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Review Article

Association between SCN5A gene variant H558R and arrhythmias: a systemic review and meta-analysis

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Abstract: Background: The SCN5A H558R polymorphism is potentially associated with several arrhythmias, including Brugada syndrome, atrial fibrillation, and sick sinus syndrome. Here we conducted a comprehensive meta-analysis to investigate the association between this polymorphism and arrhythmia risk. Methods and materials: Eligible studies extracted from the databases of PubMed, Web of Science, and Cochrane Library were evaluated. Statistical analysis was performed using Revman 5.3 and STATA 14.0 software. Results: Five studies with 746 cases and 1085 controls were extracted for the current meta-analysis. The results revealed no significant association was found between *SCN5A* H558R polymorphism group and arrhythmia risks in all five genetic models. In the stratified analysis of different arrhythmia types, a significantly increased risk of the atrial fibrillation was found to be associated with genotype change in all these five models (AG/AA: OR=1.78, 95% CI=1.33-2.39, P=0.001; GG/AA: OR=2.76, 95% CI=1.48-5.16, P=0.001; AG+GG/AA: OR=1.89, 95% CI=1.43-2.50, P=0.001; GG/AG+AA: OR=2.24, 95% CI=1.21-4.13, P=0.01; G/A: OR=1.70, 95% CI=1.35-2.13, P=0.001). Furthermore, we found that the significantly increased risk of arrhythmias in caucasian was associated with the heterzygous genotype AG in codominant (AG/AA: OR=1.93, 95% CI=1.50-2.49, P=0.001) and allele (G/A: OR=1.59, 95% CI=1.30-1.94, P=0.001) models. Conclusion: *SCN5A* H558R polymorphism may increase the risk of atrial fibrillation and the risk of arrhythmias in caucasian.

Keywords: *SCN5A* H558R polymorphism, arrhythmia, atrial fibrillation, meta-analysis

Introduction

The *SCN5A* gene encodes the alpha-subunit of the $Na_v1.5$ ion channel protein, which has a key role in the sodium inward current (I_{Na}) [1]. This current is responsible for the synchronous and rhythmic contraction of the heart [2]. The *SCN5A* encoded protein is mainly found in the heart, however it has been identified in smooth muscle cells of the intestines [3] and in macrophages [4]. Few research has paid attention on the functional role of *SCN5A* in these non-cardiac tissues. However, previous studies have revealed correlations between *SCN5A* gene variants and multiple cardiac diseases including Brugada syndrome, long QT syndrome [5], atrial fibrillation [6], sick sinus syndrome [7] and cardiomyopathies [8].

Lots of variations of the *SCN5A* gene have been identified. The histidine-558-to-arginine (H558R) polymorphism of *SCN5A* was firstly reported in patients with torsades de pointes in 2002 [9]. Several studies have been proved that it can change the expression of arrhythmogenic genotypes by modulating the phenotypic expression of several coexisting arrhythmogenic mutations [10-12]. Therefore, the association between *SCN5A* gene variant H558R and susceptibility to of arrhythmias including atrial fibrillation, atrioventricular conduction block and sick sinus syndrome has been wildly studied [13-15]. However, the results were inconsistent.

In this study, we collected all published case-control studies and prospective cohorts focused on the relationship between arrhythmia risk and *SCN5A* H558R polymorphism. A meta-analysis was carried out and our aim was to clarify the controversial results.

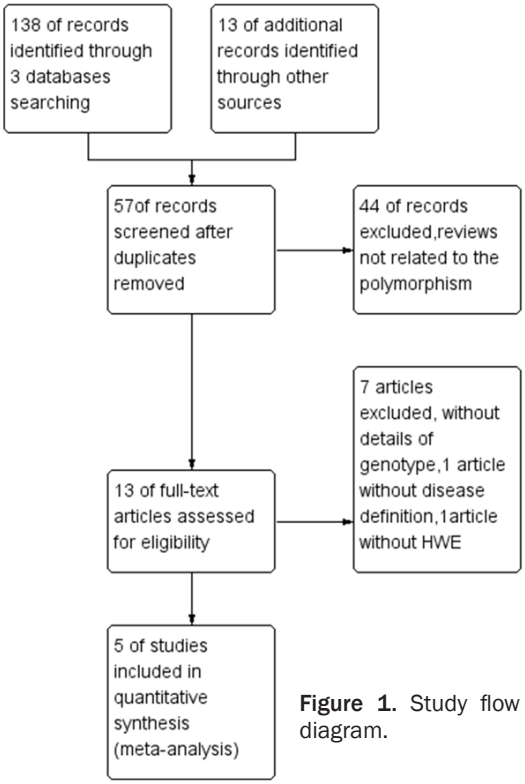

Figure 1. Study flow diagram.

Materials and methods

Publication search and data extraction

Studies published in English (from their inception to July 2016) were mainly identified by conducting a systematic search in PubMed, Web of Science, and Cochrane Library databases using the following terms: '*SCN5A*', 'H558R', and 'polymorphism'. Reference lists from relevant articles were also examined to find additional publications. Data were extracted independently by two authors using standard forms. The collected data included author name, publication year, country, ethnicity, age, gender, arrhythmia types, and genotype distributions. All the included studies met the following criteria: 1) case-control study and prospective cohorts, 2) evaluation of the association between *SCN5A* H558R polymorphism and arrhythmia risks, 3) including details of genotype frequency in cases and controls and the frequency was tested by HWE. Evaluation of evidence strength was carried out according to the modified Newcastle-Ottawa Scale (shown in Supplementary Table 1) [16].

Statistical analysis

Revman 5.3 and STATA 14.0 software was used for meta-analysis. Study heterogeneity between studies was assessed using the I^2 statistic. Dichotomous variables were quoted as a odds ratios (ORs) with 95% CI (confidence intervals). The random-effects model was used when I^2> 50%. Otherwise, the calculations were performed with the fixed-effects model [17, 18]. We used the codominant model (AG/AA, GG/AA), dominant model (AG+GG/AA), recessive model (GG/AG+AA), and allele model (G/A) to evaluate the association between polymorphism and arrhythmia risk. Subgroup analysis based on arrhythmia type and ethnicity was carried out. Sensitivity analysis and publication bias were also performed [19, 20]. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the studies

The initial search yielded 151 articles in the database; 94 reports were excluded owing to duplication. Of the remaining 57 articles, 50 did not meet the set inclusion criteria. Finally, five studies [13, 15, 21-23] with 746 cases and 1085 controls were included in the current meta-analysis (**Figure 1**). Of five studies, three were conducted in Asia and the other two were conducted in Europe or North America. Two studies focused on the relationship between polymorphism and atrial fibrillation. The rest three studies reported the sick sinus syndrome, idiopathic cardiac conduction disorders and atrioventricular conduction block respectively. Furthermore, the genotype distributions were also collected and shown in **Tables 1** and **2**.

Results of the meta-analysis for all studies

We evaluated the association between *SCN5A* H558R polymorphism and arrhythmia risks within five genetic models mentioned in the methods section. The results of this meta-analysis were shown in **Table 3**. The pooled results revealed no significant association was found between *SCN5A* H558R polymorphism group and arrhythmia risks in all five genetic models. Next, we performed stratification analysis according to the arrhythmia types and ethnicities. First, all these five studies were divided into two groups (atrial fibrillation group and conduction system disease group) according to their arrhythmia types. Sick sinus syndrome, idiopathic cardiac conduction disorders and atrioventricular conduction block belonged to

Table 1. Characteristics of studies included in this meta-analysis

Author	Year	Country	Ethnicity	Age (case/control)	Gender (case/control)	Type of arrhythmia
Chen et al.	2007	US	Caucasian	52.0±9.8/N	N/N	Atrial fibrillation
Park et al.	2012	Korean	Asian	N/N	N/N	Atrioventricular conduction block
Svetlana et al.	2015	Russian	Caucasian	N/37.16±17.05	122M124F/348M63F	Idiopathic Cardiac Conduction disorders
Shadeke et al.	2016	China	Asian	60.1/53.5	117M83F/122M78F	Astrial fibrillation
Lee et al.	2016	Korean	Asian	55.6/N	9M21F/N	Sick sinus syndrome

N: no details. M: male. F: female.

Table 2. Genotypes details of five studies included in this meta-analysis

Author	No. (Case/Control)	Genotypes case			Genotypes control			HWE for control
		AA	AG	GG	AA	AG	GG	*P* value
Chen et al.	157/314	78	63	16	198	103	13	>0.05
Park et al.	113/80	105	8	0	59	21	0	>0.05
Svetlana et al.	246/411	107	134	5	253	143	15	>0.05
Shadeke et al.	200/200	100	90	10	135	59	6	>0.05
Lee et al.	30/80	22	8	0	59	21	0	>0.05

HWE: Hardy-Weinberg equilibrium.

the conduction system disease group. In the atrial fibrillation group, the significantly increased risk of the disease was found to be associated with genotype change in all these five models (AG/AA: OR=1.78, 95% CI=1.33-2.39, P=0.001; GG/AA: OR=2.76, 95% CI=1.48-5.16, P=0.001; AG+GG/AA: OR=1.89, 95% CI=1.43-2.50, P=0.001; GG/AG+AA: OR=2.24, 95% CI=1.21-4.13, P=0.01; G/A: OR=1.70, 95% CI=1.35-2.13, P=0.001). We found that the significantly increasd risk of c arrhythmias in caucasian was associated with the heterzygous genotype AG in codominant (AG/AA: OR=1.93, 95% CI=1.50-2.49, P=0.001) and allele (G/A: OR=1.59, 95% CI=1.30-1.94, P=0.001) models. However, stratified analysis of ethnicity showed no statistically differences of arrhythmia risk with genotype change in Asians.

Sensitivity analysis and publication bias

To assess the stability of the results, sensitivity analysis was performed (shown in Supplementary Figure 1). Funnel plots were used to estimate the publication bias of the articles included in this study. There was no evidence of asymmetry in the shape of funnel plots in the codominant model (AG *vs.* AA) (**Figure 2**). Begg's test showed no evidence of publication bias (P=0.142).

Discussions

The *SCN5A* H558R polymorphism, located in the Na^+ channel cytoplasmic linker, is the most common missense polymorphism in *SCN5A* caused by a single nucleotide change (1673A>G). In this study, we found there was no association between *SCN5A* H558R polymorphism and the risk of overall cardiac arrhythmias. However, when we performed stratification analysis, we found that for atrial fibrillation, the association analyses of the codominant model (AG/AA), codominant model (GG/AA), dominant model (AG+GG/AA), recessive model (GG/AG+AA), and allele model (G/A) consistently supported that this polymorphism statistically increased the risk of atrial fibrillation. On the contrary, we also identified that cases have a *SCN5A* H558R polymorphism had higher risks to have the overall cardiac arrhythmias in caucasian than controls in codominant (AG/AA) and allele (G/A) models.

The exact function of *SCN5A* H558R polymorphism is still controversial. It has been reported that *SCN5A* H558R polymorphism modulates changes of the Na^+ channel caused by other gene mutations [10, 24]. However, no difference in Na^+ channel activation and inactivation has been observed between the hH1-H558 and the hH1-R558 clones in a vitro study [24]. For instance, Maragoni et al. showed that H558R polymorphism restored the defect caused by the LQT-3 mutation S216L [25]. Viswanathan et al. reported that H558R polymorphism could modify the abnormal gating effect caused by the proximal mutation [24]. Jiang et al. provided some evidences for the role of *SCN5A* H558R polymorphism in reducing the susceptibility to Keshan disease [26]. All these studies demon-

Table 3. Pooled ORs and 95% CIs of the overall and stratified meta-analysis for Allele model (G/A), codominant model (AG/AA), codominant model (GG/AA), dominant model (AG+GG/AA), and recessive model (GG/AG+AA)

Varibles	No.	Allele comparison			Genetic model comparison			
		OR (95% CI)	*P* value	I^2 (%)	Model type	OR (95% CI)	*P* value	I^2 (%)
All arrhythmias	5	1.20 (0.79, 1.83)	0.39	80%	Codominant model: AG/AA	1.23 (0.68, 2.19)	0.49	85%
					Codominant model: GG/AA	1.86 (0.82, 4.19)	0.14	55%
					Dominant model: AG+GG/AA	1.25 (0.72, 2.19)	0.43	84%
					Recessive model: GG/AG+AA	1.41 (0.56, 3.55)	0.47	66%
Arrhythmia types								
AF	2	1.70 (1.35, 2.13)	0.001	0%	Codominant model: AG/AA	1.78 (1.33, 2.39)	0.001	0%
					Codominant model: GG/AA	2.76 (1.48, 5.16)	0.001	0%
					Dominant model: AG+GG/AA	1.89 (1.43, 2.50)	0.001	0%
					Recessive model: GG/AG+AA	2.24 (1.21, 4.13)	0.01	0%
Conduction	3	0.76 (0.25, 2.31)	0.63	89%	Codominant model: AG/AA	0.81 (0.19, 3.44)	0.78	92%
					Codominant model: GG/AA	0.79 (0.28, 2.22)	-	-
					Dominant model: AG+GG/AA	0.80 (0.20, 3.23)	0.75	92%
					Recessive model: GG/AG+AA	0.55 (0.20, 1.53)	-	-
Ethnicity								
Asian	3	0.79 (0.24, 2.59)	0.70	89%	Codominant model: AG/AA	0.79 (0.20, 3.16)	0.74	91%
					Codominant model: GG/AA	2.25 (0.79, 6.40)	-	-
					Dominant model: AG+GG/AA	0.80 (0.20, 3.19)	0.75	91%
					Recessive model: GG/AG+AA	1.70 (0.61, 4.77)	-	-
Caucasian	2	1.59 (1.30, 1.94)	0.001	0%	Codominant model: AG/AA	1.93 (1.50, 2.49)	0.001	44%
					Codominant model: GG/AA	1.64 (0.43, 6.33)	0.47	77%
					Dominant model: AG+GG/AA	0.63 (0.08, 4.91)	0.66	95%
					Recessive model: GG/AG+AA	1.25 (0.27, 5.82)	0.78	83%

AF: atrial fibrillation. Conduction: conduction system disease.

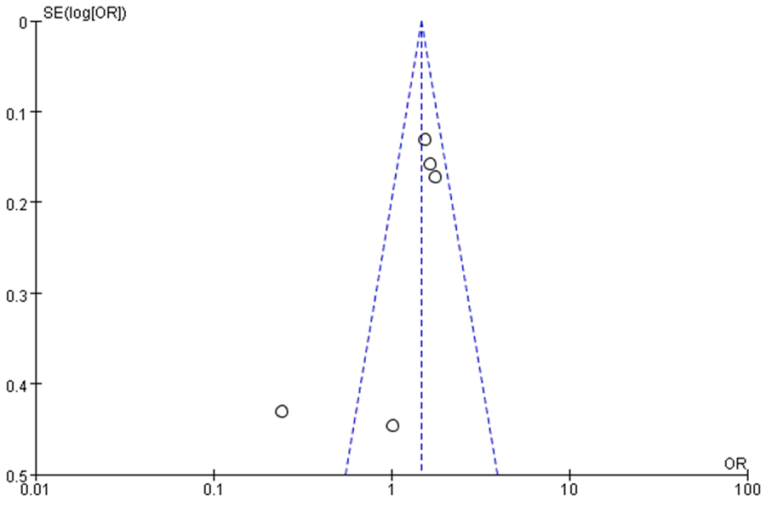

Figure 2. Funnel plots for assessing publication bias in the meta-analysis.

strated H558R polymorphism may play a role in preventing some specific cardiac arrhythmias. However, several studies also reported that *SCN5A* H558R polymorphism carriers have a higher risk to the cardiac diseases, such as atrial fibrillation [27]. Additional studies will be required not only to detect its more prevalence rate in cardiac arrhythmia but also to investigate the possible biophysical mechanisms of H558R on the channel function in coordination with other mutations.

Limitations in our analysis should also be considered. First, the conduction system diseases group contains many different cardiac problems, and the pathophysiology of these diseases differs from each other. So the grouping method is still debatable. Second, many other clinical factors such as age, sex or other mixed mutations in each study might lead to bias and haven't

been considered in the study. Last, we re-stricted our included studies published in English.

Conclusion

In sum, this meta-analysis investigated the relationship between *SCN5A* H558R polymorphism and cardiac arrhythmias risk. Although there are several limitations, our work indicates that the *SCN5A* H558R polymorphism may increase the risk of atrial fibrillation and the risk of arrhythmias in Caucasian.

Disclosure of conflict of interest

None.

Abbreviations

AF, atrial fibrillation.

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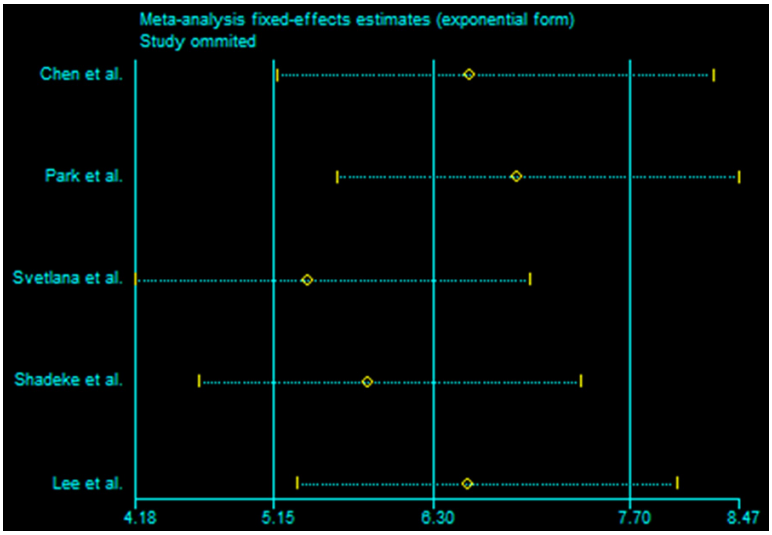
Supplementary Table 1. Quality assessment of studies included in the systematic review according to the modified Newcastle-Ottawa scale

Author	Chen et al.	Park et al.	Svetlana et al.	Shadeke et al.	Lee et al.
Selection					
Adequacy of case definition	a★	a★	a★	a★	a★
Representativeness of the cases	a★	a★	a★	a★	a★
Selection of controls	a★	b	a★	b	a★
Definition of controls	a★	a★	a★	a★	a★
Comparability					
Cases and controls of homogeneous ethnic descent	a★	a★	a★	a★	a★
Population stratification	b	b	b	b	b
Exposure					
Ascertainment of exposure	b	b	b	b	b
Same method of ascertainment for cases and controls	a★	a★	a★	a★	a★
Genotyping call rate	b	b	b	b	b
Total	6★	5★	6★	5★	6★



Supplementary Figure 1. Sensitive analysis of studies in the meta-analysis.