Association between KCNE1 G38S gene polymorphism and risk of atrial fibrillation
A PRISMA-compliant meta-analysis

Yu-Feng Jiang, MDa, Min Chen, MDa, Nan-Nan Zhang, MDa, Hua-Jia Yang, MDa, Lang-Biao Xu, MDa, Qing Rui, MDa, Si-Jia Sun, MDa, Jia-Lu Yao, MDa, Ya-Feng Zhou, PhDa,b

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), 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, $\kappa_0$ = 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, 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]
Studies in recent years have repeatedly reported that Kv7.1, the α-subunit of the slowly activating delayed rectifier potassium current (Ikr) current, is involved in the pathogenesis of AF. The Kv7.1 channel could significantly change its biophysical properties through co-expression of regulatory β-subunits attributing to KCNE1 gene. In 1989, Murari et al. first discovered KCNE1 gene, which is located in the 21q22.1-22.2 region. The β-subunits of Ikr, 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. 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 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 reported association between KCNE1 G38S polymorphism and risk of AF, whereas the other 6 studies 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). 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).

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% CIs under a fixed or random-effect model according to the quantification of the heterogeneity calculated with the I² test. I² 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 I² > 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 (GA vs. AA), recessive model (GG vs. GG+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 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 of these articles were published in Chinese and the rest 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. 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.
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, \( P < .001 \), \( \text{P heterogeneity} = .06 \)), homozygous (OR: 1.90, 95% CI: 1.61–2.24, \( P < .001 \), \( \text{P heterogeneity} = .15 \)), heterozygous (OR: 1.43, 95% CI: 1.21–1.68, \( P < .001 \), \( \text{P heterogeneity} = .60 \)), recessive (OR: 1.42, 95% CI: 1.20–1.69, \( P < .001 \), \( \text{P heterogeneity} = .001 \)), dominant genetic model (OR: 1.62, 95% CI: 1.39–1.89, \( P < .001 \), \( \text{P heterogeneity} = .71 \)) 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**

| Author       | Year | Country | Ethnicity | Age, y | Case | Control | Case | Control | Comorbidities | Source of controls | Genotyping method | Polymorphism | NOS score | HWE test |
|--------------|------|---------|-----------|--------|------|---------|------|---------|---------------|-----------------|-----------------|--------------|-----------|----------|
| 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      |
| Lou et al[20]| 2006 | China   | Asian     | 65.5 (13.2) | 49.3 (8.9)  | 63/48 | 57/44 | HTN, diabetes, CAD | PB              | PCR-RFLP         | G38S         | 8          | <0.001    |
| Zeng et al[21]| 2007| China  | Asian     | 59.0 (15.2) | 55.9 (10.2) | 95/47  | 41/79 | HTN, diabetes, CAD | PB              | Direct sequencing | G38S         | 8          | 0.01      |
| Xu et al[22]| 2008 | China   | Asian     | 65.7 (13.1) | 65.5 (11.8) | 86/61  | 89/58 | HTN, diabetes, CAD | PB              | PCR-RFLP         | G38S         | 7          | 0.27      |
| Yao et al[23]| 2011 | China   | Asian     | 63.4 (11.3) | 63.6 (5.8)  | 164/139 | 176/150 | HTN, diabetes, CAD | HB              | PCR-RFLP         | G38S         | 8          | 0.40      |
| Yao et al[24]| 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      |
| Wang et al[25]| 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[26]| 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[27]| 2014| UK     | Caucasian | 64.0 (8.0)  | 68.0 (10.0) | 26/42  | 169/34 | HTN, diabetes, CAD | HB              | Direct sequencing | G38S         | 8          | 0.22      |
| Wang et al[28]| 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[29]| 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.
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: 1.31, 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} = .41), heterozygous (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.

### Table 2

| Selection | Comparability | Exposure |
|-----------|---------------|----------|
| **Lai et al** | 5 | 5 | 5 |
| **Ni et al** | 4 | 4 | 4 |
| **Fatimi et al** | 3 | 3 | 3 |
| **Prytupa et al** | 2 | 2 | 2 |
| **Lou et al** | 1 | 1 | 1 |
| **Zeng et al** | 4 | 4 | 4 |
| **Xu et al** | 3 | 3 | 3 |
| **Yao et al** | 5 | 5 | 5 |
| **Miao et al** | 4 | 4 | 4 |
| **Mao et al** | 3 | 3 | 3 |
| **Voudris et al** | 2 | 2 | 2 |
| **Wugeti et al** | 1 | 1 | 1 |
| **Li et al** | 4 | 4 | 4 |

### Table 3

| KCNE1 G38S polymorphism genotype distribution and allele frequency in cases and controls. |
|---------------------------------------------------------------|
| **Author** | **Cases** | **Controls** | **Allele frequency (N, %)** |
|-----------|-----------|-------------|-----------------------------|
| **Cases** | **Total** | **GG** | **AG** | **AA** | **Total** | **GG** | **AG** | **AA** | **G** | **A** | **RAF** | **G** | **A** | **RAF** |
| Lai et al | 108 | 64 | 37 | 7 | 108 | 46 | 44 | 18 | 165 | 51 | 0.76 | 136 | 80 | 0.63 |
| Ni et al | 95 | 54 | 37 | 3 | 130 | 72 | 48 | 10 | 145 | 43 | 0.77 | 192 | 68 | 0.74 |
| Fatimi et al | 331 | 118 | 155 | 58 | 441 | 116 | 207 | 118 | 391 | 271 | 0.59 | 439 | 443 | 0.50 |
| Prytupa et al | 69 | 24 | 38 | 7 | 70 | 18 | 35 | 17 | 86 | 52 | 0.62 | 51 | 71 | 0.42 |
| Lou et al | 111 | 63 | 41 | 7 | 101 | 60 | 29 | 12 | 167 | 55 | 0.75 | 149 | 53 | 0.74 |
| Zeng et al | 141 | 71 | 60 | 10 | 120 | 55 | 54 | 11 | 202 | 80 | 0.72 | 164 | 76 | 0.68 |
| Xu et al | 147 | 77 | 61 | 9 | 147 | 75 | 56 | 16 | 215 | 79 | 0.73 | 206 | 88 | 0.70 |
| Yao et al (2011) | 303 | 158 | 117 | 28 | 328 | 129 | 159 | 40 | 433 | 173 | 0.71 | 417 | 239 | 0.64 |
| Yao et al (2012) | 307 | 133 | 138 | 36 | 330 | 118 | 148 | 64 | 404 | 210 | 0.66 | 384 | 276 | 0.58 |
| Miao et al | 237 | 96 | 103 | 38 | 237 | 72 | 106 | 59 | 296 | 179 | 0.62 | 250 | 224 | 0.53 |
| Mao et al | 251 | 122 | 98 | 31 | 251 | 116 | 109 | 26 | 342 | 160 | 0.68 | 341 | 161 | 0.68 |
| Voudris et al | 203 | 76 | 103 | 24 | 306 | 88 | 162 | 56 | 255 | 151 | 0.63 | 338 | 274 | 0.55 |
| Wugeti et al | 70 | 39 | 19 | 12 | 70 | 18 | 35 | 17 | 97 | 43 | 0.69 | 71 | 69 | 0.51 |
| Li et al | 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.

### 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 doubt a commonly problem to be addressed. In our meta-analysis, we calculated Egger test and drew the Beg funnel plot to assess the publication bias. Visually from the Beg 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\(^{18,21–23,25,30}\) 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
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 $I_{\text{Ks}}$.

Evidence showed $\text{KCNE1}$ gene encoding the $I_{\text{Ks}}$ channel contributed to AF. On the term of physiology, cardiac $I_{\text{Ks}}$ 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.[33] found that the onset or maintenance of AF was related to atrial fibrillation, CI = confidence interval, OR = odds ratio.

### Figure 2.
Forest plot from the meta-analysis on the association of the $\text{KCNE1} \, G38S$ 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 KCNQ1 G38S and other proteins. Accordingly, the KCNQ1 gene plays an important role in regulating cardiac rhythm.  

Understanding the genetic background is important for better personalized management in the near future. First, the KCNQ1 G38S polymorphism can be used together with other related
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.

Table 4

| Subgroup                  | Number | Odds ratio | 95% Confidence interval | P     | I² (%) |
|---------------------------|--------|------------|--------------------------|-------|--------|
| **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, 1.82)             | .04   | 25.6   |

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

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. 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 clinical 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.

References

[1] Chugh SS, Havmoeller R, Narayan K, et al. Worldwide epidemiology of atrial fibrillation: A Global Burden of Disease 2010 Study. Circulation 2014;129:837–47.
[2] Schnabel RB, Yin X, Gona P, et al. 50 Year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. Lancet 2015;386:154–62.
[3] Levy S. Changing epidemiology of atrial fibrillation. Europace 2013;15:465–6.
[4] Nguyen TN, Hilmer SN, Cumming RG. Review of epidemiology and management of the genitourinary tract: from diagnosis to developing countries. Int J Cardiol 2013;167:2412–20.
[5] Fuster, Ryden L, Cannon DS, et al. [ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary]. Rev Port Pneumol 2007;26:383.
[6] Hucker WJ, Saini H, Lubitz SA, et al. Atrial fibrillation genetics: is there a practical clinical value now or in the future? Can J Cardiol 2016;32:1305–9.
[7] Ottway R, Vandenberg JL, Gao G, et al. Stretch-sensitive KCNQ1 mutation A link between genetic and environmental factors in the pathogenesis of atrial fibrillation? J Am Coll Cardiol 2007;49:578–86.
[8] Tucker NR, Ellinor PT. Emerging directions in the genetics of atrial fibrillation. Circ Res 2014;114:1469–82.
[9] Zhao LQ, Zhang GR, Wen ZJ, et al. Common variants predict recurrence after nonfamilial atrial fibrillation ablation in Chinese Han population. Int J Cardiol 2017;227:360–6.
[10] Gundlund A, Olesen JB, Stærk L, et al. Outcomes associated with familial versus nonfamilial atrial fibrillation: A Matched Nationwide Cohort Study. J Am Heart Assoc 2016;5:e003386.
[11] Kiliszek M, Kozuk E, Franaszczuk M, et al. The 4q25, 1q21, and 16q22 polymorphisms and recurrence of atrial fibrillation after pulmonary vein isolation. Arch Med Sci 2016;12:38–44.
[12] Roberts JD, Marcus GM. Ablatogenomics: can genotype guide catheter ablation for cardiac arrhythmias? Pharmacogenomics 2016;17:1931–40.
[13] Mahda S, Lubitz SA, Rienstra M, et al. Monogenic atrial fibrillation as pathophysiological paradigms. Cardiovasc Res 2011;89:692–700.
[14] Lundby A, Tseng GN, Schmitt N. Structural basis for K(V)7.1-KCNE(x) interactions in the I(Ks) channel complex. Heart Rhythm 2010;7:708–13.
[15] Murat T, Kakizuka A, Takumi T, et al. Molecular cloning and sequence analysis of human genomic DNA encoding A novel membrane protein which exhibits a slowly activating potassium channel activity. Biochem Biophys Res Commun 1993;198:1176–81.
[16] Lai LF, Deng CL, Moss AJ, et al. Polymorphism of the gene encoding a human minimal potassium ion channel (minK). Gene 1994;151:339–40.
[17] Lai L, Su M, Yeh H, et al. Association of the human minK gene 38G allele with atrial fibrillation: evidence of possible genetic control on the pathogenesis of atrial fibrillation. Am Heart J 2002;144:485–90.
[18] Ni A, Wang R, Liang B, et al. Relevance of gene KCNE1 and lone atrial fibrillation. Shanghai Med J 2004;27:260–1.
[19] Fatimi C, Snitch F, Genuardi M, et al. Analysis of minK and eNOS genes as candidate loci for predisposition to non-valvular atrial fibrillation. Eur Heart J 2006;27:1712–8.
[20] Prystupa A, Dzida G, Myslinski W, et al. MinK gene polymorphism in the pathogenesis of lone atrial fibrillation. Kardiol Pol 2006;64:1205–11.
[21] Lou S, Lin LU, Li-Qun WU, et al. Association between human potassium channel β-subunit gene KCNE1-S38G polymorphism and atrial fibrillation. J Diagn Concepts Pract 2006;5:415–8.
[22] Zeng Z, Tan C, Teng S, et al. The single nucleotide polymorphisms of IKsPotassium channel genes and their association with atrial fibrillation in a Chinese population. Cardiology 2006;108:97–103.
[23] Xu LX, Yang WY, Zhang HQ, et al. Study on the correlation between CETP TaqIB, KCNE1 S38G and eNOS T-786C gene polymorphisms for predisposition and non-valvular atrial fibrillation. Zhonghua Lui Xing Bing Xue Za Zhi 2008;29:486–92.
[24] Yao J, Ma YT, Xie X, et al. Association of rs1805127 polymorphism of KCNQ1 gene with atrial fibrillation in Uigur population of Xinjiang. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2011;28:436–40.
[25] Yao J, Ma YT, Xie X, et al. Association of KCNE1 genetic polymorphisms with atrial fibrillation in a Chinese Han population. Genet Test Mol Biomarkers 2012;16:1343–46.
[26] Haipun M, Xiaohou Z, Ting M, et al. Association between KCNE1 (G38S) genetic polymorphism and non-valvular atrial fibrillation in an Uygur population. Woen Klin Wochenchr 2012;124:737–41.
[27] Mao T, Miao HJ, Xu GJ, et al. Association of single nucleotide polymorphism of KCNE1 and KCNE4 gene with atrial fibrillation in Xinjiang Uygur and Han population. Zhonghua Xin Xue Guan Bing Za Zhi 2013;41:916–21.
[28] Voudris KV, Apostolakis L, Karyofyllis P, et al. Genetic diversity of the KCNQ1 gene and susceptibility to postoperative atrial fibrillation. Am Heart J 2014;167:274–80. e271.
[29] Wugten N, Yu-Jun G, Juan S, et al. Correlation analysis between the delayed rectifier potassium channel KCNQ1 (G38S) polymorphism and atrial fibrillation among the senior Uygur population in Xinjiang. Genet Mol Res 2015;14:15906.
[30] Li L, Shen C, Yao Z, et al. Genetic variants of potassium voltage-gated channel genes (KCNQ1, KCNE2, and KCNE1) affected the risk of atrial fibrillation in elderly patients. Genet Test Mol Biomarkers 2015;19:359–65.
[31] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:332–6.
[32] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[33] Yang Y, Xu M, Jin Q, et al. Identification of a KCN22 gain-of-function mutation in patients with familial atrial fibrillation. Am J Hum Genet 2004;75:899–905.
[34] Barhanin J, Lesage F, Guillemaire E, et al. K(V)LQT1 and lsK (minK) proteins associate to form the I(Ks) cardiac potassium current. Nature 1996;384:78–80.
[35] Chen YH, Xu SJ, Benndahou S, et al. KCNQ1 gain-of-function mutation in familial atrial fibrillation. Science 2003;299:251–4.
[36] Zong-Jie QU, Yin YH. Correlations between MinkS38G polymorphism and atrial fibrillation in patients with chronic heart failure. Zhonghua Bing Xue Za Zhi 2008;39:1353–6.
[37] Tada H, Shiffman D, Smith JG, et al. Twelve single nucleotide polymorphisms of IKs channel genes (KCNQ1, KCNH2, and KCNE1) affected the risk of atrial fibrillation in Chinese Han population. Genet Test Mol Biomarkers 2012;16:1343–46.
[38] Haipun M, Xiaohou Z, Ting M, et al. Association between KCNE1 (G38S) genetic polymorphism and non-valvular atrial fibrillation in an Uygur population. Woen Klin Wochenchr 2012;124:737–41.
[39] Mao T, Miao HJ, Xu GJ, et al. Association of single nucleotide polymorphism of KCNE1 and KCNE4 gene with atrial fibrillation in Xinjiang Uygur and Han population. Zhonghua Xin Xue Guan Bing Za Zhi 2013;41:916–21.
[40] Voudris KV, Apostolakis L, Karyofyllis P, et al. Genetic diversity of the KCNQ1 gene and susceptibility to postoperative atrial fibrillation. Am Heart J 2014;167:274–80. e271.