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Angiotensin converting enzyme I/D polymorphism and sarcoidosis risk

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Abstract. *Background:* This meta-analysis investigates the associations of angiotensin-converting enzyme (ACE) polymorphism and risk of sarcoidosis. *Material and Method:* Two reviewers independently searched three databases including PubMed, EMBASE, and Cochrane database to identify published studies. Full texts of the selected studies were accessed and related data was extracted using a standardized data extraction form. *Results:* A total of 18 studies contained a total of 1626 patients with sarcoidosis in case group and 2465 healthy controls in control group. Results of the current meta-analysis revealed that ACE DD genotype was associated with a significantly increased risk of sarcoidosis (OR=1.21; 95%CI, 1.06–1.38; I^2=48%). In the race subgroup analysis, Asians with ACE DD genotype showed no significant increased risk of sarcoidosis (OR=1.37; 95%CI, 0.94–1.99; I^2=78%). Caucasians with ACE DD genotype had an increased sarcoidosis risk (OR=1.16; 95%CI, 1.01–1.36; I^2=24%). *Conclusions:* Our meta-analysis indicated that the ACE DD genotype correlated with an increased risk of sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 205; 32: 284-288)*

Key words: renin-angiotensin system, sarcoidosis, meta-analysis, association

Introduction

Sarcoidosis is a multi-system disease characterized by noncaseating epithelioid granulomas with unknown etiology. In the USA, the incidence of sarcoidosis varies by ethnicity. Sarcoidosis is about three times more common among African Americans than European Americans (1). A growing body of evidence indicate that genetic might play important roles in the development of sarcoidosis.

The renin-angiotensin system (RAS) is a complex regulator of blood pressure, cardiovascular remodeling and vascular tone. Several studies have demonstrated that RAS plays a pivotal role in the pathogenesis of sarcoidosis. For example, elevated serum levels of angiotensin-converting enzyme (ACE) are detected in approximately 60% of patients with sarcoidosis (2). Vorselaars et al. found that baseline and serial serum ACE levels correlate well with lung function improvement during methotrexate treatment in sarcoidosis patients (3). Hyldgaard et al. indicate that serum ACE is an important diagnostic marker of sarcoidosis with high sensitivity (4). Recent studies have shown that ACE I/D polymorphism could increase the susceptibility of sarcoidosis (5-19). However, the

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results remained controversial. In order to address this problem, we conducted this meta-analysis to investigate the correlation between ACE I/D polymorphism and the susceptibility to sarcoidosis.

Methods

Publication search

A literature research was conducted using PubMed, EMBASE, and Cochrane database, to identify studies published prior to Jan 2015. Relevant studies were identified using the terms: "sarcoidosis" and "angiotensin-converting enzyme". The search was confined to humans. A manual search of references of the original articles related with this topic was used to identify additional studies. If the data or data subsets were published in more than one paper, only the paper with the largest sample size was enrolled.

Inclusion and exclusion criteria

Studies were selected for meta-analysis if they met the inclusion criteria as follows: (1) case-control study design; (2) studies that investigated the association between the ACE I/D polymorphism and the susceptibility to sarcoidosis; (3) study subjects were sarcoidosis patients confirmed by histopathology in case group; (4) the enrolled studies provided ACE I/D polymorphism. The exclusion criteria were: (1) reviews and summaries; (2) repetitive publications; (3) no raw data of the ACE I/D polymorphism.

Data extraction

The following data were recorded from each article: first author, years of publication, country, ethnicity of participants, age, gender, numbers of cases and controls. Two investigators extracted data independently and reached agreements on all the items. If there were any disagreements between the two investigators, the data were re-examined and, following a thorough discussion and evaluation of each item, a consensus was reached.

Statistical analysis

The association of ACE I/D polymorphism and sarcoidosis risk was investigated by calculating OR with 95% CI. Hardy-Weinberg equilibrium (HWE) was calculated by Chi square-test. Heterogeneity of the combined studies was assessed with Cochran's Q-statistic test and I^2 test. The P value of Cochran's Q-statistic of below 0.05, was considered statistically significant heterogeneity. The I^2 test provides a measure of the degree of heterogeneity in the results. Typically, values of 0~25% are considered to represent no heterogeneity, 25~50% to modest heterogeneity, 50~75% to large heterogeneity and 75~100% to extreme heterogeneity. A random effects model was applied. Galbraith plot was applied to find the source of the heterogeneity. Stratified analysis was performed by race. Potential publication bias was examined by funnel plot and Begg's test. Sensitivity analysis was performed. Statistical tests were calculated with STATA version 11.0 (StataCorp, College Stations, Texas, USA).

Results

Study characteristics

18 case-control studies (17 studies) of 1626 cases and 2465 controls on the association between ACE I/D polymorphism and sarcoidosis risk were included for this meta-analysis. 4 studies of Asian population and 14 studies of Caucasian population were included. Baseline characteristics of all included studies are displayed in Table 1.

Meta-analysis

ACE DD genotype was significantly associated with an increased risk of sarcoidosis (OR=1.21; 95%CI, 1.06–1.38; I^2=48%; Figure 1). In the race subgroup analysis, Asians with ACE DD genotype showed no significant increased risk of sarcoidosis (OR=1.37; 95%CI, 0.94–1.99; I^2=78%). Caucasians with ACE DD genotype had an increased sarcoidosis risk (OR=1.16; 95%CI, 1.01–1.36; I^2=24%).

As shown in Figure 2, a single study was deleted to see if the individual data set influence the pooled ORs. We find that the corresponding pooled ORs were not altered. Galbraith plot is applied to detect the source of the heterogeneity. As shown in Figure 3, two studies were the outliers. These two studies might be the main source of the heterogeneity. Thus,

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

First author	Year	Country	Ethnicity	Age	Gender	No. of Cases	No. of Controls	HWE
Arbustini	1996	Italy	Caucasian	Adult	Mixed	61	80	Yes
Furuya	1996	Japan	Asian	Adult	Mixed	103	341	Yes
Sharma	1997	UK	Caucasian	Adult	Mixed	47	146	Yes
Tomita	1997	Japan	Asian	Adult	Mixed	207	314	Yes
Takemoto	1998	Japan	Asian	Adult	Mixed	100	96	Yes
Garrib	1998	UK	Caucasian	Adult	Mixed	54	100	Yes
Maliarik	1998	USA	Caucasian	Adult	Mixed	60	48	Yes
Pietinalho	1999	Finland	Caucasian	Adult	Mixed	59	70	Yes
Papadopoulos	2000	Sweden	Caucasian	Adult	Mixed	32	107	Yes
McGrath a	2001	UK	Caucasian	Adult	Mixed	180	386	Yes
McGrath b	2001	Czech	Caucasian	Adult	Mixed	56	179	Yes
Planck	2002	Sweden	Caucasian	Adult	Mixed	73	65	Yes
Alia	2005	Spain	Caucasian	Adult	Mixed	177	104	Yes
Salobir	2007	Slovenia	Caucasian	Adult	Mixed	105	80	Yes
Tahir	2007	India	Asian	Adult	Mixed	72	96	Yes
Biller	2009	Germany	Caucasian	Adult	Mixed	100	100	Yes
Yilmaz	2012	Turkey	Caucasian	Adult	Mixed	70	69	Yes
Sarı	2014	Turkey	Caucasian	Adult	Mixed	70	84	Yes

HWE, Hardy-Weinberg equilibrium.

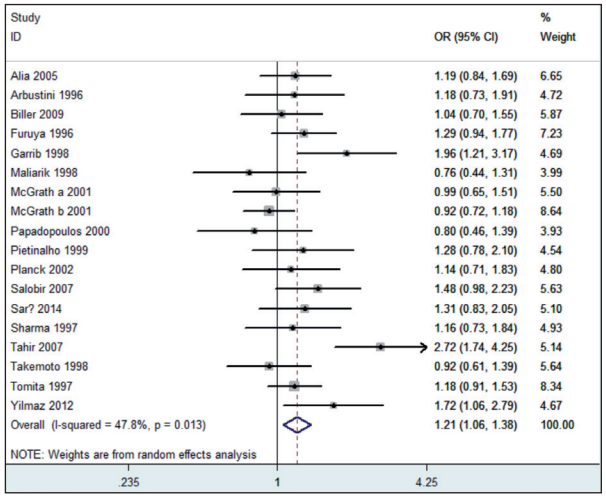

Fig. 1. Meta-analysis for the association between ACE I/D polymorphism and sarcoidosis risk

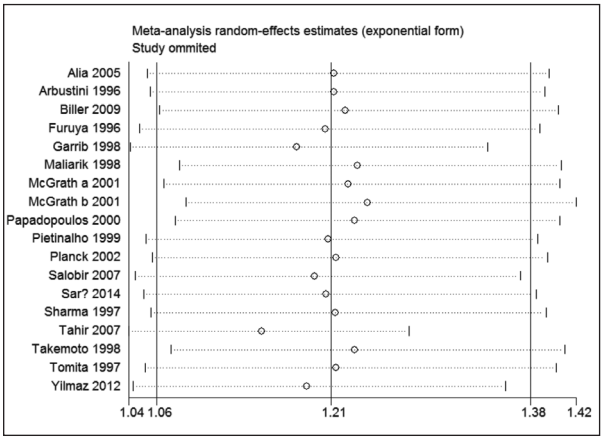

Fig. 2. Sensitivity meta-analysis for the association between ACE I/D polymorphism and sarcoidosis risk. A single study was deleted to see if the individual data set influence the pooled ORs

when we excluded these two studies, no obvious heterogeneity was found (I^2=0%, P=0.54).

The funnel plot is symmetrical, suggesting no publication bias (P=0.36) (Figure 4).

Discussion

In this meta-analysis, we investigated the association between the ACE I/D polymorphism and sarcoidosis risk including 1626 cases and 2465 controls. We found that ACE DD genotype is a risk factor of sarcoidosis. Individuals with ACE DD genotype showed an increased risk of sarcoidosis. The result suggested that subjects with ACE DD genotype may have an increased sarcoidosis risk compared to those subjects without ACE DD genotype. In the stratified analysis by ethnicity, this significant association was only seen in Caucasians. However, the lower 95% level was just above 1. On the other hand, only 4 studies with Asians population were included in meta-analysis. It is difficult to believe that this represents a real difference. Thus, more studies with

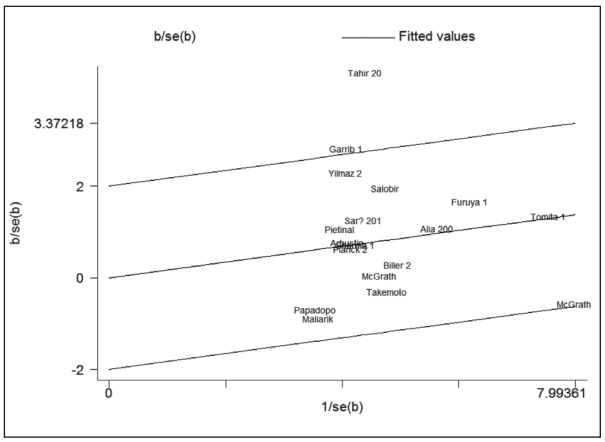

Fig. 3. Galbraith plot of ACE I/D polymorphism and sarcoidosis risk. Galbraith plot was used to find the main source of heterogeneity

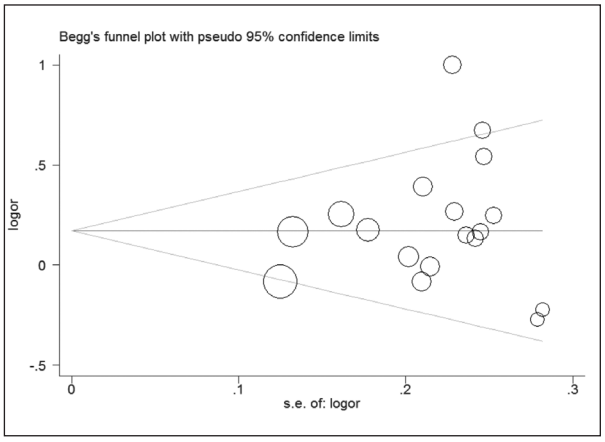

Fig. 4. Funnel plot for the association between ACE I/D polymorphism and sarcoidosis risk. The funnel plot is symmetrical, suggesting no publication bias.

Asians and Caucasians are needed to address the role of ACE I/D polymorphism on sarcoidosis risk.

Plasma and tissue ACE concentrations are associated with the ACE gene which is located on chromosome 17q23. The homozygous DD genotype is associated with a two-three folds levels of ACE (20,21). Fløe and colleagues suggested that genotyping for the I/D polymorphism increases the benefit of s-ACE since all studies found significantly different levels between genotype groups in healthy subjects (22). The mean DD/II ratio was 1.85 (range: 1.79-1.92) for all studies, 2.01 (1.92-2.10) for Caucasians and 1.64 (1.55-1.73) for Asians (22). This result indicated that ACE DD genotype might increase sarcoidosis risk. Sharma et al (23) evaluated their genotypebased reference intervals on 47 sarcoidosis patients and found 33.5% more patients to have elevated sACE than by applying standard reference intervals. These findings indicate that routine genotyping would increase the yield of sACE in diagnosing sarcoidosis, though they do not show whether routine genotyping will have a similar impact on the clinical management of these patients. More prospective studies are needed to clarify this. In addition, Kaura and colleagues reported that a patient with sarcoidosis treated with an ACE inhibitor (ACEI) had the remission for over 4 years (24). However, the effect of ACEI therapy in the treatment of sarcoidosis needs to be determined in a large clinical trial (25).

Our meta-analysis had some limitations. First, the numbers of included studies were not sufficient to do a comprehensive analysis, particularly for Asians and Africans. Second, we cannot evaluate the the effects of the gene-gene interactions because of insufficient data.

This meta-analysis suggested that ACE DD genotype might be correlated with the increased susceptibility to sarcoidosis.

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