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META-ANALYSIS

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Association Between Rs3807989 Polymorphism in Caveolin-1 (CAV1) Gene and Atrial Fibrillation: A Meta-Analysis

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Atrial fibrillation (AF) is the most common sustained arrhythmia affected by multiple cardiovascular risk factors. It is reported that caveolin-1 gene (CAV1) rs3807989 polymorphism might be associated with AF risk. The goal of this meta-analysis was to confirm the association between CAV1 rs3807989 polymorphism and susceptibility to AF.

Material/Methods: We carried out a comprehensive literature search through the electronic databases PubMed, MEDLIN, and Web of Science. We performed a meta-analysis of all selected studies based on CAV1 rs3807989 polymorphism genotypes, including 3758 cases and 6126 controls.

Results: After meta-analysis with fixed- or random-effects models, we found significant associations in all 5 comparisons: allelic model (G/A; OR=1.228, 95%CI: 1.061–1.420; *P*=0.006), homozygote model (GG/AA; OR=1.439, 95%CI: 1.094–1.894; *P*=0.009), heterozygote model (GG/GA; OR=1.257, 95%CI: 1.064–1.486; *P*=0.007), dominant model (GG/AA+GA; OR=1.287, 95%CI: 1.076–1.540; *P*=0.006), and recessive model (AA/GA+GG; OR=0.738, 95%CI: 0.629–0.867; *P*<0.001). Sensitivity analysis results revealed the overall results were robust.

Conclusions: The results revealed a significant association between CAV1 gene rs3807989 polymorphism and susceptibility to AF, suggesting that the presence of allelic G might be one of the genetic factors conferring susceptibility to AF. To confirm this association, further well-designed studies are necessary.

MeSH Keywords: Atrial Fibrillation • Caveolin 1 • Polymorphism, Single Nucleotide

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Background

Atrial fibrillation (AF) is the most common sustained arrhythmia [1] encountered in clinical settings [2]. It is associated with higher risk of mortality [3,4], accounting for approximately 1–2% of all deaths in the general population [5]. The prevalence of AF increases substantially with age, affecting around 10% of people over 80 years old [6]. About 0.77% of the Chinese population have AF [7]. However, the exact pathogenesis of AF is still unclear.

AF is usually considered to be affected by multiple cardiovascular risk factors, including advancing age, male sex, hypertension, diabetes, ischemia, valvular heart disease, left ventricular (LV) dysfunction, heart failure, and obesity [2,8,9]. Furthermore, studies have reported that genetic factors play important roles in the pathogenesis of AF, such as KCNA5 [10], KCNQ1 [11], KCNE2 [12], and NUP155 [13].

Caveolin-1 gene (CAV1) encodes a caveolae protein, usually expressed in atrial myocytes [14]. Recent genome-wide association studies (GWAS) [15,16] have reported that a single-nucleotide polymorphism (SNP), rs3807989, in CAV1gene was associated with the susceptibility to AF, and the association of this SNP with AF risk has been replicated in several populations. Olesen et al. [5] demonstrated that variants of rs3807989 in CAV1gene are associated with AF independent of traditional cardiac risk factors in Caucasians. Liu et al. [17] and Chen et al. [18] have validated the significant association between rs3807989 and AF in Chinese Han people. However, the findings from the study of Li et al. [19] conflict with the results above; they showed that the SNP rs3807989 in CAV1 gene may not be a risk factor for AF in the Chinese Han population.

In view of this disagreement, it was necessary to perform a meta-analysis to determine the association of CAV1 rs3807989 polymorphism with the risk of AF in the present study.

Material and Methods

Publication search

We searched for studies about the association of CAV1 rs3807989 polymorphism with the risk of AF in the electronic databases PubMed, MEDLIN, and Web of Science before August 20, 2015. The following keywords were used: "CAV1" or "rs3807989" or "polymorphism" or "7q31" and "Atrial fibrillation (AF)". Only studies conducted in humans were included. Concurrently, we manually reviewed the references of reviews to search for additional relevant articles. All full-text articles published in English were included. If the same population was replicated in over 1 publication, only the most recent study with complete data was included in this meta-analysis.

Inclusion and exclusion criteria

The inclusion criteria were: 1) cohort or case-control studies; 2) studies about the association between the CAV1 rs3807989 (G/A) polymorphism and risk of AF; 3) studies that provide detailed genetic frequency data (AA, GA, and GG) in AF cases and controls for extraction; 4) studies published in English; and 5) distribution of genotype in controls was in accord with Hardy-Weinberg equilibrium (HWE). The exclusion criteria were: 1) duplicated studies; 2) studies not conforming to HWE; and 3) incomplete raw data.

Data extraction and quality score assessment

In case of disagreement on the quality scores between the 2 reviewers, differences were resolved through discussion and consultation with a third reviewer. Eligible studies were extracted for available data by 2 independent reviewers. The following information was extracted from each selected study: name of the first author, year of publication, ethnicity, sample size, age, sex, incidence of hypertension and coronary artery disease, AF type, and genotypic distribution of in cases and controls. The quality of each selected study was assessed by 2 reviewers using the Newcastle-Ottawa scale (NOS) quality system [20]. All disagreements between the 2 reviewers were resolved by discussion. Genotypic distribution of the controls from selected studies was assessed using HWE with Fisher's exact test.

Statistical analyses

All statistical analyses were conducted using Stata statistical software 12. In the current meta-analysis, 5 genetic models – allelic model (G versus A), recessive model (AA versus GA + GG), dominant model (GA + AA versus GG), homozygous (GG versus AA), and heterozygous genetic models (GG versus GA) – were used to confirm the relationship of CAV1 rs3807989 polymorphism with the risk of AF using the combined odds ratios (ORs) with corresponding 95% confidence intervals (CIs). The Q-test and the I^2 statistic (range, 0–100%) were used to calculate the heterogeneity across all selected studies [21]. If $P<0.1$ or $I^2>50\%$, the study would be judged to have significant heterogeneity and the random-effects model was used to estimate the pooled OR (DerSimonian and Laird methods) [22]; otherwise, the fixed-effects model was used (the Mantel-Haenszel method) [23]. Publication bias was estimated using Begg's funnel plot [24]. Funnel plot asymmetry was determined by Egger's linear regression test [25]. A P value less than 0.05 was considered statistically significant.

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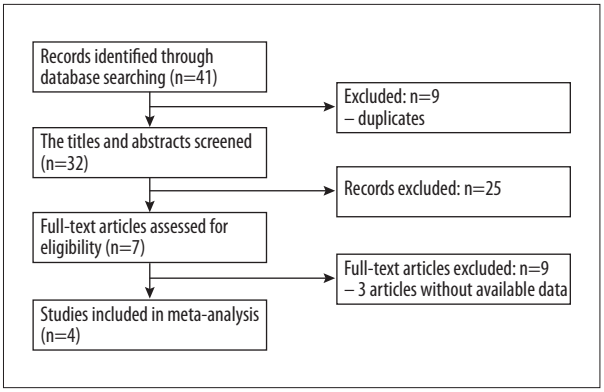

Figure 1. Flow diagram of study selection.

Results

Study characteristics

A total of 4 articles [5,17–19] involving the association of CAV1 rs3807989 polymorphism with AF risk were selected in this meta-analysis, including 3758 AF cases and 6126 controls. A detailed flow diagram of the search process for this meta-analysis is displayed in Figure 1. Table 1 shows the main characteristics of the selected studies and the characteristics of included patients are listed in Table 2. Genotypic distributions in controls from all selected studies conformed to HWE.

Meta-analysis results

As shown in Figure 2, all 5 comparisons revealed the association between CAV1 rs3807989 polymorphism and AF risk after meta-analysis with fixed- or random-effects models: allelic model (G/A; OR=1.228, 95%CI: 1.061–1.420; *P*=0.006), homozygote model (GG/AA; OR=1.439, 95%CI: 1.094–1.894; *P*=0.009), heterozygote model (GG/GA; OR=1.257, 95%CI: 1.064–1.486; *P*=0.007), dominant model (GG/AA+GA; OR=1.287, 95%CI: 1.076–1.540; *P*=0.006), and recessive model (AA/GA+GG; OR=0.738, 95%CI: 0.629–0.867; *P*<0.001). The overall analyses based on all included studies suggested allelic G carriers might have a higher risk for AF.

Sensitivity analysis

Sensitivity analysis was performed to assess the influence of each selected study on the total results. Sensitivity analysis revealed that there was no single study influencing the stability of the crude results, due to no changes in the corresponding pooled ORs (Figure 3).

Table 1. Major characteristics of the studies included in the meta-analysis.

Study [Ref.]	Year	Ethnicity	Cases			Controls			NOS	HWE
			GG	GA	AA	GG	GA	AA		
Olesen et al. [8]	2012	Caucasian	90	94	25	185	258	91	7	Yes
Li et al. [4]	2014	Chinese	459	323	57	665	468	82	8	Yes
Liu et al. [14]	2014	Chinese	364	193	37	505	396	73	8	Yes
Chen et al. [5]	2015	Chinese	1240	757	116	1724	1380	277	8	Yes

NOS – Newcastle-Ottawa scale; HWE – Hardy-Weinberg equilibrium.

Table 2. Demographics of subjects included in this meta-analysis.

Study	Age		Gender (F/M)		Hypertension		CAD		AF type (%)		
	Cases	controls	Cases	Controls	Cases	Controls	Cases	Controls	Paroxysmal	Persistent	Permanent
Olesen et al. [8]	40	65	38/171	256/278	N/A	N/A	N/A	N/A	117 (55.9%)	75 (35.9%)	17 (8.2%)
Li et al. [4]	53	52	336/473	402/803	265	240	309	N/A	495 (59.0%)	298 (35.5%)	46 (5.5%)
Liu et al. [14]	58.4	59	200/397	322/674	260	267	48	51	383 (64.2%)	196 (32.8%)	18 (3.0%)
Chen et al. [5]	65.4	57.3	887/1226	1478/1903	1067	N/A	633	N/A	1642 (77.7%)	425 (20.1)	46 (2.2)

F – female; M – male; CAD – coronary artery disease; AF – atrial fibrillation; N/A – not applicable.

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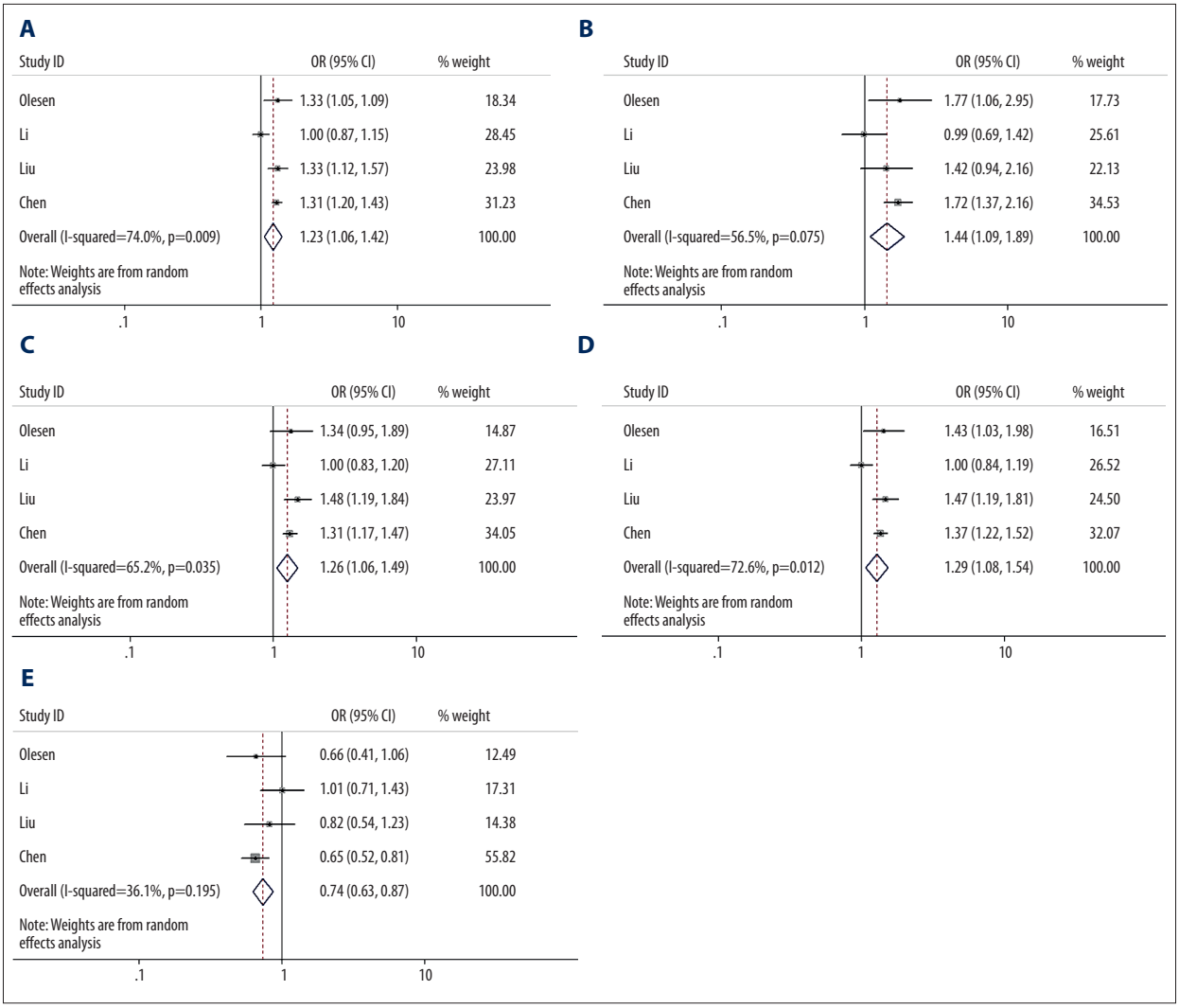

Figure 2. Forest plot for the association between caveolin-1 gene (CAV1) rs3807989 polymorphism and AF risk; (**A**) forest plot for allelic model (G *vs.* A); (**B**) forest plot for homozygote model (GG *vs.* AA); (**C**) forest plot for heterozygote model (GG *vs.* GA); (**D**) forest plot for dominate model (GG *vs.* GA+AA); (**E**) forest plot for the recessive model (AA *vs.* GA+GG).

Publication bias

We used Begg's funnel plot and Egger's test to estimate publication bias. Begg's funnel plot showed an approximately symmetrical shape (Figure 4) and no publication bias was observed in Egger's test (p= 0.666).

Discussion

We found a significant association of CAV1 gene rs3807989 polymorphism with AF risk under 5 comparisons: allelic, homozygous, heterozygous, dominant, and recessive genetic models. These findings suggested that individuals with G allele of CAV1 gene rs3807989 polymorphism may experience a higher risk of AF.

As the most common clinical sustained arrhythmia with complex pathogenesis, AF reportedly has a hereditary susceptibility. In the past few years, numerous case-control and cohort studies have strongly demonstrated the important roles of multiple genetic variants on genetic predisposition to AF [26]. GWASs have identified several susceptibility *loci* on chromosomes 3p22, 5q35, 7q31, 12p12, and 12q24 that are potentially associated with AF. Three GWASs [15,16,27] identified SNP rs3807989 in CAV1 to be related with AF risk in populations of European ancestry. However, several subsequent replication studies yielded inconsistent results; some studies indicated a significant association of rs3807989 with AF, but the others revealed no association [17,19].

The SNP rs3807989 is located on the chromosome of 7q31 in the second intron of CAV1 gene encoding caveolin-1. Caveolin-1

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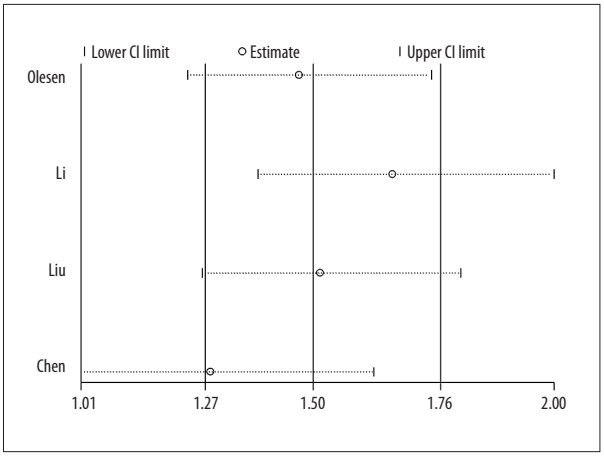

Figure 3. Sensitivity analysis performed in allelic model. This figure displays the influence of each study on the overall OR.

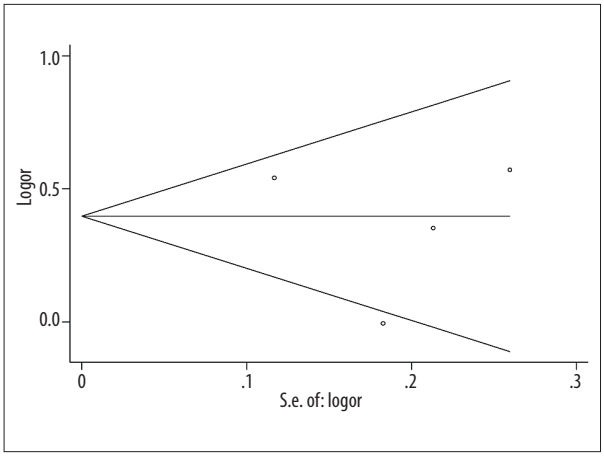

Figure 4. A funnel plot was used to analyze the publication bias.

(CAV1) is a key isoform of caveolae, which are 50- to 100-nm plasma membrane vesicles that play roles in cell signaling [28] and are rich in cholesterol [14]. The CAV1 gene has also been found to be highly expressed in cardiomyocytes [29]. CAV1 directly or indirectly influences many biological functions of these cells. Moreover, the roles of CAV1 in the regulation of plasma lipoprotein metabolism has also been shown [30]. In addition, AF risk is reportedly associated with mutations and genomic variants in genes that encode ion channels. It was reported that caveolin-1 interacts with potassium channel subunit Kir2.1, generating potassium current IK1, which affects AF development [31]. Caveolin-1 also has an influence in cardiac potassium channels KCNH2 [32] and HCN4 [33]. Furthermore, caveolin-1 was shown to affect transforming growth factor beta 1 (TGF-b1) signaling [34], which has roles in atrial fibrosis [35]. Therefore, it is possible that SNP rs3807989 may enhance risk of AF by regulating the function of these cardiac potassium channels and altering TGF-b1 signaling.

In this meta-analysis, we pooled all eligible studies to analyze the association between CAV1 gene rs3807989 polymorphism and AF risk, with a sample size of 3758 AF cases and 6126 controls. We found that SNP rs3807989 was associated with increased AF risk. However, several limitations in this meta-analysis should be considered. Firstly, in view of the influence of multiple factors on AF, the results would be more precise if individual data were adjusted with some other variables associated with AF risk, including coronary heart disease, hypertension, and family history.

Secondly, in this meta-analysis we only included the studies published in English, which might have biased the results. Finally, only investigating the CAV1 gene rs3807989 polymorphism without considering other genes or polymorphisms might have provided insufficient statistical power; therefore, further investigation of the interaction of this polymorphism with other risk factors for AF is required.

Conclusions

Our results revealed a significant association between CAV1 gene rs3807989 polymorphism and susceptibility to AF, suggesting that the presence of allelic G might be one of the genetic factors conferring susceptibility to AF. To confirm this association, further well-designed studies are necessary.

Competing interests

The authors declare that they have no competing interests.

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