Systematic Review and Meta-Analysis

Medicine®

OPEN

The dominant models of KCNJ11 E23K and KCNMB1 E65K are associated with essential hypertension (EH) in Asian

Evidence from a meta-analysis

Wang Zhancheng, MD[a], Ji Wenhui, BS[b,*], Jiang Yun, MD[a], Wang Lingli, MD[a], Huang Huijun, MD[a], Shen Yan, MD[a], Li Jin, BS[a]

Abstract

Background: The K^+ channel, subfamily J, member-11 (KCNJ11) E23K and β1 subunit of large-conductance Ca^{2+}-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 ($P = .006$, OR [95%CI] = 0.45 [0.25, 0.79]) and KCNMB1 E65K ($P = .04$, OR [95% CI] = 0.91 [0.83, 1.00]) were significantly associated with essential hypertension risk. No significant association was detected between the allelic and recessive models of KCNJ11 E23K and KCNMB1 E65K 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 ($P = .003$, OR [95%CI] = 0.83 [0.74, 0.94]), but not in Caucasian ($P = .74$, OR [95%CI] = 1.02 [0.89, 1.18]).

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 Ca^{2+}-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 (K_{ATP}) plays especially important role in the cellular responses of tissues under stress.[7] Kir6.2 was one of the essential subunits of K_{ATP}., 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 K_{ATP} 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]

Editor: Stefano Omboni.

The work was funded by the Foundation of Health and Family Planning Department of Shanghai Xuhui District (SHXH201607).

The authors declare no conflict of interest.

Supplemental Digital Content is available for this article.

[a] Department of Cardiology, Shanghai Eighth People's Hospital, [b] Department of Internal medicine, Huajing Community Health Service Centre for Xuhui District, Shanghai, China.

[*] Correspondence: Ji Wenhui, Department of Internal medicine, Huajing Community Health Service Centre for Xuhui District, Shanghai 200231 China (e-mail: wenhuiji_doctor@126.com).

Medicine (2019) 98:23(e15828)

Received: 8 January 2019 / Received in final form: 4 May 2019 / Accepted: 6 May 2019

http://dx.doi.org/10.1097/MD.0000000000015828

However, no association was observed between rs5219 and EH in other populations.[17,18]

The large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channel that is consisted of a pore-forming α subunit and a tissue-specific regulatory β subunit, was reported to regulate vascular tone and may determine the blood pressure.[19] The β1 subunit is encoded by β1 subunit of the large-conductance Ca^{2+}-dependent K^+ channel (KCNMB1) gene.[20] Rs11739136 (E65K) is a non-synonymous SNP in the exon 3 of KCNMB1. The minor T allele may resulte 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.[25] 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 "β1 subunit of large-conductance Ca^{2+} -activated 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.[26] 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 I^2 and Q statistic. An I^2 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];

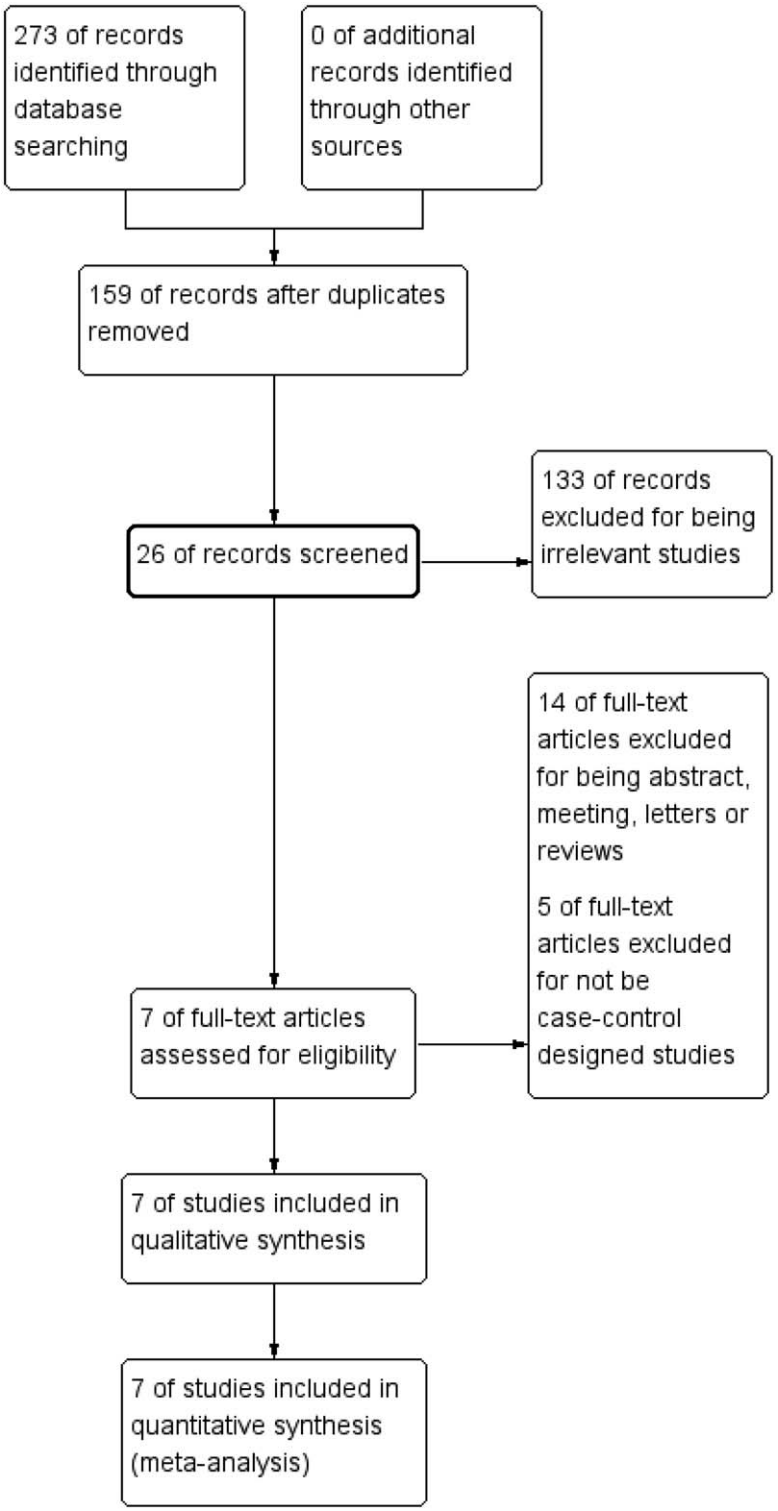


Figure 1. PRISMA flow chart of studies inclusion and exclusion.

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]).

Table 1

The characters of included studies.

first author	Year	Ethnicity	Age	Male,%	BMI	SBP	DBP	TC	TG	LDL-C	HDL-C	Case	Control	NOS
Han	2017	Chinese	48.28 ± 9.14/46.89 ± 9.60	44.2/38.2	26.27 ± 4.50/24.86 ± 3.84	148.75 ± 19.46/117.85 ± 11.01	95.67 ± 12.35/75.19 ± 7.25	4.66 ± 1.20/4.52 ± 1.03	1.41 ± 0.99/1.27 ± 0.87	2.35 ± 0.80/2.33 ± 0.72	1.49 ± 0.50/1.49 ± 0.42	267	259	7
ISAKOVA	2017	Kyrgyz	na	na	na	na	na	na	na	na	na	152	109	6
Li	2012	Chinese	71.8 ± 6.1/72.4 ± 5.5	60.0/52.0	24.5 ± 3.3/23..5 ± 3.1	135.7 ± 20.3/124.1 ± 12.8	80.3 ± 14.3/75 ± 9.8	na	na	na	na	250	250	6
Wang-1	2016	Chinese	47.31 ± 8.68/45.9 ± 9.2		26.18 ± 4.23/25.14 ± 3.98	150.72 ± 18.83/117.50 ± 11.4l	95.47 ± 11.29/75.35 ± 7.44	4.72 ± 1.24/4.60 ± 1.04	1.36 ± 0.93/1.22 ± 0.72	2.29 ± 0.80/2.26 ± 0.68	1.55 ± 0.50/1.55 ± 0.41	237	221	7
Nielsen	2008	Danish	na	na	na	na	na	na	na	na	na	3481	2248	9
Wang-2	2016	Chinese	47.15 ± 8.71/45.82 ± 9.26	na	26.13 ± 4.44/25.09 ± 4.09	149.65 ± 18.40/117.20 ± 11.36	95.22 ± 11.43/75.24 ± 7.33	4.70 ± 1.25/4.57 ± 1.04	1.36 ± 0.90/1.21 ± 0.76	2.31 ± 0.78/2.25 ± 0.70	1.54 ± 0.51/1.56 ± 0.46	277	247	6
Zhao	2008	Chinese	54.6 ± 10.1/54.2 ± 9.3	50.0/51.0	25.2 ± 3.66/23.1 ± 3.4	157.9 ± 24.4/114.4 ± 10.2	95.2 ± 12.1/73.3 ± 7.5	5.13 ± 0.97/4.92 ± 0.99	1.67 ± 1.04/1.41 ± 0.84	3.09 ± 0.89/2.96 ± 0.89	1.27 ± 0.33/1.32 ± 0.32	2411	2348	9

BMI = body mass index, DBP = diastolic blood pressure, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, na = not available, NOS = Newcastle-Ottawa scale, SBP = Systolic blood pressure, TC = total cholestero, TG = triglycerides.

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 (allelic 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_{ATP}) is composed of four essential subunits: Kir6.1, Kir6.2, sulphonylurea receptor (SUR) 1, and SUR2.[8] The K_{ATP} channel in the smooth muscle cells is composed of Kir6.2 and SUR2B (high affinity SUR subunit).[27] Others components are important in response to stress and changes in blood pressure.[27] 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_{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_{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

The results of meta-analysis for KCNJ11 E23K and KCNMB1 E65K and essential hypertension.

Gene	Genetic Models	Subgroup	Number of studies	Numbers		Test of association		Model	Test of heterogeneity	
				Case	Control	OR[95% CI]	*P* value		*P* value	I^2 (%)
KCNJ11	Allelic	total	4	1726	1764	0.85 [0.57, 1.27]	.43	R	<.0001	88
	Dominant	total	4	863	882	0.45 [0.25, 0.79]	.006	R	.0001	86
	Recessive	total	4	863	882	0.93 [0.56, 1.52]	.76	R	.03	66
KCNMB1	Allelic	total	4	12872	10204	0.96 [0.88, 1.04]	.35	F	.33	12
		Asian	3	5910	5708	0.92 [0.83, 1.03]	.15	F	.35	6
		Caucasian	1	6962	4496	1.02 [0.89, 1.16]	.79	-	-	-
	Dominant	total	4	6436	5102	0.91 [0.83, 1.00]	.04	F	.16	42
		Asian	3	2955	2854	0.83 [0.74, 0.94]	.003	F	.81	0
		Caucasian	1	3481	2248	1.02 [0.89, 1.18]	.74	-	-	-
	Recessive	total	4	6436	5102	0.84 [0.61, 1.14]	.25	F	.70	0
		Asian	3	2955	2854	0.78 [0.54, 1.14]	.20	F	.58	0
		Caucasian	1	3481	2248	0.95 [0.56, 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.

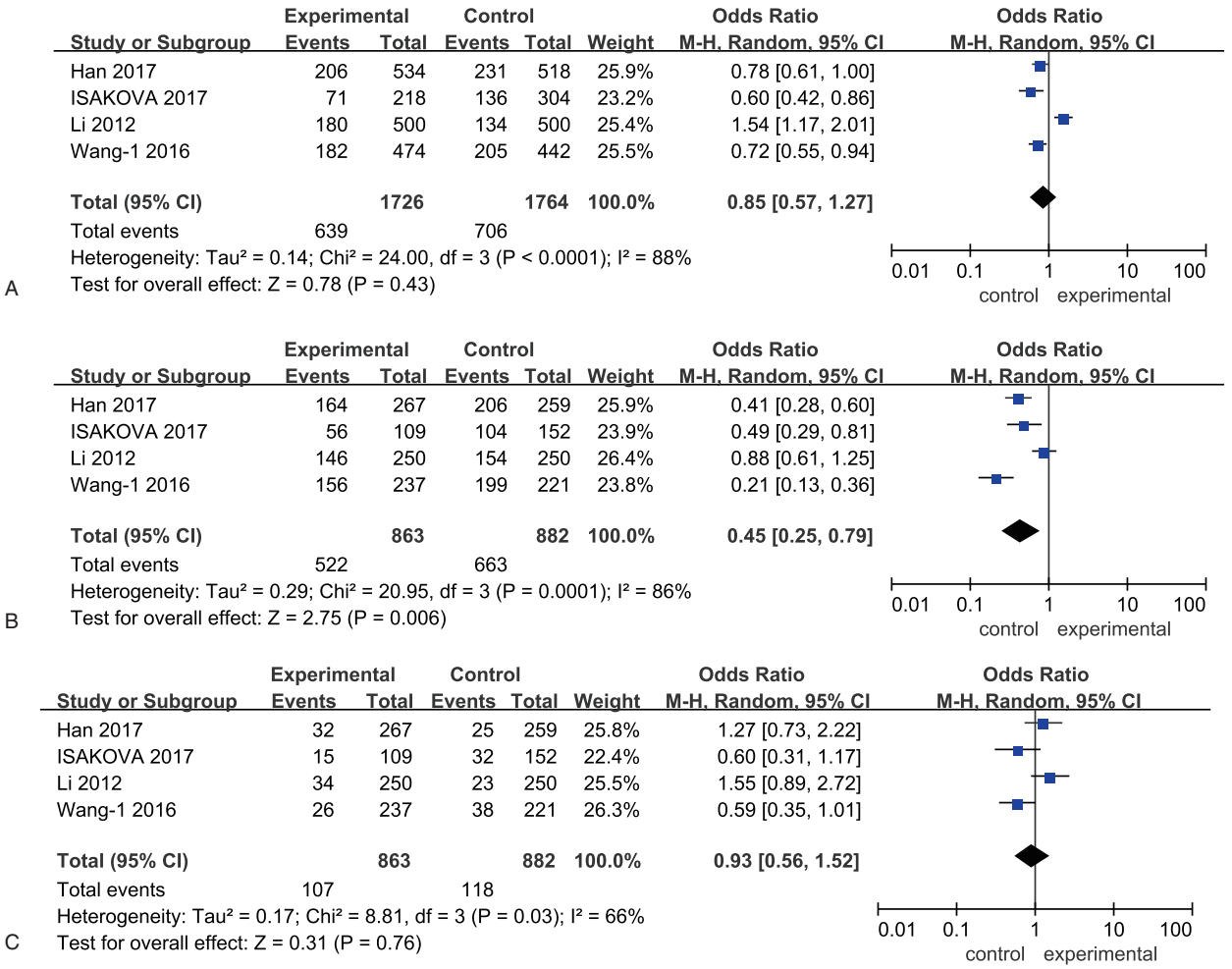


Figure 2. Forest plots of odds ratios for the association between KCNJ11 E23K and essential hypertension. A, allelic model; B, dominant model; C, recessive model.

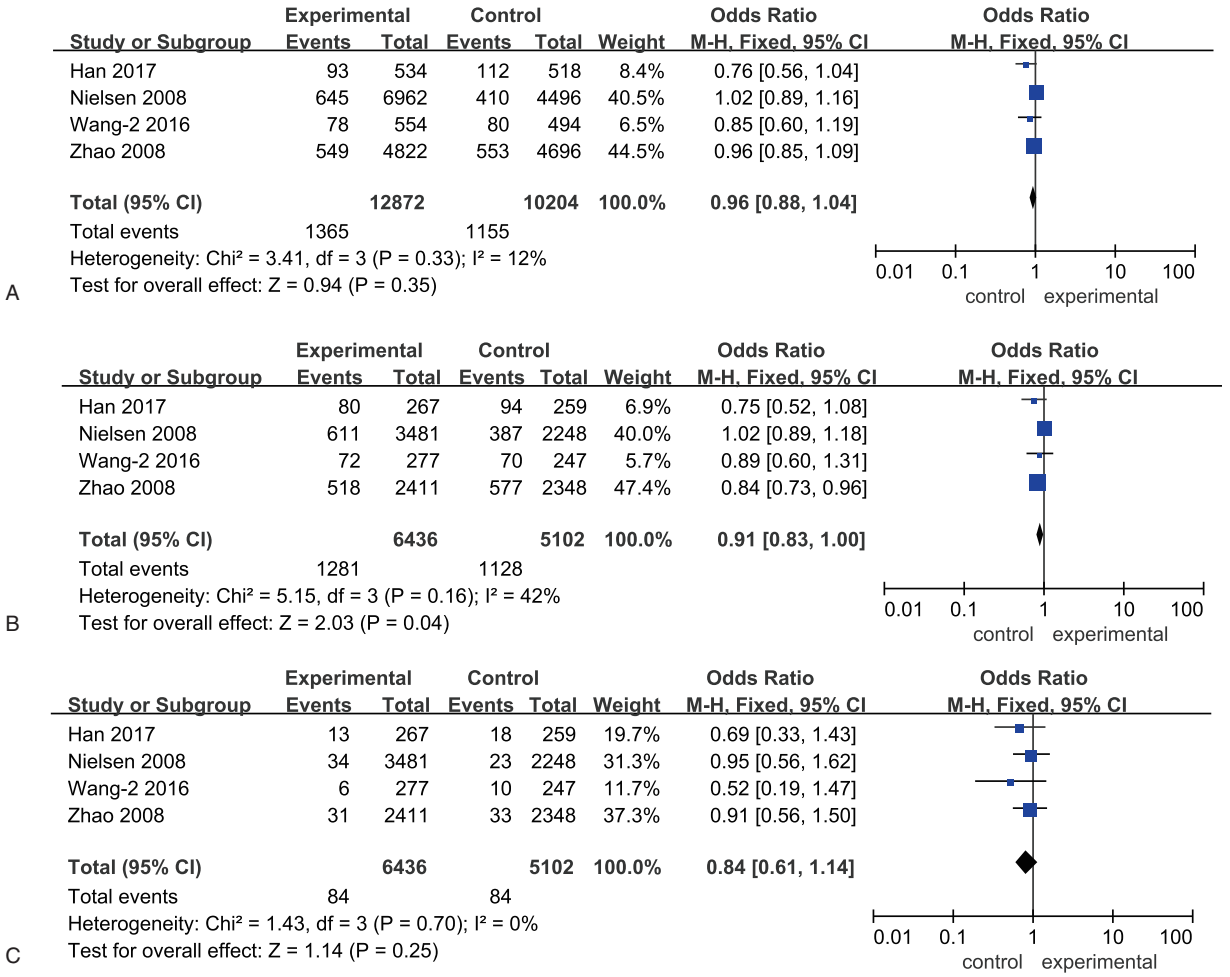


Figure 3. Forest plots of odds ratios for the association between KCNMB1 E65K and essential hypertension. A, allelic model; B, dominant model; C, recessive model.

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 BK_{Ca} 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 BK_{Ca}, 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 BK_{Ca} has a 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 BK_{Ca} channel and the transient outward potassium current are reduced, which reduces the negative feedback inhibition of BK_{Ca} 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

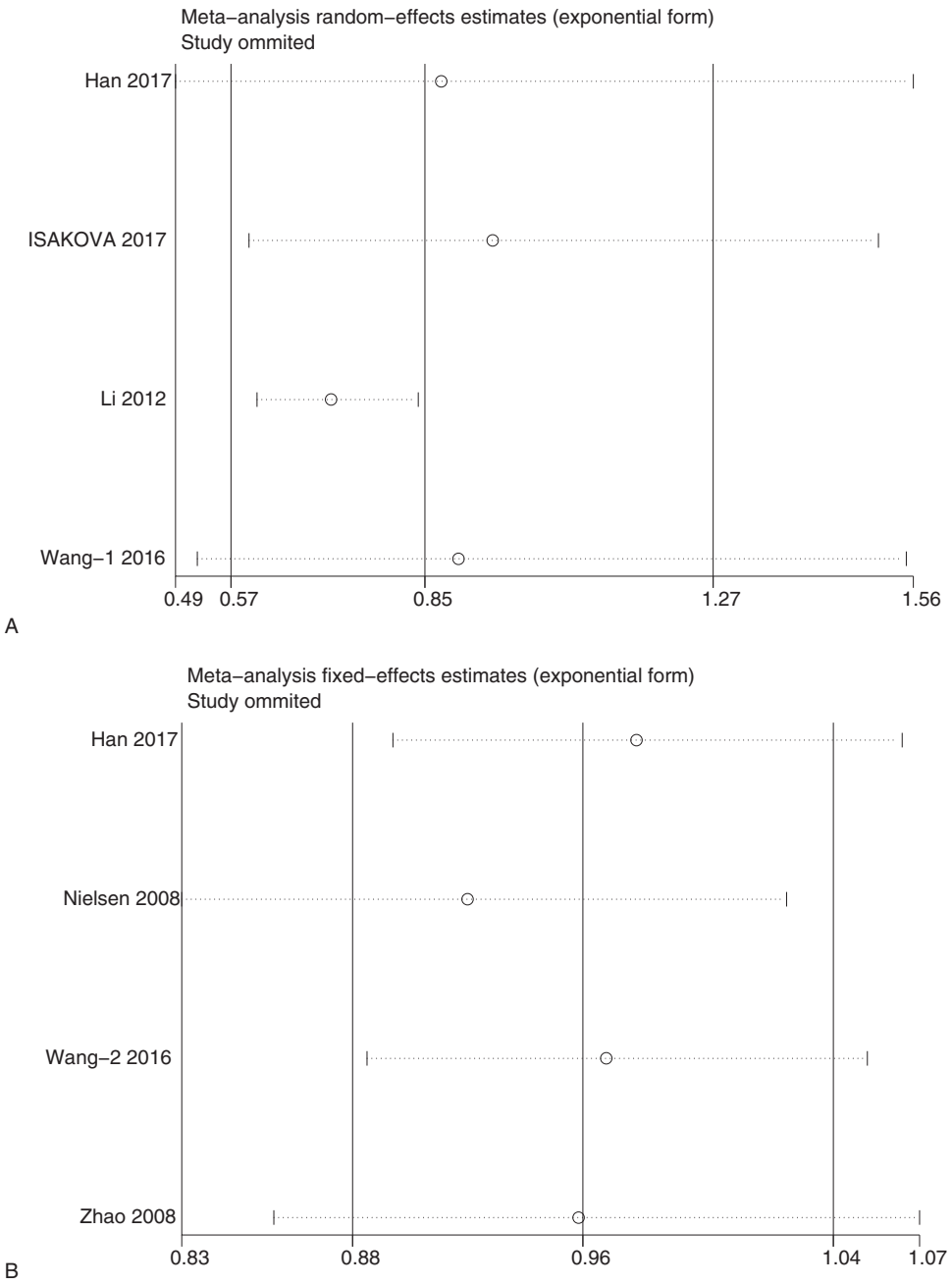
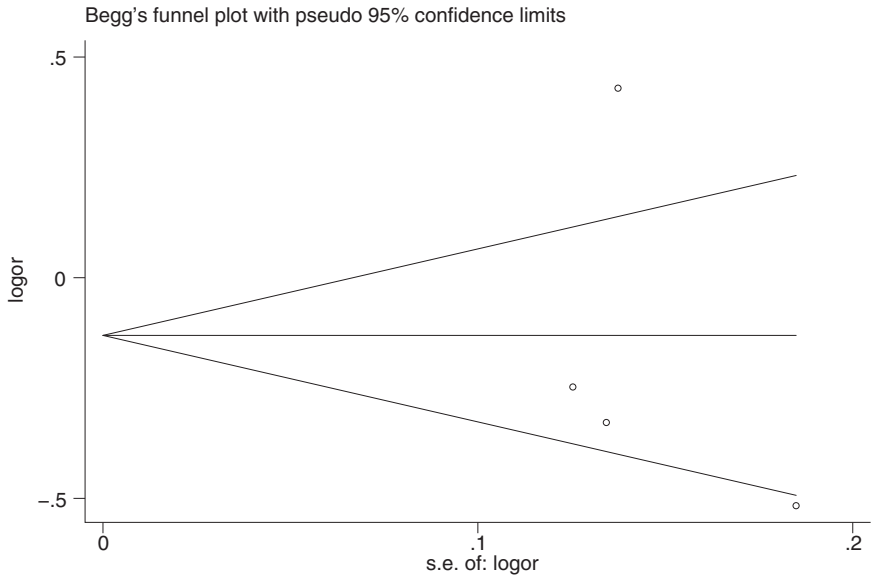


Figure 4. Sensitivity analyses between KCNJ11 E23K and KCNMB1 E65K and essential hypertension. A, KCNJ11 E23K; B, KCNMB1 E65K.

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 derive from the study design, the source of controls, the differences of genetic background, and the environment presented among different country. Although the great heterogeneity among studies had no effect on the pooled result, yet the heterogeneity could not be neglected completely.

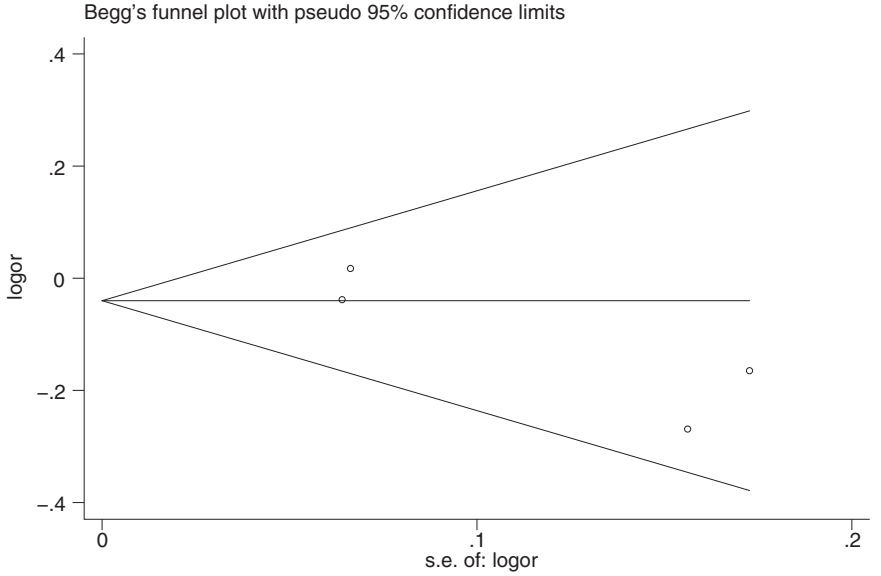
5. Conclusions

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



A

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.6378147	1.69894	0.38	0.743	-6.672136	7.947765
bias	-5.504646	12.054	-0.46	0.693	-57.36882	46.35953



B

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.1207034	.0672909	1.79	0.215	-.1688261	.4102328
bias	-2.045676	.7859909	-2.60	0.121	-5.427522	1.33617

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

Data curation: Wang ZC, Wang LL, Huang HJ.
Formal analysis: Wang ZC, Wang LL, Huang HJ.
Methodology: Wang ZC, Yun Jiang, Wang LL, Yan Shen.
Project administration: Wenhui Ji.
Software: Yun Jiang, Huang HJ, Yan Shen.
Writing – original draft: Wenhui Ji.
Writing – review & editing: Wenhui Ji, Jin Li.

References

[1] Cabadak H, Orun O, Nacar C, et al. The role of G protein β3 subunit polymorphisms C825T, C1429T, and G5177A in Turkish subjects with essential hypertension. Clin Exp Hypertens 2011;33:202–8.
[2] Hui P, Nakayama T, Morita A, et al. Common single nucleotide polymorphisms in Japanese patients with essential hypertension: aldehyde dehydrogenase 2 gene as a risk factor independent of alcohol consumption. Hypertens Res 2007;30:585–92.
[3] Watson T, Goon PK, Lip GY. Endothelial progenitor cells, endothelial dysfunction, inflammation, and oxidative stress in hypertension. Antioxid Redox Signal 2008;10:1079–88.
[4] BolXed JJ. Essential hypertension: an approach to its etiology and neurogenic pathophysiology. Int J Hypertens 2013;2013:547809.
[5] Pojoga L, Gautier S, Blanc H, et al. Genetic determination of plasma aldosterone levels in essential hypertension. Am J Hypertens 1998;11:856–60.
[6] Ríosgonzález BE, Ibarracortés B, Ramírezlópez G, et al. Association of polymorphisms of genes involved in lipid metabolism with blood pressure and lipid values in Mexican hypertensive individuals. Dis Markers 2014;2014:150358.
[7] Haider S, Antcliff JF, Proks P, et al. Focus on Kir6.2: a key component of the ATP-sensitive potassium channel. J Mol Cell Cardiol 2005;38:927–36.
[8] Gögelein H, Hartung J, Englert HC. Molecular basis, pharmacology and physiological role of cardiac K(ATP) channels. Cell Physiol Biochem 1999;9:227–41.
[9] Rizvi S, Raza ST, Rahman Q, et al. Role of GNB3, NET, KCNJ11, TCF7L2 and GRL genes single nucleotide polymorphism in the risk prediction of type 2 diabetes mellitus. Biotech 2016;6:255.
[10] Rasheed MA, Kantoush N, Elghaffar NA, et al. Expression of JAZF1, ABCC8, KCNJ11and Notch2 genes and vitamin D receptor polymorphisms in type 2 diabetes, and their association with microvascular complications. Ther Adv Endo Metab 2017;8:97–108.
[11] Rangaraju A, Krishnan S, Aparna G, et al. Genetic variants in post myocardial infarction patients presenting with electrical storm of unstable ventricular tachycardia. Ind Pacing Electrophy 2018;18: S0972629217301973.
[12] Jeron A, Hengstenberg C, Holmer S, et al. KCNJ11 polymorphisms and sudden cardiac death in patients with acute myocardial infarction. J Mol Cellular Cardiol 2004;36:287–93.
[13] Kane GC, Behfar A, Dyer RB, et al. KCNJ11 gene knockout of the Kir6.2 KATP channel causes maladaptive remodeling and heart failure in hypertension. Hum Mol Genet 2006;15:2285–97.
[14] Lenin M, Ramasamy R, Kulkarani S, et al. Association of KCNJ11 (RS5219) gene polymorphism with biochemical markers of glycemic status and insulin resistance in gestational diabetes mellitus. Meta Gene 2018;16.
[15] Koo BK, Cho YM, Park BL, et al. Polymorphisms of KCNJ11 (Kir6.2 gene) are associated with Type 2 diabetes and hypertension in the Korean population. Diabet Med 2010;24:178–86.
[16] Han Y, Wang L, Zhang L, et al. Association between potassium channel SNPs and essential hypertension in Xinjiang Kazak Chinese patients. Exper Ther Med 2017;14:1999–2006.
[17] Jiayue L, Zongbin L, Mei Z, et al. Mutational analysis of KCNJ11 in Chinese elderly essential hypertensive patients. J Geriat Cardiol 2012;9:153–7.
[18] Isakova ZT, Talaibekova ET, Asambaeva DA, et al. Association of the polymorphic marker Glu23Lys in the KCNJ11 gene with hypertension in Kyrgyz patients. Terapevticheskii Arkhiv 2017;89:14–7.
[19] Fernandez-Fernandez JM, Tomas M, Vazquez E, et al. Gain-of-function mutation in the KCNMB1 potassium channel subunit is associated with low prevalence of diastolic hypertension. J Clin Invest 2004;113:1032–9.
[20] Gollasch M, Tank J, Luft FC, et al. The BK channel beta1 subunit gene is associated with human baroreflex and blood pressure regulation. J Hypertens 2002;20:927–33.
[21] Zhao Q, Wang L, Yang W, et al. Interactions among genetic variants from contractile pathway of vascular smooth muscle cell in essential hypertension susceptibility of Chinese Han population. Pharmacogenet Genomics 2008;18:459–66.
[22] Wang LJ, Zhang WW, Qian YF, et al. Association between KCNMB1 polymorphism and essential hypertension in Xinjiang Kazak population. J Xi'an Jiaotong Univ (Med Sci) 2016;37:78–81.
[23] Wang LJ, Zhang WW, Zhang L, et al. Correlation analysis betw een KCNJll polymorphism and essential hypertension in Kazakh from Xinjiang. J Pract Med 2016;32:894–6.
[24] Nielsen T, Burgdorf KS, Grarup N, et al. The KCNMB1 Glu65Lys polymorphism associates with reduced systolic and diastolic blood pressure in the Inter99 study of 5729 Danes. J Hyperten 2008;26:2142.
[25] Boccia S. PRISMA: an attempt to improve standards for reporting systematic review and meta-analysis. Epidemiol Biostat Pub Health 2009;6:E382.
[26] Wells GA, Shea BJ, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. Appl Eng Agricul 2012;18:727–34.
[27] Hansen JB. Towards selective Kir6.2/SUR1 potassium channel openers, medicinal chemistry and therapeutic perspectives. Curr Med Chem 2006;13:361–76.
[28] Ko JM, Yang S, Kim SY, et al. E23K polymorphism of the KCNJ11gene in Korean children with type 1 diabetes. World J Pediatr 2012;8:169–72.
[29] Jeron A, Hengstenberg C, Holmer S, et al. KCNJ11 polymorphisms and sudden cardiac death in patients with acute myocardial infarction. J Mol Cellular Cardiol 2004;36:290–3.
[30] Yokoshiki H, Sunagawa M, Seki T, et al. ATP-sensitive K + channels in pancreatic, cardiac, and vascular smooth muscle cells. Am J Physiol 1998;274:25–37.
[31] Minami K, Miki T, Kadowaki T, et al. Roles of ATP-sensitive K + channels as metabolic sensors: studies of Kir6.x null mice. Diabetes 2004;53:S176–80.
[32] Miki T, Liss B, Minami K, et al. ATP-sensitive K+ channels in the hypothalamus are essential for the maintenance of glucose homeostasis. Nat Neurosci 2001;4:507–12.
[33] Lorca RA, Stamnes SJ, Pillai MK, et al. N-terminal isoforms of the large-conductance Ca2-activated K+ channel are differentially modulated by the auxiliary β1-subunit. J Bio Chem 2014;289:10095.
[34] Kun A. NS11021, a novel opener of large-conductance Ca(2+)-activated K(+) channels, enhances erectile responses in rats. British J Pharmacol 2010;158:1465–76.
[35] Tomás M, Vázquez E, Fernándezfernández JM, et al. Genetic variation in the KCNMA1 potassium channel alpha subunit as risk factor for severe essential hypertension and myocardial infarction. J Hyperten 2008; 26:2147.
[36] Torres YP, Morera FJ, Carvacho I, et al. A marriage of convenience: beta-subunits and voltage-dependent K+ channels. J Biologi Chem 2007;282:24485–9.