weinberg equilibrium, KCNJ11 = K+ channel, subfamily J, member-11, KCNMB1 = β1 subunit of large-conductance Ca2+-activated K+ channel, LDL-C = low-density lipoprotein cholesterol, NOS = Newcastle-Ottawa scale, OR = odds ratio, SBP = Systolic blood pressure, SUR = sulphonylurea receptor, TC = total cholesterol, TG = triglycerides.

Keywords: essential hypertension, KCNJ11, KCNMB1, meta-analysis

1. Introduction

Essential hypertension (EH), characterized by significant and persistent elevations in arterial pressure, is a multifactorial disorder, involving an interaction of genetic, lifestyle, and environmental factors.[1,2] The etiology and pathophysiology of EH may refer to vascular inflammation and endothelial dysfunction.[3,4] Although multiple studies have provided evidence of the role of genes in the determination of blood pressure levels and hypertension,[5,6] the identities of the contributing genes remain controversial.

ATP-sensitive potassium channel (KATP) plays especially important role in the cellular responses of tissues under stress.[7] Kir6.2 was one of the essential subunits of KATP, which was encoded by the K+ inwardly rectifying channel, subfamily J, member-11 (KCNJ11) gene.[8] Previous studies have shown that some polymorphisms or mutations of the KCNJ11 gene may reduce the sensitivity of KATP to ATP and was associated with type 2 diabetes (T2D)[9,10] and cardiovascular diseases.[11,12] Knockout of the KCNJ11 gene may lead to maladaptive remodeling and heart failure in hypertension.[13] The rs5219 is one of the most common polymorphisms in KCNJ11 gene that encoding a glutamate-to-lysine amino acid substitution at position 23 (E23K). It was suggested to alter the polarity of the ATP-binding region.[14] Koo et al has reported a significant association between rs5219 and EH risk in Korean.[15] Furthermore, the GA+AA genotype and A allele were shown to be associated with EH in Xinjiang Kazak Chinese.[16]
However, no association was observed between rs5219 and EH in other populations.\(^{17,18}\)

The large-conductance \(\text{Ca}^{2+}\)-activated \(\text{K}^+\) (BK\(_{Ca}\)) channel that is consisted of a pore-forming \(\alpha\) subunit and a tissue-specific regulatory \(\beta\) subunit, was reported to regulate vascular tone and may determine the blood pressure.\(^{19}\) The \(\beta1\) subunit is encoded by \(\beta1\) subunit of the large-conductance \(\text{Ca}^{2+}\)-dependent \(\text{K}^+\) channel (KCNNB1) gene.\(^{20}\) Rs11739136 (E65K) is a non-synonymous SNP in the exon 3 of KCNMB1. The minor T allele may result in a gain of function of the BK\(_{Ca}\) channel and was suggested to be associated with low prevalence of moderate and severe diastolic hypertension in a Spanish population.\(^{19}\) A previous study on the Han Chinese population demonstrated that a reduced function of BK\(_{Ca}\) channels with KCNMB1 rs11739136 is associated with EH susceptibility.\(^{21}\) However, no association was detected between rs11739136 and EH in Caucasian and other populations in Asia.\(^{16,22}\)

These inconsistencies may due to the relatively small sample sizes in distinct studies. Therefore, we performed a large-scale meta-analysis of all eligible published studies to derive a more precise quantitative assessment of the association between KCNJ11 E23K and KCNMB1 E65K polymorphisms and EH risk.

### 2. Materials and methods

#### 2.1. Patient and public involvement

There was no Patient and Public Involvement in present meta-analysis. And the ethical approval was not necessary for a meta-analysis.

#### 2.2. Selection of published studies

This meta-analysis followed the Cochrane collaboration definition and PRISMA 2009 guidelines for meta-analysis and systematic review.\(^{23}\) We have searched the Pubmed, Embase, Web of Science, and Chinese National Knowledge Infrastructure (CNKI) databases (last updated on December 31, 2018) using the keywords: “\(K\) channel, subfamily J, member-11” or “KCNJ11” and “\(\beta1\) subunit of large-conductance \(\text{Ca}^{2+}\) -activated \(\text{K}^+\) channel” or “KCNMB1” and “single nucleotide polymorphism” or “SNP” or “polymorphism” and “essential hypertension” or “EH”. No language and publication year was limited. Other relevant references of identified studies were retrieved by cross-references.

#### 2.3. Inclusion/exclusion criteria

Inclusion criteria:
1. case-control study;
2. regarding to the genetic association between KCNJ11 E23K and KCNMB1 E65K polymorphisms and EH;
3. the genotype frequencies were available for polymorphisms;
4. the distribution of genotypes in control group were in Hardy-Weinberg equilibrium (HWE).

Exclusion criteria:
1. Duplicated studies, abstract, letter, review, case report, or meeting;
2. unavailable genotype or allele data in case or control groups;
3. The genotype distribution in control group was not in Hardy-Weinberg disequilibrium.

#### 2.4. Data extraction

Two independent authors (Ji WH and Jiang Y) screened the relevant articles according to the inclusion and exclusion criteria and extracted the information from each eligible publication manually. Any disagreements were resolved by discussion. Information were extracted as following: the first author, published year, ethnicity, means age in cases and control, percentage of male in case and control, Body Mass Index (BMI), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), number of cases and controls.

#### 2.5. Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the study quality.\(^{24}\) Total score ranged from 0 (lowest quality) to 8 (highest quality). A study with a score of 6 or higher was classified as high quality. Only the high quality studies were selected in the present study.

#### 2.6. Statistical analyses

Review Manage version 5.2.0 (The Cochrane Collaboration, 2012) and STATA version 12.0 software (StataCorp LP, College Station, TX) were applied to carry out statistical analysis. The strength of associations between allelic, dominant and recessive models of KCNJ11 E23K and KCNMB1 E65K polymorphisms and essential hypertension risk were evaluated by calculating the pooled odds ratios (ORs) and their corresponding 95% confidence interval (CIs). To test the heterogeneity among studies, we assumed the \(P\) and Q statistic. An \(P\) value more than 50% was regarded as significant heterogeneity and a fixed-effect model (Mantel-Haenszel) was used. Otherwise, a random-effect model (DerSimonian and Laird) was used. Sensitivity analysis was performed to assess the stability of results. The publication bias was evaluated by Begg test and Egger test. A \(P < .05\) was considered statistically significant.

### 3. Results

#### 3.1. Characteristics of the studies

As shown in Figure 1, a total of 273 publications were retrieved. After screening the title, abstract, and context of each study, 114 were excluded for being duplicated records. One hundred thirty-three were excluded for being irrelevant articles. Fourteen were removed for being abstract, meeting, letters or reviews. And 5 were excluded for being not case-control designed studies. Finally, 7 eligible articles with 7075 cases and 5082 controls were included in the present study\(^{16–18,21–24}\) (Fig. 1). The main characteristics of involved studies were shown in Table 1. And the NOS quality assessments of included studies were listed in Table s1, http://links.lww.com/MD/D18. All the included studies were of relatively high-quality (NOS score ≥6).

#### 3.2. Results of meta-analysis

Significant associations were detected between the dominant model of KCNJ11 E23K and KCNMB1 E65K and EH risk (KCNJ11 E23K: \(P=.006,\) OR [95%CI]=0.45 [0.25, 0.79];
KCNMB1 E65K: $P = .04$, OR [95%CI] = 0.91 [0.83, 1.00]) (Table 2, Figs. 2 and 3). No significant association was found between the allelic and recessive models of KCNJ11 E23K and KCNMB1 E65K and EH risk ($P > .05$) (Table 2, Figs. 2 and 3). Subgroup analysis stratified by ethnicity was canceled in KCNJ11 E23K for there were all of Asian population. In addition, the results showed that the dominant model of KCNMB1 E65K was associated with EH risk in Asian population ($P = .003$, OR [95% CI] = 0.83 [0.74, 0.94]), but not in Caucasian ($P = .74$, OR [95% CI] = 1.02 [0.89, 1.18]).
3.3. Heterogeneity

No significant heterogeneity was found in all the genetic models of KCNMB1 E65K in overall groups. Significant heterogeneities were observed in all the genetic models of KCNJ11 E23K in overall groups. The heterogeneity in this polymorphism for all models were contributed mainly by Li et al. Removal of this study from meta-analysis gave 0% heterogeneities (allele model: \( P = .49 \), dominant model: \( P = .06 \), recessive model: \( P = .10 \). For limited included articles in present study, we failed to figure out the source of heterogeneity in subgroup analysis.

3.4. Sensitive analysis and publication bias

Sensitivity analysis on the overall risk estimate by excluding one study at a time was confirmed. The ORs were not significantly altered (Fig. 4). We performed the Begg and Egger tests to evaluate the publication bias. None of funnel plots explored the evidence of publication bias (Fig. 5). No obvious publication bias was observed for KCNJ11 E23K and KCNMB1 E65K and EH.

4. Discussion

In the present study, we have investigated the association between KCNJ11 E23K and KCNMB1 E65K and EH risk and confirmed that the dominant model of KCNJ11 E23K and KCNMB1 E65K were susceptible factors for EH in Asian population.

ATP-sensitive potassium channel (K\(_{\text{ATP}}\)) is composed of four essential subunits: Kir6.2, SUR1, and SUR2.[8] The K\(_{\text{ATP}}\) channel in the smooth muscle cells is composed of Kir6.2 and SUR2B (high affinity SUR subunit).[1,2] Others components are important in response to stress and changes in blood pressure.[2,7] The KCNJ11 (Kir6.2) is a candidate gene for multiple diseases including type 2 diabetes,[9,10] type 1 diabetes,[28] and myocardial infarction.[29] The KCNJ11 E23K variant has shown to be a susceptible factor for type 2 diabetes.[9,10] The KK genotype of KCNJ11 E23K may increase the risk of type 2 diabetes.[10] Furthermore, the genotype of E23K was shown to be significantly associated with diastolic blood pressure.[17] However, researches has reported that Kir6.2 was not expressed in vessels and played no distinct role in the arterial system in a knockout mouse model.[30,31] The relationship between hypertension and polymorphisms might be a secondary result. As hypertension is one of the manifestations of metabolic syndrome, which may be stemmed from these polymorphisms. In the present study, we firstly confirmed a significant association between the dominant model of KCNJ11 E23K and EH risk by a meta-analysis. At present, the mechanism by which the KCNJ11 E23K mutation affects blood pressure levels is unclear and needs further study. Given the close relationship between T2D and hypertension, this association may be only a secondary outcome of T2D or disease severity. However, it is easy to speculate that the increase in K\(_{\text{ATP}}\) channel activity observed in the presence of the KCNJ11 E23K variant has a direct effect on the cardiovascular system and is therefore associated with hypertension susceptibility. In addition, KCNJ11 E23K mutation may alter the activity of K\(_{\text{ATP}}\) channel in the central nervous system and regulate the sympathetic nervous system. Activation of the sympathetic nervous system is considered to play an important role in the occurrence, maintenance and occurrence of hypertension. dysregulation of
### Table 2

| Gene      | Genetic Models | Subgroup  | Number of studies | Case | Control | OR [95% CI]  | P value | Model | Test of association | Numbers | Test of heterogeneity | I² (%) |
|-----------|----------------|-----------|-------------------|------|---------|--------------|---------|-------|---------------------|---------|-----------------------|--------|
| KCNJ11    | Allelic        | total     | 4                 | 1726 | 1764    | 0.85 [0.57, 1.27] | .43     | R     | < .0001             | 86      | 88                    |        |
|           |                | Dominant  | 4                 | 863  | 882     | 0.45 [0.25, 0.79] | .006    | R     | .0001               | 86      | 66                    |        |
|           |                | Recessive | 4                 | 863  | 882     | 0.93 [0.56, 1.52] | .76     | R     | .03                 | 66      | 66                    |        |
| KCNMB1    | Allelic        | total     | 4                 | 12872| 10204   | 0.96 [0.88, 1.04] | .35     | F     | .33                 | 12      | 12                    |        |
|           |                | Asian     | 3                 | 5910 | 5708    | 0.92 [0.83, 1.03] | .15     | F     | .35                 | 6       | 6                     |        |
|           |                | Caucasian | 1                 | 6902 | 4406    | 1.02 [0.89, 1.16] | .79     | -     | -                   | -       | -                     |        |
|           | Dominant       | total     | 4                 | 6436 | 5102    | 0.91 [0.83, 1.00] | .04     | F     | .16                 | 42      | 42                    |        |
|           |                | Asian     | 3                 | 2955 | 2854    | 0.83 [0.74, 0.94] | .003    | F     | .80                 | 0       | 0                     |        |
|           |                | Caucasian | 1                 | 3481 | 2248    | 1.02 [0.89, 1.16] | .74     | -     | -                   | -       | -                     |        |
|           | Recessive      | total     | 4                 | 6436 | 5102    | 0.94 [0.81, 1.14] | .26     | F     | .70                 | 0       | 0                     |        |
|           |                | Asian     | 3                 | 2955 | 2854    | 0.78 [0.54, 1.14] | .20     | F     | .58                 | 0       | 0                     |        |
|           |                | Caucasian | 1                 | 3481 | 2248    | 0.95 [0.66, 1.62] | .86     | -     | -                   | -       | -                     |        |

* *= not available, CI = confidence interval, F = fixed model, KCNJ11 = K+ channel, subfamily J, member-11, KCNMB1: β1 subunit of large-conductance Ca²⁺-activated K⁺ channel, OR = odds ratio, R = random model.

![Figure 2](https://via.placeholder.com/150)

**Figure 2.** Forest plots of odds ratios for the association between KCNJ11 E23K and essential hypertension. A, allelic model; B, dominant model; C, recessive model.
hormone secretion other than insulin caused by E23K mutation may also affect blood pressure control.\[32\]

The regulation of vascular tone was mainly depending on the activity of ion channel. Research has identified that the BKCa in smooth muscle tissue plays an important role in physiological processes of maintaining membrane potential and regulating muscle tension.\[33\] The human KCNMB1 gene that encoding the β1 subunit of BKCa, locates in 5q34. A mutation (rs11739136) of A to G in the exon 3 of KCNMB1 may cause a E65K change in protein. The changed function of BKCa has an effect on multiple cardiovascular diseases such as hypertension and arrhythmia.\[34,35\] Due to the down-regulation or deletion of the β1 subunits, the open probability of BKCa channel and the transient outward potassium current are reduced, which reduces the negative feedback inhibition of BKCa channel, which leads to depolarization of cell membrane, contraction of vascular smooth muscle and raised blood pressure.\[36\]

Correlation analysis between KCNMB1 E65K variants and hypertension showed that the E65K mutation caused an increase in the sensitivity of the BK channel to calcium ions, making the blood vessels easier to relax.\[19\] Sent et al showed that women over 55 years of age with K allele carriers had a lower risk of moderately higher diastolic blood pressure. In addition, Nielsen et al have not only confirmed the protective effect of the K allele on diastolic blood pressure, but also verified that the systolic blood pressure of K allele carriers was significantly lower than that of non-carriers.\[24\] Zhao et al further indicated that K allele act as protective factor to reduce the prevalence of hypertension in the Chinese population.\[21\]

These results suggest that KCNMB1 gene polymorphism is closely related to the development of high blood pressure. In the present meta-analysis study, we enrolled four studies with 7075 EH patients and 5682 healthy controls and found the dominant model of KCNMB1 E65K was a protective factor for EH. Interestingly, the relationship between the KCNJ11 E23K and KCNMB1 E65K genotype and blood pressure phenotypes has not previously been described in other racial/ethnic groups, suggesting that such an effect of the E23K and E65K genotype on blood pressure changes may be specific to Asian populations.

Nonetheless, we also wish to acknowledge the limitations in our study. First, the number of study included in the present study

| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|---------------------|-------|----------------|-------|--------|----------------------------|----------------------------|
| Han 2017          | 93                  | 534   | 112            | 518   | 8.4%   | 0.76 [0.56, 1.04]            | 0.76 [0.56, 1.04]          |
| Nielsen 2008      | 645                 | 6962  | 410            | 4495  | 40.5%  | 1.02 [0.89, 1.16]            | 1.02 [0.89, 1.16]          |
| Wang-2 2016       | 78                  | 554   | 80             | 494   | 6.5%   | 0.85 [0.60, 1.19]            | 0.85 [0.60, 1.19]          |
| Zhao 2008         | 549                 | 4822  | 553            | 4696  | 44.5%  | 0.96 [0.85, 1.09]            | 0.96 [0.85, 1.09]          |
| Total (95% CI)    | 12872               |       | 10204          |       | 100.0% | 0.96 [0.88, 1.04]            | 0.96 [0.88, 1.04]          |

Test for overall effect: Z = 0.94 (P = 0.35)

| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|---------------------|-------|----------------|-------|--------|----------------------------|----------------------------|
| Han 2017          | 80                  | 267   | 94             | 259   | 6.9%   | 0.75 [0.52, 1.08]            | 0.75 [0.52, 1.08]          |
| Nielsen 2008      | 611                 | 3481  | 387            | 2248  | 40.0%  | 1.02 [0.80, 1.30]            | 1.02 [0.80, 1.30]          |
| Wang-2 2016       | 72                  | 277   | 70             | 247   | 5.7%   | 0.89 [0.60, 1.31]            | 0.89 [0.60, 1.31]          |
| Zhao 2008         | 518                 | 2411  | 577            | 2348  | 47.4%  | 0.84 [0.73, 0.96]            | 0.84 [0.73, 0.96]          |
| Total (95% CI)    | 6436                |       | 5102           |       | 100.0% | 0.91 [0.83, 1.00]            | 0.91 [0.83, 1.00]          |

Test for overall effect: Z = 2.03 (P = 0.04)

| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|---------------------|-------|----------------|-------|--------|----------------------------|----------------------------|
| Han 2017          | 13                  | 267   | 18             | 259   | 19.7%  | 0.69 [0.33, 1.43]            | 0.69 [0.33, 1.43]          |
| Nielsen 2008      | 34                  | 3481  | 23             | 2248  | 31.3%  | 0.95 [0.56, 1.62]            | 0.95 [0.56, 1.62]          |
| Wang-2 2016       | 6                   | 277   | 10             | 247   | 11.7%  | 0.52 [0.19, 1.47]            | 0.52 [0.19, 1.47]          |
| Zhao 2008         | 31                  | 2411  | 33             | 2348  | 37.3%  | 0.91 [0.56, 1.50]            | 0.91 [0.56, 1.50]          |
| Total (95% CI)    | 6436                |       | 5102           |       | 100.0% | 0.84 [0.61, 1.14]            | 0.84 [0.61, 1.14]          |

Test for overall effect: Z = 1.14 (P = 0.25)

Figure 3. Forest plots of odds ratios for the association between KCNMB1 E65K and essential hypertension. A, allelic model; B, dominant model; C, recessive model.
was relatively small. In the subgroup analysis of KCNMB1 E65K, there was only one study conducted in Caucasian. Second, further subtle adjusted analysis such as gender, age, smoking, environmental factors, and other lifestyle should be carried out if more detailed individual information was available. Third, heterogeneity among studies for KCNJ11 E23K was existed, which may be derived from the study design, the source of controls, the differences of genetic background, and the environment presented among different countries. Although the great heterogeneity among studies had no effect on the pooled result, yet the heterogeneity could not be neglected completely.

5. Conclusions

The current meta-analysis indicated that the dominant of KCNJ11 E23K and KCNMB1 E65K were associated with EH in Asian. Certainly, to further evaluate the association between KCNJ11 E23K and KCNMB1 E65K and EH susceptibility, a
Figure 5. Publication bias of literatures for allelic, dominant and recessive models of KCNJ11 E23K and KCNMB1 E65K were tested by Begg funnel plot and Egger test. A, KCNJ11 E23K; B, KCNMB1 E65K.
well-designed large-scale multicenter study is warranted to confirm the findings.

Author contributions

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