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KCNE1 112G>A polymorphism and atrial fibrillation risk: a meta-analysis

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ABSTRACT. KCNE1, a membrane protein that spans the membrane once is responsible for modulating potassium channel functions and plays an important role in the etiology of arrhythmia. Emerging evidence indicates that a common polymorphism (112G>A; rs1805127 G>A) in the *KCNE1* gene contributes to atrial fibrillation (AF) risk; however, these studies showed inconclusive results. In this meta-analysis, we derived a more precise estimation of the association between the *KCNE1* 112G>A polymorphism and AF risk. The following databases were searched: Web of Science (1945-2013), the Cochrane Library Database (Issue 12, 2013), PubMed (1966-2013), EMBASE (1980-2013), CINAHL (1982-2013), and the Chinese Biomedical Database (1982-2013). The crude odds ratios with their 95% confidence intervals were calculated. Nine case-control studies were included, with a total of 1792 AF patients and 1924 healthy controls. The meta-analysis results indicated that the *KCNE1* 112G variant is associated with an increased risk of AF. Further subgroup analysis based on ethnicity revealed significant associations between the *KCNE1* 112G variant and an increased risk of AF among both Asians and Caucasians. No publication bias was detected in this meta-analysis. In conclusion, our results indicate that the *KCNE1* 112G polymorphism may be a risk factor for AF. *KCNE1* 112G>A may be

useful as a biomarker for predicting the development of AF.

Key words: Atrial fibrillation; KCNE1; Meta-analysis; Polymorphism; Susceptibility

INTRODUCTION

Atrial fibrillation (AF) is regarded as the most common sustained cardiac arrhythmia in clinical practice and is a major risk factor for hemodynamic complications, stroke, and heart failure (Kanji et al., 2012; Lévy, 2013). It has been well-established that common risk factors such as old age, male sex, hypertension, heart failure, ischemic heart disease, valvular heart diseases, diabetes, obesity, hyperthyroidism, alcohol abuse, smoking, and pulmonary diseases may be involved in AF development (Nguyen et al., 2013). Recently, a large body of evidence from relevant clinical studies suggested that AF is a multifactorial disease that can be induced by complex interactions between environmental and genetic factors (Mahida and Ellinor, 2012). Although the exact mechanisms in human AF remain poorly understood, the activation of inward rectifier potassium channels is thought to contribute to the initiation and maintenance of AF (Atienza et al., 2006). Therefore, it was hypothesized that functional mutations in candidate genes related to the potassium channel alter channel functions and increase the risk of electrical remodeling, thereby affecting an individual's susceptibility to AF (Chen et al., 2003; Ellinor et al., 2006).

KCNE1 (also known as minK), a single-span membrane protein, is capable of modulating the voltage-gated potassium channel KCNQ1 by slowing its activation and enhancing its channel conductance to generate a slow and delayed rectifier potassium current (I_{Ks}), which is crucial for atrial repolarization in cardiac cellular electrophysiology (Kang et al., 2008). As an important member of the KCNE family first identified in 1988, KCNE1 is thought to be expressed in various tissues including the heart, ear, colon, uterus, and lymphocytes (Takumi et al., 1988; Mustapha et al., 2007). The human *KCNE1* gene has been mapped to chromosome 21 (21q22.1-q22.2) and encodes the β-subunit of the I_{Ks} channel (Chevillard et al., 1993; Splawski et al., 1998). Thus far, several single-nucleotide polymorphisms (SNPs) have been identified in the *KCNE1* gene, while the 112G>A polymorphism (rs1805127 G>A; G38S) is the most widely investigated variant (Aydin et al., 2005). It is well accepted that the *KCNE1* 112G>A polymorphism results in a glycine or serine amino acid substitution at codon 38, and is responsible for stronger I_{Ks} currents and high expression of KCNQ1 (Lai et al., 1994; Ehrlich et al., 2005). Moreover, various studies have shown that increased outward current in atrial myocytes, combined with shortened atrial action potentials, may contribute to the susceptibility to AF (Temple et al., 2005; Ellinor et al., 2006; Andalib et al., 2008). Therefore, the *KCNE1* 112G>A polymorphism may be important in the pathogenesis of AF (Lai et al., 2002; Fatini et al., 2006). Several recent studies have indicated that the *KCNE1* 112G>A polymorphism is significantly correlated with an increased risk of AF (Prystupa et al., 2006; Xu et al., 2008; Yao et al., 2011; Mao et al., 2012). However, other studies have identified no relationship between the *KCNE1* 112G>A polymorphism and susceptibility to AF (Ni et al., 2004; Lou et al., 2006; Zeng et al., 2007). Because of the conflicting results of previous studies, we performed a meta-analysis of relevant data to comprehensively evaluate the association between the *KCNE1* 112G>A polymorphism and AF risk.

MATERIAL AND METHODS

Literature search

Six electronic databases were searched, including the Web of Science (1945-2013), the Cochrane Library Database (Issue 12, 2013), PubMed (1966-2013), EMBASE (1980-2013), CINAHL (1982-2013), and the Chinese Biomedical Database (CBM) (1982-2013). Searches were not limited by language, gender, or age. We used the following keywords and MeSH terms in conjunction with a highly sensitive search strategy: ("genetic polymorphism" or "polymorphism" or "SNP" or "mutation" or "variation" or "variant") and ("atrial Fibrillation" or "auricular Fibrillation" or "AF") and ("KCNE1" or "minK"). We also conducted a manual search to identify other potential articles based on references identified in individual articles.

Selection

The following parameters were used as inclusion criteria: 1) the study design must be a clinical case-control study focused on the association between the *KCNE1* 112G>A polymorphism and AF risk; 2) all patients should meet the diagnostic criteria for AF; 3) the genotype frequencies of healthy controls should be in Hardy-Weinberg equilibrium (HWE); 4) the study must provide sufficient information regarding the genotype frequencies of the *KCNE1* 112G>A polymorphism. The most recent or the largest sample size publication was included when the authors published several studies using the same subjects.

Data collection

Data were systematically extracted by 2 authors from each study included using a standardized form. The form used for data extraction documented the most relevant items including the first author, publication year, country, language, study design, ethnicity, sample size, gender, age, detecting sample, genotype method, genotype frequencies, and evidence of HWE.

Methodological assessment

Methodological quality was evaluated separately by 2 observers using the STROBE quality score systems (da Costa et al., 2011). Forty assessment items related to quality appraisal were used in this meta-analysis, with scores ranging from 0-40. The studies included were classified into 3 levels: low quality (0-19), moderate quality (20-29), and high quality (30-40).

Statistical analysis

Meta-analysis was performed using the STATA statistical software (version 12.0, Stata Corporation; College Station, TX, USA). Odds ratios (OR) and 95% confidence intervals (95%CI) were calculated. The *Z* test was used to estimate the statistical significance of pooled ORs. Heterogeneity among studies was estimated using the Cochran's *Q*-statistic and I^2 tests (Jackson et al., 2012). We also quantified the effects of heterogeneity using the I^2 test (ranges from 0-100%), which represents the proportion of inter-study variability contributing to heterogeneity rather than to chance (Peters et al., 2006). If the *Q*-test showed a $P < 0.05$ or the I^2

value was >50% indicating significant heterogeneity, the random-effects model was applied; otherwise, the fixed-effects model was used. We also explored reasons for heterogeneity using subgroup analyses and meta-regression analyses. To evaluate the influence of single studies on the overall estimate, sensitivity analysis was performed. Funnel plots and Egger's linear regression test were applied to investigate publication bias (Zintzaras and Ioannidis, 2005). All analyses were calculated using the STATA statistical software.

RESULTS

Study characteristics

In accordance with the inclusion criteria, 9 case-control studies (Lai et al., 2002; Ni et al., 2004; Fatini et al., 2006; Lou et al., 2006; Prystupa et al., 2006; Zeng et al., 2007; Xu et al., 2008; Yao et al., 2011; Mao et al., 2012) were included in this meta-analysis and 72 articles were excluded (Figure 1). A total of 3716 subjects were analyzed in this meta-analysis, including 1792 AF patients and 1924 healthy controls. The publication years of the studies involved ranged from 2002-2012. Overall, 7 studies were conducted in Asians and 2 studies in Caucasians. Three studies used hospital-based controls, while the other 6 studies used population-based controls. The DNA samples used in testing for *KCNE1* 112G>A polymorphism were extracted from blood in all 8 studies. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was performed in 7 studies, while the other 2 studies used direct sequencing methods. None of the populations in the studies included deviated from HWE (all $P > 0.05$). Quality scores of the studies included were all higher than 20 (moderate to high quality). The study characteristics and methodological quality scores are summarized in Table 1.

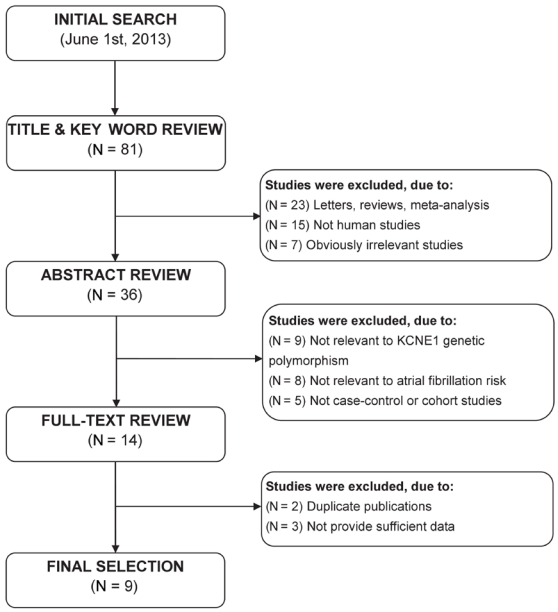

Figure 1. Flow chart of the literature search and study selection process. Nine case-control studies were included in this meta-analysis.

Table 1. Main characteristics and methodological quality of all eligible studies.

First author	Year	Country	Ethnicity	Number		Gender (M/F)		Age (years)		Source		Genotype method	SNP ID	STROBE score
				Case	Control	Case	Control	Case	Control	Case	Control			
Ni et al.	2004	China	Asian	94	130	63/31	87/43	55.0 ± 7.5	54.0 ± 7.0	HB	PB	Direct sequencing	rs1805127 (G>A)	29
Lou et al.	2006	China	Asian	111	101	63/48	57/44	65.5 ± 13.2	49.3 ± 8.5	HB	PB	Direct sequencing	rs1805127 (G>A)	25
Xu et al.	2008	China	Asian	147	147	86/61	89/58	65.7 ± 13.1	65.5 ± 11.8	HB	HB	PCR-RFLP	rs1805127 (G>A)	28
Yao et al.	2011	China	Asian	303	328	164/139	178/150	63.4 ± 11.3	63.6 ± 5.8	HB	PB	PCR-RFLP	rs1805127 (G>A)	27
Mao et al.[a]	2012	China	Asian	251	251	153/98	153/98	65.2 ± 9.7	65.2 ± 9.7	HB	HB	PCR-RFLP	rs1805127 (G>A)	30
Mao et al.[b]	2012	China	Asian	237	237	144/93	144/93	67.3 ± 10.3	67.4 ± 10.2	HB	HB	PCR-RFLP	rs1805127 (G>A)	30
Lai et al.	2002	Taiwan	Asian	108	108	59/49	59/49	63.4 ± 11.5	63.4 ± 11.5	HB	PB	PCR-RFLP	rs1805127 (G>A)	32
Fatini et al.	2006	Italy	Caucasian	331	441	198/133	258/183	72.9 ± 9.2	72.3 ± 10.6	HB	PB	PCR-RFLP	rs1805127 (G>A)	34
Prystupa et al.	2006	Poland	Caucasian	69	61	32/37	21/40	55.0 ± 10.0	53.0 ± 9.0	HB	HB	PCR-RFLP	rs1805127 (G>A)	30
Zeng et al.	2007	China	Asian	141	120	95/47	41/79	59.0 ± 15.2	55.9 ± 10.2	HB	PB	PCR-RFLP	rs1805127 (G>A)	31

M = male; F = female; PB = population-based; HB = hospital-based; PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism; SNP = single nucleotide polymorphism. [a]Han people; [b]Uygur people.

Quantitative data synthesis

Meta-analysis findings regarding the relationships between the *KCNE1* 112G variant and AF risk are shown in Table 2. The meta-analysis results revealed that the *KCNE1* 112G variant was associated with an increased risk of AF (A allele *vs* G allele: OR = 0.74, 95%CI = 0.67-0.82, P < 0.001; GA+AA *vs* GG: OR = 0.73, 95%CI = 0.64-0.83, P < 0.001; AA *vs* GG+GA: OR = 0.65, 95%CI = 0.54-0.79, P < 0.001; AA *vs* GG: OR = 0.57, 95%CI = 0.46-0.70, P < 0.001) (Figure 2). Subgroup analysis by ethnicity indicated that the *KCNE1* 112G variant was strongly correlated with an increased risk of AF among both Asians and Caucasians (Figure 3). Results of further subgroup analyses by source of controls revealed significant associations between the *KCNE1* 112G variant and susceptibility to AF in population-based, hospital-based, and PCR-RFLP subgroups (as shown in Table 2), but not in the direct sequencing subgroup (all P > 0.05). Meta-regression confirmed that none of potential factors were dominant sources of heterogeneity (Table 3). Sensitivity analysis indicated that the overall pooled ORs were not influenced by a single study (Figure 4). No evidence of asymmetry was observed in the funnel plots (Figure 5). The Egger test revealed no evidence of publication bias (all P > 0.05).

DISCUSSION

In the present meta-analysis, we found that the *KCNE1* 112G>A polymorphism was associated with an increased risk of AF, indicating that the 112G variant is important in the development of AF. Although the exact mechanism by which the *KCNE1* 112G>A polymorphism contributes to the risk of AF remains poorly understood, a possible explanation may be that the 112G variant is likely associated with an increased I_{Ks} current and high KCNQ1 membrane expression, which may be a genetic determinant of AF (Lai et al., 2002; Zeng et al., 2007; Haijun et al., 2012). KCNE1 is the founding member of the KCNE family of membrane proteins, which are considered to act as selective potassium channel modulators in regulating cellular electrophysiology (Takumi et al., 1988). Moreover, the cardiac I_{Ks} channel complex is composed of the KCNQ1 channel and KCNE1 auxiliary subunits (Wang et al., 2011). KCNQ1, a widely expressed tetrameric voltage-gated potassium channel, is regulated by KCNE1 to produce an I_{Ks} current critical to heartbeats (Jespersen et al., 2005). Previous studies indicate that gain or loss-of-function mutations in the genes encoding potassium channels and accessory β-subunits are involved in AF development (Mahida et al., 2011). Therefore, genetic variations in the *KCNE1* gene may contribute to the susceptibility to AF (Andalib et al., 2008; Tsai et al., 2008). In particular, *KCNE1* 112G>A (rs1805127 G>A), a common functional polymorphism in the human *KCNE1* gene that results in an amino acid substitution at G38S, may lead to overexpression of the KCNE1 protein, followed by an increase in the I_{Ks} current, as well as enhance expression of the KCNQ1 membrane; these factors contribute to an increased risk of AF (Ehrlich et al., 2005; Olesen et al., 2012).

We also carried out subgroup analysis to comprehensively evaluate the relationship between the *KCNE1* 112G>A polymorphism and AF pathogenesis. The results of subgroup analysis by ethnicity also revealed significant associations between the *KCNE1* 112G>A variant and the risk of AF among both Asians and Caucasians, suggesting that no ethnic differences existed in individuals' susceptibility to AF. Further subgroup analyses based on the sources

Table 2. Meta-analysis of the association between the *KCNE1* 112G>A polymorphism and atrial fibrillation risk.

Subgroups	A allele *vs* G allele (allele model)				GA + AA *vs* GG (dominant model)				AA *vs* GG + GA (recessive model)				AA *vs* GG (homozygous model)				AA *vs* GA (heterozygous model)			
	OR	95%CI	P	P_h	OR	95%CI	P	P_h	OR	95%CI	P	P_h	OR	95%CI	P	P_h	OR	95%CI	P	P_h
Overall	0.74	[0.67-0.82]	<0.001	0.070	0.73	[0.64-0.83]	<0.001	0.161	0.65	[0.54-0.79]	<0.001	0.294	0.57	[0.46-0.70]	<0.001	0.339	0.75	[0.61-0.92]	0.005	0.207
Ethnicity																				
Caucasians	0.64	[0.53-0.78]	<0.001	0.095	0.61	[0.46-0.81]	0.001	0.318	0.63	[0.45-0.88]	0.007	0.125	0.52	[0.35-0.76]	0.001	0.228	0.73	[0.51-1.05]	0.086	0.055
Asians	0.78	[0.70-0.87]	<0.001	0.183	0.76	[0.66-0.89]	<0.001	0.179	0.67	[0.53-0.85]	0.001	0.311	0.59	[0.46v0.76]	<0.001	0.305	0.75	[0.59-0.97]	0.028	0.300
Source of control																				
Population-based	0.72	[0.63-0.81]	<0.001	0.418	0.69	[0.59-0.82]	<0.001	0.230	0.59	[0.46-0.75]	<0.001	0.737	0.50	[0.38-0.65]	<0.001	0.795	0.67	[0.52-0.88]	0.004	0.579
Hospital-based	0.75	[0.55-1.01]	0.058	0.017	0.78	[0.63-0.97]	0.025	0.144	0.78	[0.57-1.06]	0.113	0.102	0.70	[0.50-0.99]	0.040	0.143	0.88	[0.63-1.22]	0.428	0.072
Genotype method																				
PCR-RFLP	0.72	[0.62-0.84]	<0.001	0.044	0.69	[0.60-0.80]	<0.001	0.217	0.67	[0.55-0.82]	<0.001	0.199	0.58	[0.46-0.72]	<0.001	0.197	0.78	[0.63-0.96]	0.022	0.197
Direct sequencing	0.88	[0.65-1.20]	0.421	0.750	1.01	[0.69-1.48]	0.957	0.622	0.46	[0.21-1.00]	0.049	0.781	0.49	[0.22-1.09]	0.079	0.699	0.40	[0.18-0.92]	0.032	0.947

OR = odds ratios; 95%CI = 95% confidence interval; P_h = P value of heterogeneity test; PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

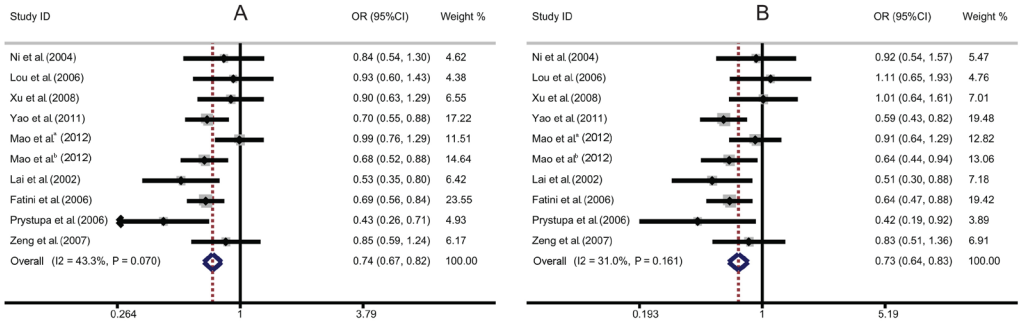

Figure 2. Forest plots of the association between the *KCNE1* 112G>A polymorphism and atrial fibrillation risk under the allele (**A**) and dominant (**B**) models. [a]Han people; [b]Uygur people.

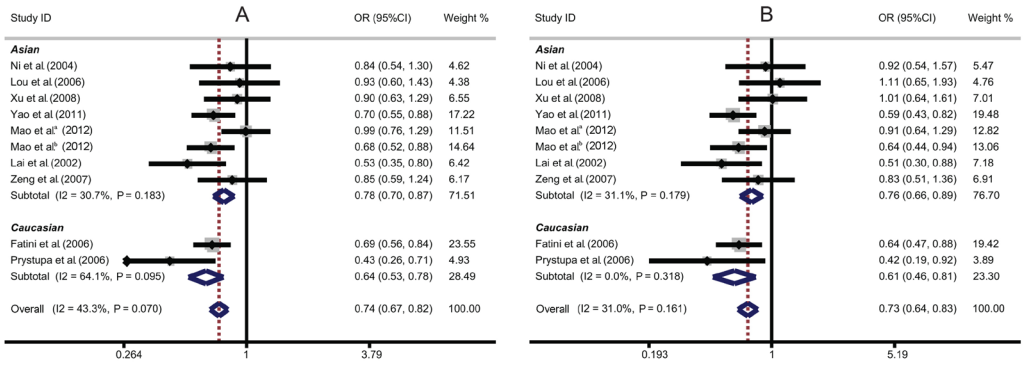

Figure 3. Subgroup analyses based on ethnicity for the association between the *KCNE1* 112G>A polymorphism and atrial fibrillation risk under the allele (**A**) and dominant (**B**) models. [a]Han people; [b]Uygur people.

Table 3. Univariate and multivariate meta-regression analyses of potential sources of heterogeneity.

Heterogeneity factors	Coefficient	SE	z	P	95%CI	
					LL	UL
Publication year						
Univariate	0.004	0.026	0.14	0.892	-0.047	0.054
Multivariate	-0.002	0.032	-0.01	0.994	-0.065	0.064
Ethnicity						
Univariate	0.263	0.206	1.28	0.201	-0.140	0.666
Multivariate	0.150	0.230	0.65	0.515	-0.302	0.602
Source of control						
Univariate	-0.093	0.164	-0.57	0.569	-0.416	0.229
Multivariate	-0.164	0.211	-0.78	0.437	-0.578	0.250
Genotype method						
Univariate	-0.375	0.220	-1.71	0.088	-0.806	0.055
Multivariate	-0.415	0.272	-1.53	0.127	-0.947	0.118

SE = standard error; 95%CI = 95% confidence interval; UL = upper limit; LL = lower limit.

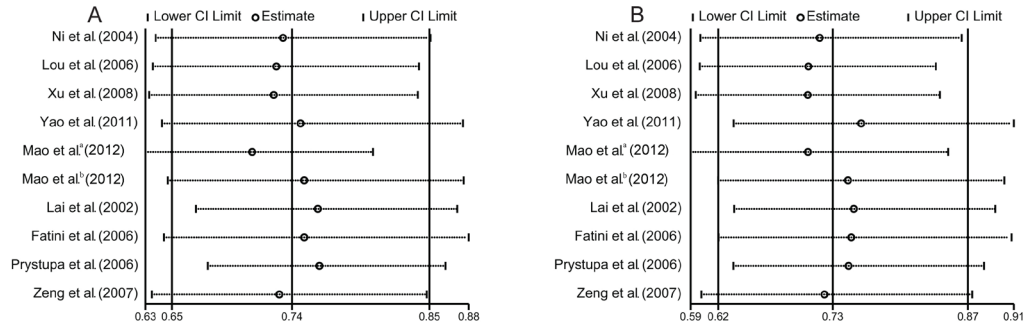

Figure 4. Sensitivity analyses for the associations between the *KCNE1* 112G>A polymorphism and atrial fibrillation risk under the allele (**A**) and dominant (**B**) models. Results were computed by omitting each study in turn. Meta-analysis random-effects estimates (exponential form) were used. The two ends of the dotted lines represent the 95%CI. [a]Han people; [b]Uygur people.

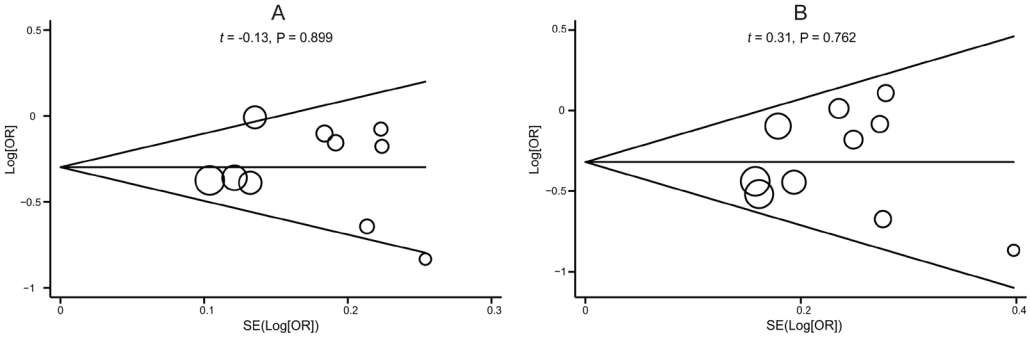

Figure 5. Begger's funnel plot for the associations between the *KCNE1* 112G>A polymorphism and atrial fibrillation risk under the allele (**A**) and dominant (**B**) models. Each point represents a separate study for the indicated association. Log[OR] = natural logarithm of OR; SE = standard error. Horizontal line = mean magnitude of the effect.

of control and genotyping method indicated that the *KCNE1* 112G>A polymorphism is closely correlated with the development of AF in population-based, hospital-based, and PCR-RFLP subgroups; however, no evidence of association was observed in the direct sequencing subgroup, which may have resulted from the small sample size. Therefore, further investigations involving larger sample size are required. Thus, our findings are consistent with those of previous studies, suggesting that the *KCNE1* 112G>A polymorphism has an important impact on an individual's susceptibility to AF and that this polymorphism may be a valuable biomarker for predicting the risk of AF.

The current meta-analysis also has several limitations. First, our results lacked sufficient statistical power to assess the relationships between the *KCNE1* 112G>A polymorphism and the pathogenesis of AF because of the small number of subjects. Because some studies were small, our meta-analysis may show relatively wide confidence intervals, restraining our

ability to draw conclusions. In addition, the small number of studies may constrain the general applicability of our findings, and thus the conclusions of our meta-analysis should be regarded as preliminary. Second, meta-analyses are retrospective studies that can exhibit subject selection bias, thereby impacting the reliability of the results. Third, our meta-analysis failed to obtain original data from the relevant studies included, which may limit further evaluation of the potential role of the *KCNE1* 112G>A polymorphism in AF development. Although our study has several limitations, this is the first meta-analysis focusing on the correlation between the *KCNE1* 112G>A polymorphism and susceptibility to AF. Furthermore, we used a highly sensitive literature search strategy of electronic databases. A manual search of the reference lists from the relevant articles was also conducted to identify other potentially relevant articles. The selection process of eligible articles was based on strict inclusion and exclusion criteria. Importantly, rigorous statistical analysis provided a basis for pooling information from individual studies.

In summary, our meta-analysis revealed that the *KCNE1* 112G>A polymorphism may be significantly correlated with the pathogenesis of AF. Thus, the *KCNE1* 112G>A polymorphism might be useful as a biomarker for predicting the risk of developing AF. However, further prospective studies examining the homogeneity of this relationship are required for more accurate statistical analysis.

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