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Association between *KCNE1 G38S* gene polymorphism and risk of atrial fibrillation

A PRISMA-compliant meta-analysis

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Abstract

Background: Previous case-control studies on association between KCNE1 G38S polymorphism and risk of atrial fibrillation (AF) have been published but because of the conflicting results and small sample size of individual studies, the consolidated result is still controversial.

Objectives: The aim of this study was to explore the relationship between KCNE1 G38S polymorphism and risk of AF.

Methods: We performed a comprehensive literature search on PubMed, Embase, OVID, Web of Science, Wan Fang, and CNKI databases up to March 10, 2017 in English and Chinese languages. Two of the authors individually extracted study data and assessed the study quality using Newcastle-Ottawa scale. Odds ratios (ORs) and 95% confidence intervals (CIs) were combined in different genetic models for evaluation using a random-effect model or fixed-effect model according to interstudy heterogeneity.

Results: There were totally 14 independent case-control studies of 2810 patients and 3080 healthy controls included. Significant associations were found between KCNE1 G38S polymorphism and AF in overall population under all genetic models: allelic (OR: 1.34, 95% CI: 1.24–1.45, $P < .001$), homozygous (OR: 1.90, 95% CI: 1.61–2.24, $P < .001$), heterozygous (OR: 1.43, 95% CI: 1.21–1.68, $P < .001$), recessive (OR: 1.42, 95% CI: 1.20–1.69, $P < .001$), dominant genetic model (OR: 1.62, 95% CI: 1.39–1.89, $P < .001$). Subgroup analyses indicated similar association in Chinese and white.

Conclusions: The G38S polymorphism in the KCNE1 gene can significantly increase the risk of AF in both Chinese and white.

Abbreviations: CI = confidence interval, HB = hospital-based, HWE = Hardy–Weinberg equilibrium, I_{Ks} = slowly activating delayed rectifier potassium current, NOS = Newcastle-Ottawa scale, OR = odds ratio, PB = population-based, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, RAF = risk allele frequency.

Keywords: atrial fibrillation, G38S, gene, KCNE1, polymorphism

1. Introduction

Atrial fibrillation (AF) occupies the leading position of sustained tachyarrhythmia with an increasing prevalence in human,[1] which is associated with stroke, myocardial infarction, and heart failure and brings large economic burden to the patients' families and the society.[2,3] However, the pathogenesis of AF has not been fully clarified. Age, male sex, hypertension, ischemic heart disease, heart failure, valvular heart diseases, obesity, diabetes, hyperthyroidism, smoking, alcohol abuse, and pulmonary diseases are recognized as risk factors in the development of AF.[4] However, some AF patients younger than 60 years without common risk factors are considered as having lone AF.[5]

With the rapid development of sequencing technology, much progress has been made in genetic investigation on AF. The role of genetics is becoming robust. Recently, a great number of rare variants in specific genes has been detected to be associated with AF.[6] There have been >30 genes encoding proteins regarding to AF published so far. Currently, plenty of studies indicated that mutations in ion channel genes increased the risk of AF.[7] It has been indicated that loss-of-function potassium channel mutations can result in prolongation of atrial action potentials, which is associated with early afterdepolarizations and AF.[8] Mutations in such genes are likely to be associated with disease causality or susceptibility and sometimes present clear family segregation.[9,10] Understanding its genetic background is important for better personalized management in the near future.[11,12]

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Y-FJ and MC contributed equally to this work. Y-FJ and Y-FZ designed the study. Y-FJ, MC, N-NZ, and H-JY did the literature search, data extraction, statistical analysis, and drafted the figures. Y-FJ wrote the first draft of the report, and L-BX, QR, S-JS, J-LY, and Y-FZ helped to write the final version. All authors read and met the ICMJE criteria for authorship. All authors agree with the results and conclusions of the report.

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Studies in recent years have repeatedly reported that $K_V7.1$, the α-subunit of the slowly activating delayed rectifier potassium current (I_{Ks}) current, is involved in the pathogenesis of AF.[13] The $K_V7.1$ channel could significantly change its biophysical properties through co-expression of regulatory β-subunits attributing to *KCNE1* gene.[14] In 1989, Murai et al[15] first discovered *KCNE1* gene, which is located in the 21q22.1-22.2 region. The β-subunits of I_{Ks} encoded by KCNE1 contain 130 amino acids, which was also termed as Mink protein. The functional G38S polymorphism (A >G) of *KCNE1* gene results in a serine to glycine substitution.[16] Based on these, KCNE1 may be a promising biomarker for assessing the risk of AF.

For the past 10 years, many case-control designed studies[17–30] regarding *KCNE1* G38S polymorphism and AF have been published, but because of the low statistical power and small sample size of individual studies, the consolidated result is still controversial. Among the 14 studies, 8 of them[17,19,20,24–26,28,29] reported association between KCNE1 G38S polymorphism and risk of AF, whereas the other 6 studies[18,21–23,27,30] reported no significant association. So we conducted the present meta-analysis to evaluate the association between KCNE1 G38S polymorphism and AF.

2. Methods

We performed our meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[31] Since our meta-analysis was based on previously published studies, the ethical approval and patient consent were not required.

2.1. Search strategy

We performed a systematic computerized literature search of to identify relevant articles in PubMed, Embase, OVID, Web of Science, Wan Fang, and CNKI databases up to March 10, 2017, combined with a manual search of reference lists from identified articles in English and Chinese languages. The following combination of medical subject headings or suitable key words was used in the literature search: AF, G38S, rs1805127, KCNE1, polymorphism, variant, and mutation. We have also searched the references of relevant review articles and of all the obtained case-control studies individually to discover possible eligible studies (Supplementary Digital Content http://links.lww.com/MD/B758).

2.2. Selection and exclusion criteria

We have pre-established criteria to elaborate the selection for studies obtained in this meta-analysis. The inclusion criteria were: studies with case-control designs; studies investigated the association of the KCNE1 G38S polymorphism and susceptibility to AF; studies that provided sufficient data to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for extraction. The criteria for exclusion were: studies that provided too limited data for extraction; review articles, abstracts-only articles, meta-analyses, and unpublished studies; inclusion of data duplicated in other studies.

2.3. Data extraction

Two of the authors (Y-FJ, MD, and MC, MD) individually extracted all useful data of each study involving in this meta-analysis. Conflicts were discussed with a third investigator (Y-FZ, PhD). Extraction of study data includes: author; publication year; country of the work established, ethnicities, number of patients and control individuals, source of controls, genotyping method, and genotypes distribution. We made attempts to contact the original authors for detailed information if the data were incomplete or missing in the publication. Study quality was evaluated according to the 9-point Newcastle-Ottawa Scale (NOS).[32]

2.4. Statistical analysis

For each study included in this meta-analysis, we performed Hardy–Weinberg equilibrium (HWE) tests for evaluation of included populations. We investigate the strength of the associations between KCNE1 G38S polymorphism and susceptibility to AF by combining ORs and 95% 95% CIs under a fixed or random-effect model according to the quantification of the heterogeneity calculated with the I^2 test. I^2 ranges between 0 to 100% and represents the extent of interstudy heterogeneity. A random-effect model (Der Simonian and Laird method) for pooled analysis should be adopted when I^2 >50% indicating heterogeneity among studies. Otherwise the fixed-effect model (Mantel-Haenszel method) should be used. We also performed subgroup analyses to identify the possible underlying heterogeneity according to ethnicity, study sample size, source of control, and genotyping methods. The overall and subgroup analyses were both conducted in 5 genetic models: allele (G allele distribution frequency of KCNE1 gene G38S polymorphism), homozygote model (GG vs. AA), heterozygote model (AG vs. AA), recessive model (GG vs. AG+AA) and dominant model (GG+AG vs. AA), respectively. Sensitivity analysis was performed by combining ORs repeatedly with omission of each study to identify potential alternation of the overall meta result. We have also investigated publication bias via calculating Egger test and drawing Begg funnel plot. $P>.05$ was considered that there was no statistically significant bias of publication. Meta-analysis was performed using Stata version 14.0 (Stata Corporation).

3. Results

3.1. Study characteristics

The search of the 6 databases identified 162 records in total. After removing duplicated studies, there were 58 studies left for screening and 37 of records were excluded. Twenty-one studies were read by full-text, and 7 of full-text articles were excluded because of unmatched study design (n=4), insufficient data (n=1), and not relevant to AF (n=2). Figure 1 shows the complete procedure of the study selection and exclusion. There were eventually 14 studies[17–30] of 2810 cases and 3080 controls eligible for this meta-analysis on the relationship between *KCNE1* gene G38S polymorphism and AF. Characteristics of the studies included for meta-analysis are shown in Table 1. Four[18,23,24,27] of these articles were published in Chinese and 10[17,19–22,25,26,28–30] in English. The sample sizes ranged from 130 to 888 of all eligible studies. The races of the included studies were Chinese (n=11) and white (n=4). All the included studies except Andrzej et al[20] fitted in with the HWE test. The results of NOS are shown in Table 2. The NOS of all eligible studies in our meta-analysis was >6 points, representing a good study quality. Genotype distribution and allele frequency in cases and controls of each study are shown in Table 3.

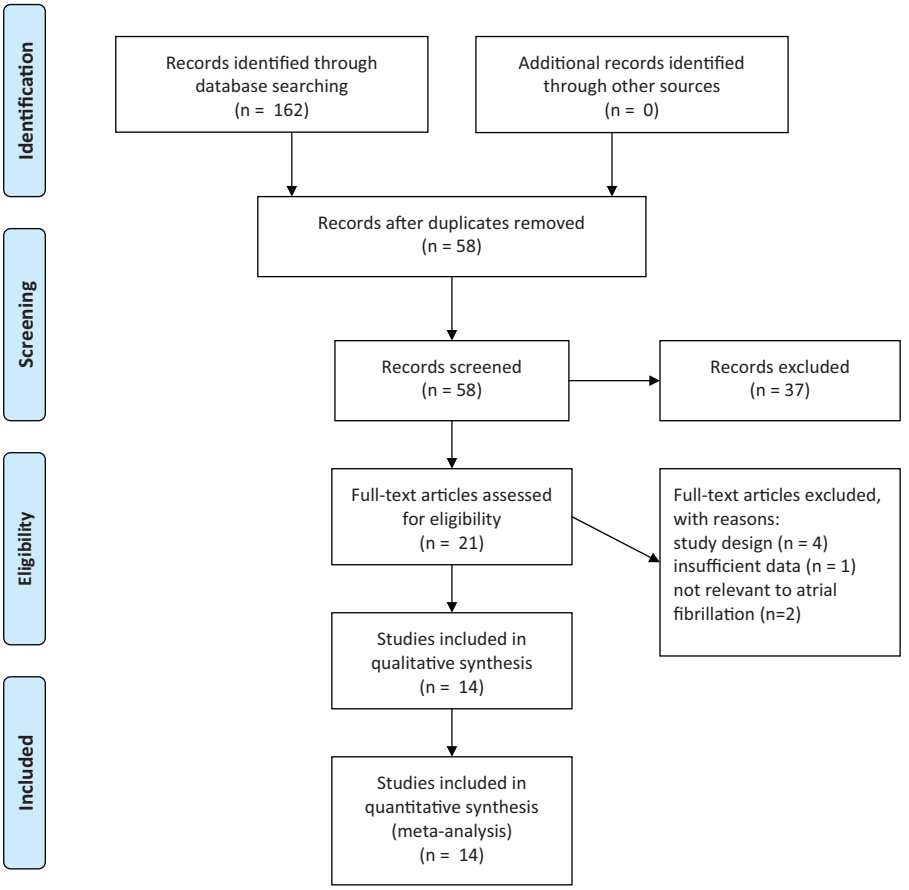

Figure 1. The PRISMA flow diagram of the study selection and exclusion.

3.2. Quantitative synthesis

The present meta-analysis indicated significant association between *KCNE1* gene G38S polymorphism and AF under allelic (OR: 1.34, 95% CI: 1.24–1.45, $P<.001$, $P_{heterogeneity}=.06$), homozygous (OR: 1.90, 95% CI: 1.61–2.24, $P<.001$, $P_{heterogeneity}=.15$), heterozygous (OR: 1.43, 95% CI: 1.21–1.68, $P<.001$, $P_{heterogeneity}=.60$), recessive (OR: 1.42, 95% CI: 1.20–1.69, $P<.001$, $P_{heterogeneity}=.01$), dominant genetic model (OR: 1.62, 95% CI: 1.39–1.89, $P<.001$, $P_{heterogeneity}=.71$) in the whole population (Fig. 2).

In the subgroup analyses by ethnicity (Fig. 3), the association grew stronger with higher ORs in white under all genetic models:

Table 1

Characteristics of the studies included for meta-analysis.

Author	Year	Country	Ethnicity	Age, y		Sex (M/F)		Comorbidities	Source of controls	Genotyping method	Polymorphism	NOS score	HWE test
				Case	Control	Case	Control						
Lai et al[17]	2002	China	Asian	63.4 (11.5)	63.4 (11.5)	59/49	59/49	HTN, diabetes, CAD	HB	PCR–RFLP	G38S	7	0.19
Ni et al[18]	2004	China	Asian	55.0 (7.5)	54.0 (7.0)	63/31	87/43	None	PB	Direct sequencing	G38S	8	0.62
Fatini et al[19]	2006	Italy	Caucasian	72.9 (9.2)	72.3 (10.6)	198/133	258/183	HTN, diabetes, CAD	HB	PCR–RFLP	G38S	8	0.20
Prystupa et al[20]	2006	Poland	Caucasian	55.0 (10.0)	53.0 (9.0)	32/37	21/40	None	PB	PCR–RFLP	G38S	8	<0.001
Lou et al[21]	2006	China	Asian	65.5 (13.2)	49.3 (8.5)	63/48	57/44	HTN, diabetes, CAD	PB	Direct sequencing	G38S	8	0.01
Zeng et al[22]	2007	China	Asian	59.0 (15.2)	55.9 (10.2)	95/47	41/79	HTN, diabetes, CAD	PB	PCR–RFLP	G38S	8	0.66
Xu et al[23]	2008	China	Asian	65.7 (13.1)	65.5 (11.8)	86/61	89/58	HTN, diabetes, CAD	HB	PCR–RFLP	G38S	7	0.27
Yao et al[24]	2011	China	Asian	63.4 (11.3)	63.6 (5.8)	164/139	178/150	HTN, diabetes, CAD	HB	PCR–RFLP	G38S	8	0.40
Yao et al[25]	2012	China	Asian	63.3 (11.3)	63.5 (5.7)	165/142	177/153	HTN, diabetes, CAD	HB	PCR–RFLP	G38S	8	0.15
Miao et al[26]	2012	China	Asian	67.3 (10.3)	67.4 (10.2)	144/93	144/93	HTN, diabetes, CAD	HB	PCR–RFLP	G38S	8	0.11
Mao et al[27]	2013	China	Asian	65.2 (9.7)	65.2 (9.7)	153/98	153/98	HTN, diabetes, CAD	HB	Direct sequencing	G38S	8	0.96
Voudris et al[28]	2014	UK	Caucasian	64.0 (9.0)	68.0 (10.0)	264/42	169/34	HTN, diabetes, CAD, renal failure	HB	Direct sequencing	G38S	8	0.22
Wugeti et al[29]	2015	China	Asian	65.3 (4.2)	62.3 (7.4)	48/22	48/22	HTN, diabetes, CAD	HB	Direct sequencing	G38S	7	0.99
Li et al[30]	2015	China	Asian	72.9 (5.3)	73.2 (6.6)	237/201	246/204	HTN, diabetes, CAD	HB	PCR–RFLP	G38S	8	0.36

Case-control design was used in all the included studies. CAD = coronary artery disease, HB = hospital-based, HTN = hypertension, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle-Ottawa scale, PB = population based, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, year = publication year.

Table 2

The results of Newcastle-Ottawa Scale.

	Selection	Comparability	Exposure
Lai et al[17]	★★★	★★	★★
Ni et al[18]	★★★★	★★	★★
Fatini et al[19]	★★★	★★	★★★
Prystupa et al[20]	★★★★	★★	★★
Lou et al[21]	★★★★	★★	★★
Zeng et al[22]	★★★★	★★	★★
Xu et al[23]	★★★	★★	★★
Yao et al[24]	★★★	★★	★★★
Yao et al[25]	★★★	★★	★★★
Miao et al[26]	★★★	★★	★★★
Mao et al[27]	★★★	★★	★★★
Voudris et al[28]	★★★	★★	★★★
Wugeti et al[29]	★★★	★★	★★
Li et al[30]	★★★	★★	★★★

allelic (OR: 1.49, 95% CI: 1.28–1.73, $P<.001$, $P_{heterogeneity}=.18$), homozygous (OR: 2.76, 95% CI: 1.38–5.54, $P=.01$, $P_{heterogeneity}=.04$), heterozygous (OR: 1.51, 95% CI: 1.13–2.04, $P=.006$, $P_{heterogeneity}=.99$), recessive (OR: 2.03, 95% CI: 1.12–3.68, $P=.02$, $P_{heterogeneity}=.01$), dominant genetic model (OR: 1.75, 95% CI: 1.32–2.31, $P<.001$, $P_{heterogeneity}=.81$). In the Chinese subgroup, we also found significant association under allelic (OR: 1.30, 95% CI: 1.19–1.42, $P<.001$, $P_{heterogeneity}=.11$), homozygous (OR: 1.77, 95% CI: 1.45–2.16, $P<.001$, $P_{heterogeneity}=.41$), heterozygous (OR: 1.39, 95% CI: 1.14–1.69, $P=.001$, $P_{heterogeneity}=.36$), recessive (OR: 1.34, 95% CI: 1.13–1.59, $P=.001$, $P_{heterogeneity}=.04$), dominant genetic model (OR: 1.57, 95% CI: 1.31–1.88, $P<.001$, $P_{heterogeneity}=.54$). In summary, our meta-analysis suggested that G38S polymorphism in the *KCNE1* gene significantly increase the risk of AF, particularly in white. We also conducted subgroup analyses according to source of control, sample size, and genotyping method. The detailed information was presented in Table 4. Similar association was indicated in both Chinese and white. Similar association was observed in each subgroup that G38S polymorphism in the *KCNE1* gene significantly increase the risk of AF.

3.3. Sensitivity analysis

We conducted the sensitivity analysis to discover whether the omission of each study will alter the pooled ORs quantitatively. As shown in Figure 4, no altered results are shown after the individual study was omitted, which provided reliable evidence to prove the increased risk of the KCNE1 G38S polymorphism to AF susceptibility (Fig. 4).

3.4. Publication bias

When performing a meta-analysis, publication bias is no doubtfully a common problem to be addressed. In our meta-analysis, we calculated Egger test and drew the Begg funnel plot to assess the publication bias. Visually from the Begg funnel plot (Fig. 5), we could see all the 14 studies were symmetrically distributed on the 2 sides, which indicated no publication bias in our meta-analysis (Egger test: $P=.08$).

4. Discussion

To date, many case-control studies focusing on the relationship between KCNE1 G38S polymorphism and risk of AF have been published, but the results remain controversial. Of the 14 studies included in our study, 8 studies[17,19,20,24–26,28,29] reported association between KCNE1 G38S polymorphism and risk of AF, whereas the other 6 studies[18,21–23,27,30] reported no significant association. Because of the conflicting results and small sample size of individual studies, the consolidated result is still controversial. Therefore, we conducted the present meta-analysis to investigate the relationship between KCNE1 G38S polymorphism and risk of AF.

Our meta-analysis consolidated 14 eligible studies on the KCNE1 G38S polymorphism and the relationship of AF. All of the results indicated that the KCNE1 G38S polymorphism would increase the risk of AF. Furthermore, subgroup analyses showed a higher risk of having AF in subjects with the risk allele in the white population, than in the Chinese population. Stratified analysis by ethnicity, sample size, source of control, and genotyping method presented the same situation. Although one study[20] did not fit the HWE test in the control group, omission of this study during the sensitivity analysis did not alter

Table 3

KCNE1 G38S polymorphism genotype distribution and allele frequency in cases and controls.

	Genotype (N)								Allele frequency (N, %)					
	Cases				Controls				Cases			Controls		
Author	Total	GG	AG	AA	Total	GG	AG	AA	G	A	RAF	G	A	RAF
Lai et al[17]	108	64	37	7	108	46	44	18	165	51	0.76	136	80	0.63
Ni et al[18]	94	54	37	3	130	72	48	10	145	43	0.77	192	68	0.74
Fatini et al[19]	331	118	155	58	441	116	207	118	391	271	0.59	439	443	0.50
Prystupa et al[20]	69	24	38	7	61	3	45	13	86	52	0.62	51	71	0.42
Lou et al[21]	111	63	41	7	101	60	29	12	167	55	0.75	149	53	0.74
Zeng et al[22]	141	71	60	10	120	55	54	11	202	80	0.72	164	76	0.68
Xu et al[23]	147	77	61	9	147	75	56	16	215	79	0.73	206	88	0.70
Yao et al (2011)[24]	303	158	117	28	328	129	159	40	433	173	0.71	417	239	0.64
Yao et al (2012)[25]	307	133	138	36	330	118	148	64	404	210	0.66	384	276	0.58
Miao et al[26]	237	96	103	38	237	72	106	59	295	179	0.62	250	224	0.53
Mao et al[27]	251	122	98	31	251	116	109	26	342	160	0.68	341	161	0.68
Voudris et al[28]	203	76	103	24	306	88	162	56	255	151	0.63	338	274	0.55
Wugeti et al[29]	70	39	19	12	70	18	35	17	97	43	0.69	71	69	0.51
Li et al[30]	438	175	224	39	450	169	221	60	574	302	0.66	559	341	0.62

Case-control design was used in all the included studies. RAF = risk allele frequency, risk allele = G allele.

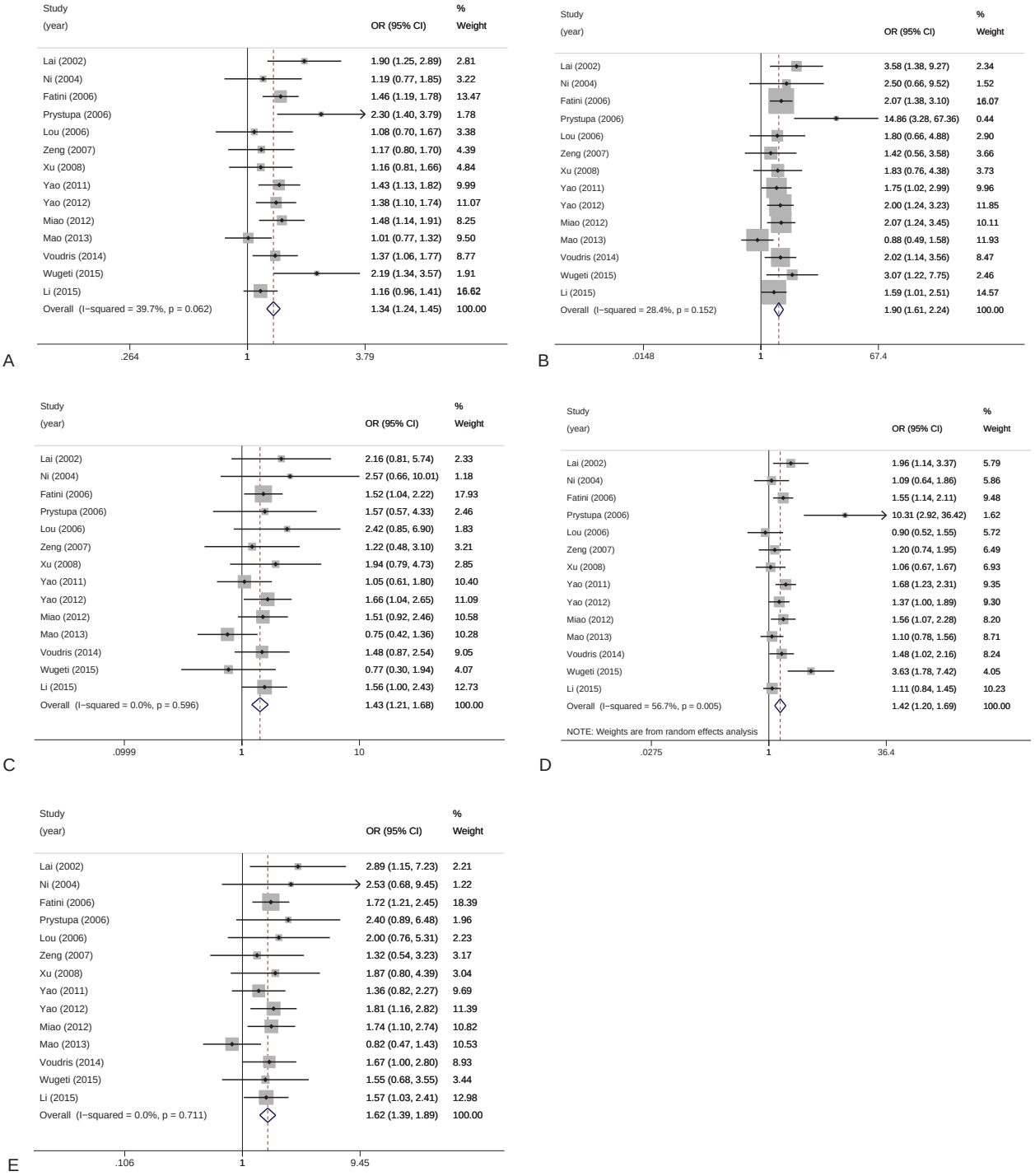

Figure 2. Forest plot from the meta-analysis on the association of the KCNE1 G38S polymorphism and AF risk in (A) allele model: G vs. A; (B) homozygote model: GG vs. AA; (C) heterozygote model: AG vs. AA; (D) recessive model: GG vs. AG + AA; and (E) dominant model: GG + AG vs. AA. AF = atrial fibrillation, CI = confidence interval, OR = odds ratio.

the conclusions made in the meta-analysis. No publication bias was observed in our meta-analysis.

At present, the pathogenesis of AF has not been fully recognized. Lone AF may be associated with irregular ionic currents, whereas acquired AF is usually caused by atrial structural remodeling. Mutation in genes encoding the ion channel was considered as the pathologic factor of AF that reduced the I_{Ks}.[33] Evidence showed *KCNE1* gene encoding the I_{Ks} channel contributed to AF.[34] On the term of physiology, cardiac I_{Ks} channel is involved in the atrial repolarization, especially in the terminal stage of action potential, which can result in shortening of the frequency-dependent action potential time interval and electricity remodeling of the atrial tissue. Chen et al[35] found that the onset or maintenance of AF was related to

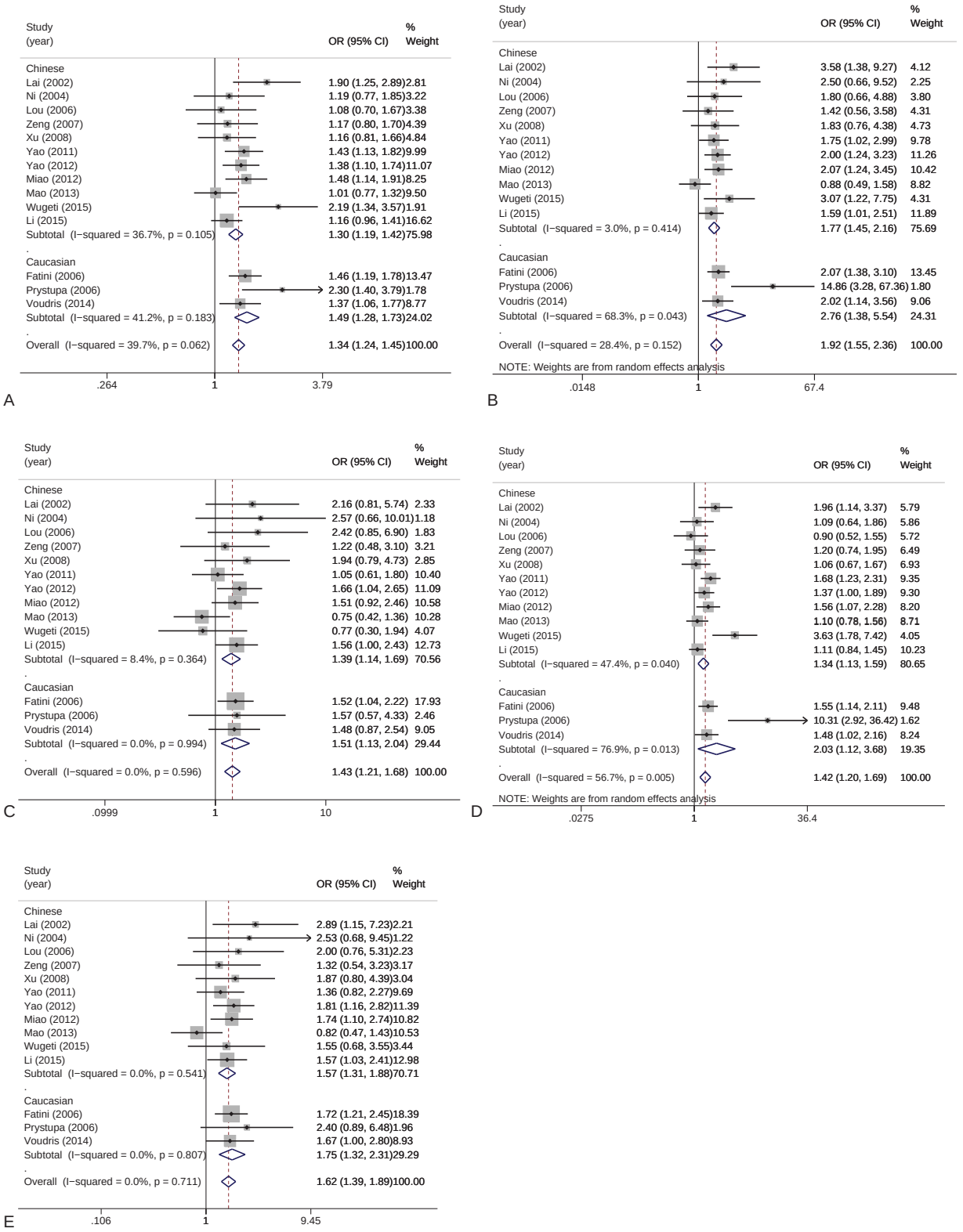

Figure 3. Subgroup meta-analysis by ethnicity of the relationship between the KCNE1 G38S polymorphism and AF risk in (A) allele model: G vs. A; (B) homozygote model: GG vs. AA; (C) heterozygote model: AG vs. AA; (D) recessive model: GG vs. AG + AA and (E) dominant model: GG + AG vs. AA. AF = atrial fibrillation, CI = confidence interval, OR = odds ratio.

the arrhythmia matrix formed by interaction of proteins encoded by KCNE1 G38S and other proteins. Accordingly, the *KCNE1* gene plays an important role in regulating cardiac rhythm.[36]

Understanding the genetic background is important for better personalized management in the near future. First, the KCNE1 G38S polymorphism can be used together with other related

Table 4

Subgroup analyses of association between KCNE1 G38S polymorphism and atrial fibrillation.

Subgroup		Number	Odds ratio	95% Confidence interval	*P*	I^2 (%)
Allele model						
Source of control	HB	10	1.35	(1.24, 1.46)	<.001	41.3
	PB	4	1.34	(0.98, 1.83)	.07	51.6
Sample size	≥300	7	1.32	(1.21, 1.44)	<.001	24.8
	<300	7	1.46	(1.16, 1.85)	.002	53.3
Genotyping method	PCR–RFLP	9	1.38	(1.26, 1.51)	<.001	31.5
	Direct sequencing	5	1.27	(1.01, 1.61)	.043	53.1
Homozygote model						
Source of control	HB	10	1.17	(1.09, 1.25)	<.001	57.5
	PB	4	1.15	(1.08, 1.22)	.19	65.9
Sample size	≥300	7	1.16	(1.07, 1.27)	<.001	64.5
	<300	7	1.14	(1.03, 1.26)	.01	60.9
Genotyping method	PCR–RFLP	9	1.17	(1.09, 1.27)	<.001	56.7
	Direct sequencing	5	1.10	(1.00, 1.22)	.06	58.1
Heterozygote model						
Source of control	HB	10	1.39	(1.18, 1.65)	<.001	2.8
	PB	4	1.76	(1.04, 2.97)	.04	0.0
Sample size	≥300	7	1.39	(1.16, 1.66)	<.001	5.8
	<300	7	1.61	(1.11, 2.34)	.01	0.0
Genotyping method	PCR–RFLP	9	1.51	(1.25, 1.81)	<.001	0.0
	Direct sequencing	5	1.43	(1.21, 1.68)	.27	41.3
Recessive model						
Source of control	HB	10	1.41	(1.26, 1.58)	<.001	46.0
	PB	4	1.48	(0.78, 2.82)	.23	76.2
Sample size	≥300	7	1.39	(1.25, 1.55)	<.001	11.2
	<300	7	1.63	(1.05, 2.52)	.03	74.3
Genotyping method	PCR–RFLP	9	1.46	(1.20, 1.78)	<.001	55.4
	Direct sequencing	5	1.35	(0.94, 1.94)	.11	65.2
Dominant model						
Source of control	HB	10	1.59	(1.36, 1.87)	<.001	0.0
	PB	4	1.92	(1.16, 3.17)	.01	0.0
Sample size	≥300	7	1.55	(1.31, 1.84)	<.001	7.1
	<300	7	1.96	(1.38, 2.79)	<.001	0.0
Genotyping method	PCR–RFLP	9	1.71	(1.43, 2.03)	<.001	0.0
	Direct sequencing	5	1.38	(1.02, 1.88)	.04	25.6

HB = hospital-based, PB = population based, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

polymorphisms for risk stratification of developing AF.[37] People with high genetic risk scores are at approximately twice incidence of AF and 23% increased risk of stroke. Second, specific polymorphisms are associated with recurrence of AF after catheter ablation.[38,39] Identification of these polymorphisms helps to determine the optimized therapy for individuals to receive ablation or drug therapy. Third, genetic risk scores for stroke in AF patients can guide clinicians on anticoagulant therapy.

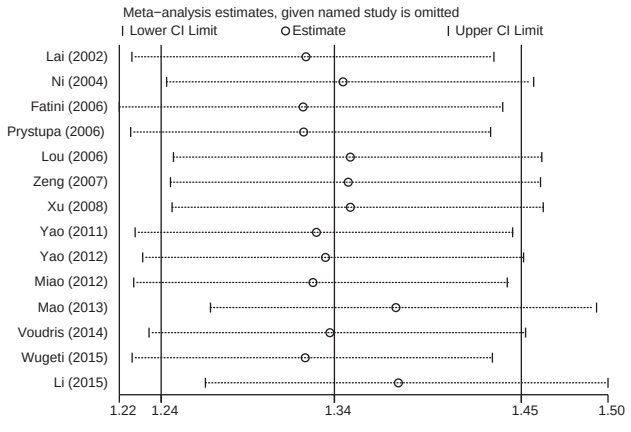

Figure 4. Sensitivity analysis of the pooled OR coefficients on the relationship between KCNE1 G38S polymorphism and AF risk. AF = atrial fibrillation, CI = confidence interval, OR = odds ratio.

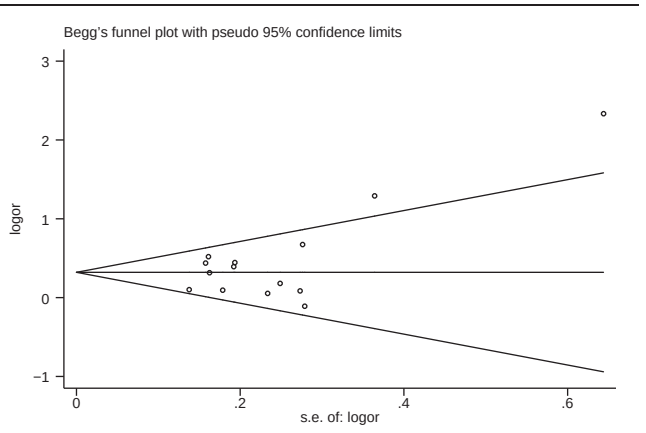

Figure 5. Begg funnel plot with pseudo 95% confidence limits in recessive model.

In recent years, preclinical studies regarding genetic therapy on AF have been carried out. The key procedure of genetic therapy includes targeted delivery, tissue specificity, and functional expression.[40] With the development of genetic therapy, we will gain more treatment options for AF. However, many aspects remain unknown. For example, how to ensure the inherent safety of genetic therapy in modifying the myocardium? How would the genetic material be delivered? Such issues should have been addressed before genetic therapy would be implemented in clinical practice.

Our meta-analysis did have some limitations. First, one study did not fit the HWE test in the control group. After omission of this study during the sensitivity analysis, it did not alter the conclusions made in the meta-analysis. Second, all of the 14 studies included in this meta-analysis were written in English and Chinese, so studies in other languages and possible unpublished articles did not attend this meta-analysis, which may cause selection bias. Third, there were no studies including Africans. Fourth, the genetic susceptibility may also depend on the coincidence of several gene polymorphisms acting together, which may influence the results.

By performing this meta-analysis, we finally concluded that the G38S polymorphism in the *KCNE1* gene significantly increases the risk of AF in both Chinese and white. As a variant in the potassium ion channel, it could be a promising loci for genetic therapy in the clinical management of AF in the future and more case-control studies need to be carried out to further validate and strengthen the conclusion of this meta-analysis.

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