



The relationship between the insertion/deletion gene polymorphism of ACE and atrial fibrillation in Chinese population: a meta-analysis

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Abstract

Introduction: In this study, we aimed to explore the relationship between the I/D gene polymorphism of ACE and the risk of AF in Chinese population. **Materials and methods:** Studies searched in several databases from beginning to July 2019 were included in our study. After screening by evaluation, thirteen articles were selected. **Results:** Our results showed that I/D gene polymorphism of ACE increased the risk of AF. The stratified analyses by case types and control sources suggested a markedly increased association in lone AF, hypertensive patients with AF, and un-typed AF, as well as in studies with hospital person and healthy person. The stratified geographical analysis indicated the risk of AF increased significantly in North China. **Conclusions:** All in all, our results indicated the marked relationship between I/D gene polymorphism of ACE and the increased risk of AF in Chinese population.

Keywords: atrial fibrillation; insertion/deletion; gene polymorphism; angiotensin-converting enzyme.

Practical Application: Explore the relationship between the gene polymorphism of ACE and the risk of AF in Chinese population.

1 Introduction

Atrial fibrillation (AF) is the most common persistent arrhythmia with highest incidence among all the atrial arrhythmias. With the increase of age, the incidence of AF is increasing, and it can reach 10% in people over 75 years old (Hart & Halperin, 2001). The mortality in patients with AF is much higher than that in patients without AF (Benjamin EJ et al., 1998). There are many causes of atrial fibrillation, mainly diseases of the heart itself. Common factors include genetic factors, hypertension and heart disease, such as coronary heart disease (Fatkin et al., 2007). To date, several candidate genes, such as angiotensin-converting enzyme (ACE), have been implicated in cardiovascular disease, such as essential hypertension, myocardial infarction, and so on (Sayed-Tabatabaei et al., 2006; Zintzaras et al., 2008; Rudnicki & Mayer, 2009). Among these candidate gene polymorphisms, the insertion (I) or deletion (D) of 287 bp Alu repeat sequence is a hotspot of AF gene variants. It has been reported that the polymorphism includes homozygous D/D, I/I and heterozygous I/D. Yamashita *et al.* was the first one to investigate the relationship between gene polymorphism of I/D in ACE and AF in Japanese in 1997 (Yamashita et al., 1997). In addition, many epidemiological studies which have been performed to explore the relationship between polymorphism of ACE-I/D and individual susceptibility to AF were inconsistent. The reason may be due to the ethnic and regional differences of the subjects and the limit of the number of subjects per time. To decrease the interfere factors of genetic differences, we conducted a meta-analysis to explore the relationship between the polymorphism of ACE-I/D and the risk of AF in Chinese.

2. Subjects and methods

2.1 Identification of eligible studies

Articles published in PubMed, Embase, Web of Science, the Cochrane Library, the Chinese Biomedical Database, and CNKI databases from beginning to July 2019 were searched. The following terms were used: angiotensin converting enzyme AND atrial fibrillation AND polymorphism. Literature search is not limited to language. Moreover, the reference lists of identified studies were manually checked to include other potentially eligible articles. We would select papers when they satisfied those criteria: (1) studies with case-control or cohort; (2) the studies which were to explore the relationship between gene polymorphism of I/D in ACE and the risk of AF; (3) studies with genotype or allele frequencies in patients and control person; (4) studies reported in Chinese population; (5) studies with complete data. However, if studies were review, letter, case report, and editorial article, then they were excluded.

2.2 Data extraction

Data were extracted from eligible articles by 2 researchers, respectively. They firstly screened the titles and abstracts of all eligible literatures. If the title and abstract were inconclusive, the full text was reviewed. If the two researchers had different suggestion, it was up to them to discuss. Each study was collected available genotype data for the following characteristics: name of first author, case type, publication year, source of controls, geographic area, sample size, and gene polymorphism of ACE-I/D.

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2.3 Statistical analysis

The pooled OR and 95% CIs were used to evaluate the relationship between gene polymorphism and AF. This study detected the relevance between D allele and AF risk which was relative to the I allele, and the comparison between homozygote DD and II, DD and (II+ID), and (DD+ID) and II. Chi-square based Q-test was carried out to evaluate the heterogeneity. If two studies had no significant heterogeneity, OR was pooled using the fixed-effects model. If not, the random-effects model was used. The consistency between the two models was compared to explore sensitivity. The potential publication bias was assessed through funnel plot. Statistical analysis was performed with Stata12.0. It was considered to be statistically different when $P < 0.05$.

3 Results

3.1 The included studies

After searching the articles from these databases, 18 relevant articles were preliminarily included. Finally, there were 13 studies (Wang et al., 2003; Tsai et al., 2004; Chen et al., 2007; Chang et al., 2007; Tsai et al., 2008; Wei et al., 2008; Huang et al., 2009; Yang et al., 2009; Wang et al., 2011;

Zhang et al., 2011; Zhang et al., 2012; Nan et al., 2012; Jin et al., 2013) in this study. In addition, a total of 2029 patients with AF and 3371 control person were included. They were used to evaluate the relationship between gene polymorphism of ACE-I/D and AF risk in Chinese. According to case types of included studies, 686 non-familial structural AF cases, 534 hypertensive patients with AF and 246 lone AF cases were identified. The controls were selected from hospitalized patients. The basic information of each individual article were shown in Table 1.

3.2 The relationship between gene polymorphism of ACE-I/D and AF

The relationship between gene polymorphism of ACE-I/D and AF was illustrated in Table 2. In the overall population, the pooled results showed an increased AF risk with the polymorphism (Table 2, Figure 1). The stratified analysis by case type indicated a significant increased association for lone AF, hypertensive patients with AF, and un-typed AF (Table 2). The stratified analysis by controls also showed a notably increased correlation both in studies with hospital-based controls and in studies with healthy controls (Table 2). The stratified geographic analysis suggested a markedly increased risk of AF in North

Table 1. Characteristics of the studies that were included in the meta-analysis.

References	Case type	Source of controls	Geographic location	Case number	Control number	Cases			Controls			HWE in control, P-value
						II	ID	DD	II	ID	DD	
Wang et al. (2003)	Lone AF	Healthy subjects	Beijing	53	50	16	26	11	18	24	8	1.000
Wang et al. (2003)	Hypertensive patients with AF	Hospitalized patients	Beijing	32	38	11	16	5	13	18	7	0.861
Tsai et al. (2004)	Non-familial structural AF	Hospitalized patients	Taiwan	250	250	98	98	54	84	105	61	0.016
Chen et al. (2007)	Persistent AF	Hospitalized patients	Zhejiang	40	36	13	20	7	13	17	6	0.912
Chang et al. (2007)	Non-familial structural AF	Hospitalized patients	Heilongjiang	189	194	87	52	50	120	44	30	<0.001
Tsai et al. (2008)	Non-familial structural AF	Hospitalized patients	Taiwan	227	1009	89	88	50	297	496	216	0.739
Wei et al. (2008)	Documented structural AF	Patients/healthy subjects	Yunnan	55	63	14	23	18	23	28	12	0.509
Huang et al. (2009)	Hypertensive patients with AF	Hospitalized patients	Fujian	97	529	37	40	20	264	222	43	0.700
Yang et al. (2009)	Non-familial structural AF	Hospitalized patients	Guangdong	20	30	7	6	7	8	8	14	0.015
Wang et al. (2011)	AF	Hospitalized patients	Chongqing	148	157	60	70	18	68	69	20	0.703
Zhang et al. (2011)	AF	Hospitalized patients	Hubei	120	120	32	49	39	52	46	22	0.046
Zhang et al. (2012)	Lone AF	Healthy subjects	Shanghai	193	297	68	87	38	129	139	29	0.337
Nan et al. (2012)	AF	Hospitalized patients	Xinjiang	200	200	32	90	78	68	80	52	0.006
Jin et al. (2013)	Hypertensive patients with AF	Hospitalized patients	Henan	405	398	143	157	105	146	200	52	0.199

Table 2. Association of the ACE I/D gene polymorphism and AF in Chinese population.

	Analysis model	n	ORr(95%CI)	ORf(95%CI)	P _h
D vs. I	Total analysis	14	1.29 (1.07-1.55)	1.26 (1.16-1.37)	0.000
	Lone AF	2	1.43 (1.12-1.81)	1.43 (1.12-1.81)	0.585
	Hypertensive patients with AF	3	1.40 (1.11-1.77)	1.40 (1.19-1.65)	0.218
	Non-familial structural AF	4	1.00 (0.66-1.52)	0.98 (0.85-1.12)	0.000
	AF	3	1.55 (1.06-2.26)	1.57 (1.30-1.88)	0.018
	Healthy subjects as controls	2	1.43 (1.12-1.81)	1.43 (1.12-1.81)	0.585
	Hospitalized patients as controls	11	1.25 (1.00-1.56)	1.23 (1.12-1.34)	0.000
	North China	5	1.51 (1.23-1.87)	1.51 (1.32-1.73)	0.107
	South China	9	1.19 (0.94-1.52)	1.12 (1.01-1.25)	0.000
	DD vs. II	Total analysis	14	1.65 (1.17-2.32)	0.99 (0.82-1.19)
Lone AF		2	2.26 (1.36-3.75)	2.26 (1.36-3.74)	0.463
Hypertensive patients with AF		3	2.20 (1.31-3.71)	2.19 (1.57-3.05)	0.171
Non-familial structural AF		4	1.00 (0.55-1.81)	0.99 (0.77-1.27)	0.004
AF		3	2.17 (1.10-4.28)	2.30 (1.60-3.30)	0.037
Healthy subjects as controls		2	2.26 (1.36-3.75)	2.26 (1.36-3.74)	0.463
Hospitalized patients as controls		11	1.53 (1.02-2.29)	1.49 (1.26-1.77)	0.000
North China		5	2.24 (1.71-2.92)	2.23 (1.72-2.91)	0.400
South China		9	1.46 (0.91-2.33)	1.27 (1.03-1.56)	0.000
DD vs. II+ID		Total analysis	14	1.54 (1.20-1.99)	1.55 (1.34-1.78)
	Lone AF	2	2.04 (1.28-3.24)	2.03 (1.28-3.23)	0.388
	Hypertensive patients with AF	3	2.25 (1.43-3.53)	2.30 (1.70-3.11)	0.196
	Non-familial structural AF	4	1.10 (0.32-3.51)	1.10 (0.87-1.38)	0.056
	AF	3	1.62 (1.06-2.47)	1.66 (1.22-2.26)	0.176
	Healthy subjects as controls	2	2.04 (1.28-3.24)	2.03 (1.28-3.23)	0.388
	Hospitalized patients as controls	11	1.46 (1.08-1.96)	1.48 (1.27-1.73)	0.001
	North China	5	1.96 (1.55-2.47)	1.96 (1.56-2.47)	0.511
	South China	9	1.42 (1.00-2.01)	1.32 (1.10-1.59)	0.003
	DD+ID vs. II	Total analysis	14	1.28 (1.00-1.65)	1.19 (1.06-1.35)
Lone AF		2	1.39 (0.99-1.96)	1.39 (0.99-1.96)	0.859
Hypertensive patients with AF		3	1.21 (0.90-1.63)	1.19 (0.94-1.51)	0.279
Non-familial structural AF		4	0.93 (0.54-1.62)	0.89 (0.73-1.09)	0.000
AF		3	1.84 (1.07-3.16)	1.81 (1.37-2.39)	0.026
Healthy subjects as controls		2	1.39 (0.99-1.96)	1.39 (0.99-1.96)	0.859
Hospitalized patients as controls		11	1.24 (0.92-1.69)	1.15 (1.01-1.32)	0.000
North China		5	1.54 (1.01-2.35)	1.46 (1.20-1.78)	0.010
South China		9	1.16 (0.85-1.57)	1.06 (0.91-1.23)	0.001

China via the four model, while there was no significant risk in South China (Table 2).

3.3 Sensitive analysis and publication bias diagnosis

The sensitivity of this meta-analysis was assessed by comparing the pooled results between the two models. The ORs of marked

combinations did not change. Furthermore, the sensitivity analysis showed that the data were metastable (Table 2). The publication bias was evaluated by Begg's funnel plot (Figure 2), in which the shape did not show remarkable asymmetry. Moreover, the results of Egger's test suggested that there was no noteworthy publication bias in all studied articles (Figure 3).

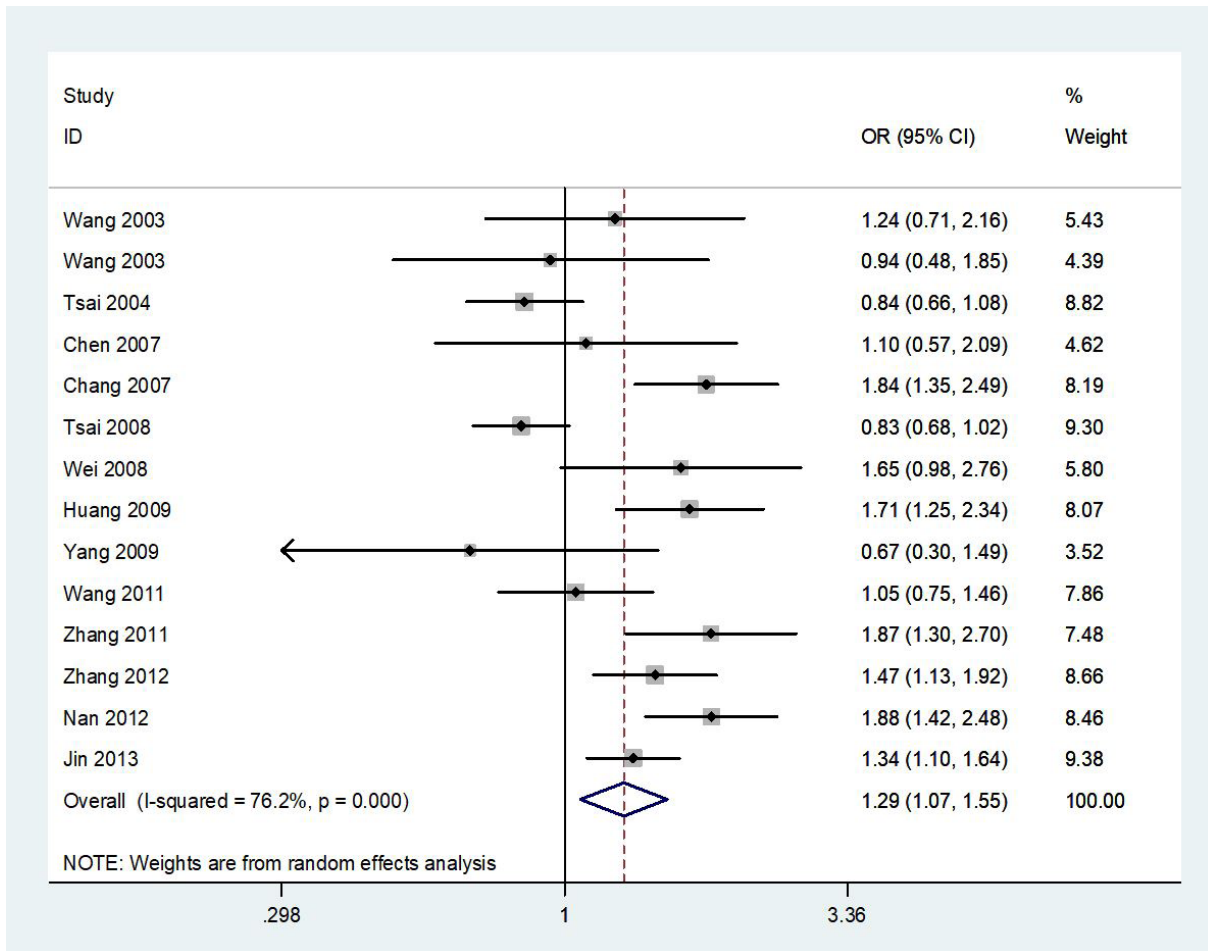


Figure 1. Forest plot for the association between ACE I/D gene polymorphism and AF under the allele random-effect model.

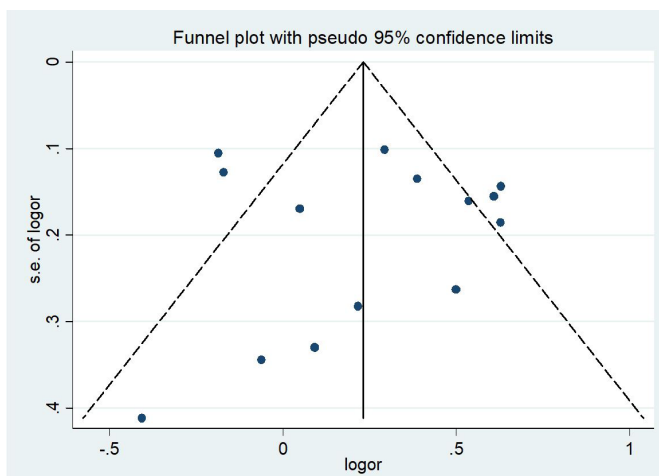


Figure 2. Publication bias assessment of ACE I/D gene polymorphism and AF susceptibility with Begg's funnel plot.

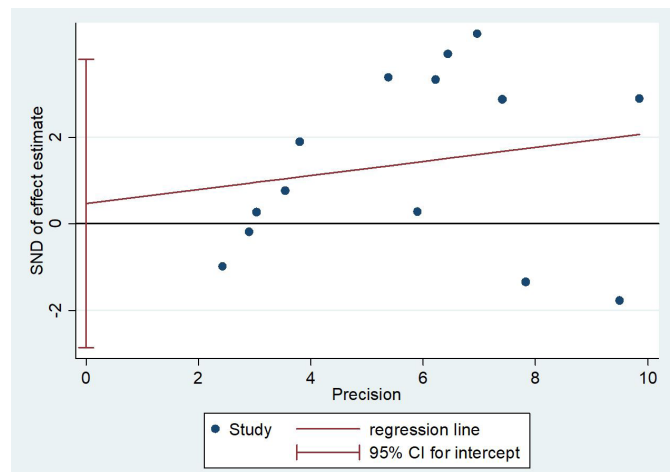


Figure 3. Egger's linear regression for the Begg's funnel plot.

4 Discussion

In recent years, more and more studies began to pay attention to the genetic susceptibility of AF. More importantly, some studies have shown that genetic variation of ACE I/D gene plays an significant role in the occurrence and development of

AF (Chang et al., 2007; Huang et al., 2009; Zhang et al., 2011; Zhang et al., 2012; Nan et al., 2012; Jin et al., 2013). ACE is an important component of renin - Angiotension - aldosterone. Some studies have shown that ACE I/D gene is highly expressed in heart tissue. ACE can act on adrenal cortex, promote the

secretion of aldosterone, and lead to atrial fibrosis and uneven conduction, resulting in the increased substrate of AF. The effect of gene polymorphism of ACE-I/D on the progression of AF has been studied, but the results are not consistent. This may be due to the differences in sample size, cardiovascular disease and race.

Therefore, we conducted this study to estimate the relationship between gene polymorphism of ACE-I/D and AF risk, and the article about Chinese was limited to reduce the effect of racial differences. Our results indicated that gene polymorphism of ACE I/D was markedly associated with AF risk in Chinese. We further performed subgroup analyses to investigate the validity of case type, source of controls and geographical location. Significant association was found about gene polymorphism of ACE-I/D on AF risk in all the subgroups for lone AF, hypertensive patients with AF, un-typed AF, studies with hospital-based controls, studies with healthy controls and the population from North China, while no association was found in non-familial structural AF and the population from South China.

Previously, there were two published meta-analyses which had paid attention to gene polymorphism of ACE-I/D and its association with AF risk (Liu et al., 2011; Ma et al., 2015). Liu et al. (2011) conducted a meta-analysis in which there were 18 case-control studies with 7577 patients and there were no marked associations between the gene polymorphism of ACE-I/D and AF risk in genetic additive model and dominant model, but there was a marked relevance in the recessive model. However, the authors suggested that their results cannot show an association between gene polymorphism of ACE-I/D and AF risk. In 2015, Ma et al (Ma et al., 2015) performed an evaluation of the relevance in 23 case-control studies. Their results indicated that gene polymorphisms of ACE I/D were notably associated to ethnicity, as well as AF. To some extent, those results indicated that gene polymorphism of ACE-I/D might be related to AF risk in Chinese.

There were some advantages in our study. We strictly implemented the inclusion and exclusion criteria to decrease selection deviation in highest measure. In addition, the inclusion of non-English articles will also minimize bias. Furthermore, we explored the effect of the geographic area and case type with regard to the risk of AF with relevance to polymorphism of ACE-I/D. However, there were also some limitations. There were only data from a single ethnic group in this conducted (ethnic-specific) meta-analysis. Besides, we had not study other factors involved in AF, including age, smoking, etc. It could cause potential bias. Furthermore, the etiology of osteoporosis is very complex, which is regulated by activities of gene-gene and gene-environment interactions. Due to the lack of relevant data, we did not consider the interaction of these factors.

In conclusion, we provided strong evidence to indicate that gene polymorphisms of ACE-I/D were related to AF risk in Chinese. In addition, subgroup analysis revealed a marked correlation in various AF case types and geographic areas. However, the gene polymorphisms of ACE-I/D is not the only factor related to AF risk, and further studies are necessary to explore the potential relevance with gene-gene and gene-environment interactions.

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