Meta-analytical association between angiotensin-converting enzyme gene polymorphisms and sarcoidosis risk

R. Zhu[1], L.Q. Bi[2], H. Kong[2], S.L. Tilley[3], H. Wang[2] and W.P. Xie[2]

[1]Department of Respiratory Medicine, The Huai'an First People's Hospital, Nanjing Medical University, Huai'an, China
[2]Department of Respiratory Medicine, The First Affiliated Hospital, Nanjing Medical University, Nanjing, China
[3]Pulmonary Immunobiology Laboratory, University of North Carolina, Chapel Hill, NC, USA

Corresponding author: W.P. Xie
E-mail: wpxie@njmu.edu.cn

ABSTRACT. Previous reports identified an association between sarcoidosis and an insertion/deletion (I/D) polymorphism in angiotensin-converting enzyme. Our meta-analysis of articles published between March 1996 and June 2013 identified studies in the PubMed, EMBASE, and the China National Knowledge Infrastructure databases. We examined whether angiotensin-converting enzyme polymorphisms influence sarcoidosis susceptibility. The strength of the association between I/D polymorphisms and sarcoidosis risk was measured based on the odds ratio and 95% confidence interval. Analysis was based on recessive and dominant models. Ethnic subgroup analysis from 18 articles (1882 cases and 3066 controls) showed that DD homozygote carriers were at a slightly increased risk of sarcoidosis compared with II homozygotes and DI heterozygotes (P = 0.03). Comparison of DD plus DI *vs* II revealed no significant association with sarcoidosis in group

and ethnic subgroup analysis. We found that the I/D polymorphism in the angiotensin-converting enzyme gene was not associated with a major risk of sarcoidosis.

Key words: Angiotensin-converting enzyme; Meta-analysis; Polymorphism; Sarcoidosis

INTRODUCTION

Sarcoidosis is a chronic systemic inflammatory disorder characterized by the accumulation of CD4+ T lymphocytes and macrophages, as well as the presence of non-caseating epithelioid granulomas in the affected organs [Newman et al., 1997; American Thoracic Society (ATS) et al., 1999]. Although it has been hypothesized that there may be an infectious or environmental etiology to sarcoidosis (Saidha et al., 2012), the cause of this disease remains obscure. Evidence of familial and ethnic clustering strongly suggests that a genetic predisposition exists (Rybicki et al., 1997a). Numerous studies have focused on the role of genetic factors in the susceptibility to sarcoidosis (Iannuzzi, 2007; Kieszko et al., 2010; Suzuki et al., 2012; Pabst et al., 2013). Among these factors, the angiotensin-converting enzyme (ACE) gene is one of the most extensively studied. ACE is a metallopeptidase found in many tissues of the body, including endothelial cells, which function predominantly to convert angiotensin I to angiotensin II and inactivate bradykinin (Bernstein et al., 2013). ACE is also present in the epithelioid cells of granulomas, and approximately 50-60% of patients with sarcoidosis have increased serum levels of ACE; thus, an ACE assay is the most widely used laboratory test for sarcoidosis. In both healthy individuals and patients with sarcoidosis, 38-47% of phenotypic variations in serum ACE levels are accounted for by the insertion (I) or deletion (D) of a 287-bp sequence in intron 16 of the ACE gene, with the DD genotype associated with higher levels of ACE. Numerous studies worldwide have investigated the potential association between this polymorphism and sarcoidosis, but the results have been inconsistent.

To further explore whether such an association exists, Medica et al. (2007) performed a meta-analysis of 12 case-control studies published before March 2005 that examined the relationship between ACE genetic polymorphisms and sarcoidosis. The results of their analysis suggested that the risk of sarcoidosis was not substantially influenced by the ACE genotype. However, the number of included studies was relatively small, and a subgroup analysis based on ethnicity was not conducted. However, a more recent meta-analysis by Song et al. (2013), extending the number of studies to 17 (1556 cases and 2381 controls), found contrasting results. These authors found a significant association between sarcoidosis and the D allele of the ACE gene; furthermore, comparisons with a recessive model (DD *vs* DI + II) revealed a small but significant increase in sarcoidosis susceptibility with the DD genotype (odds ratio [OR] = 1.251). Interestingly, the authors also carried out subgroup analysis by ethnicity and determined that the DD + DI genotypes (i.e., a dominant model) were associated with sarcoidosis in East Asians [OR = 1.342; 95% confidence interval (CI) = 1.041-1.729], whereas the DD genotype (i.e., recessive model) was associated with sarcoidosis in Europeans (OR = 1.215; 95%CI = 1.070-1.463).

Because additional relevant studies have been published that were not included in either of these conflicting analyses, we examined whether ACE genetic polymorphisms were associated with an increased risk of sarcoidosis by performing a meta-analysis of all eligible studies published between March 1996 and June 2013.

MATERIAL AND METHODS

Search strategy

We systematically searched the PubMed, EMBASE, and China National Knowledge Infrastructure electronic databases to identify articles published between March 1996 and June 2012 that evaluated the association between polymorphisms of the ACE gene and sarcoidosis risk. Two independent researchers (R. Zhu and L.Q. Bi) conducted literature searches using the following search terms: "sarcoidosis" and "angiotensin-converting enzyme" or "ACE" in combination with "polymorphism", "mutation", or "variant". All languages were included, and special consideration was given to case-control studies. To avoid the potential loss of any relevant article, an additional search was performed of the references cited in the identified articles using the "related articles" link. Any discrepancies were resolved through discussion, with arbitration by a third author if necessary.

Study selection

The studies included in our meta-analysis met the following inclusion criteria: 1) the study examined the association between the ACE I/D gene polymorphism and sarcoidosis; 2) the study was a case-control trial; 3) the diagnosis of sarcoidosis was made in accordance with established criteria: a compatible clinical and radiological picture; histological demonstration of non-caseating granulomas in 1 or more tissues, with negative stains and cultures for mycobacteria and fungi or a positive Kveim test; exclusion of other granulomatous disease; and genotype frequencies were reported; 4) the genotype distributions in both cases and controls were available for estimating an OR with a 95%CI. The following studies were excluded: 1) studies reporting allele frequencies; 2) repeat or overlapping publications; 3) abstracts, letters, editorials, reviews, and congress communications.

Data extraction

Two authors (R. Zhu and L.Q. Bi) independently assessed all potentially relevant studies and reached a consensus on all items. Any discrepancies were resolved through discussion, with arbitration by a third author if necessary. The following data were collected from each study: first author, publication year, ethnicity of cases and controls, total number of cases and controls, ages of cases and controls, genotyping methods, and genotype distributions in cases and controls. Furthermore, information required to test Hardy-Weinberg equilibrium was extracted, or calculated manually if unavailable.

Statistical analysis

For each study, we first examined whether the genotype distribution in the controls was in Hardy-Weinberg equilibrium using the open-source Review Manager version 4.2.10 software (http://www.cc-ims.net/RevMan/download/revman-4) and the STATA 10.0 software (http://www.stata.com; Stata Corporation, College Station, TX, USA).

The strength of the association between the I/D polymorphism and sarcoidosis risk was measured by determining the OR and 95%CI. The statistical significance of the summary

OR was determined using a Z-test. Analysis was first carried out based on a recessive model (DD *vs* DI + II) and a dominant model (DD + DI *vs* II). Heterogeneity was evaluated using a χ^2-based Q statistic, and was considered to be statistically significant when the P value was <0.10. When the P value was >0.10, the pooled OR for each study was calculated using a fixed-effect model; otherwise, a random-effect model was used. The significance of the pooled ORs was determined using a Z-test, and P < 0.05 was considered to indicate statistical significance. Subgroup analyses were performed by ethnic group to evaluate ethnicity-specific effects. Sensitivity analysis was performed by sequentially excluding individual studies to assess the stability of the results. Publication bias was assessed by visual inspection of asymmetry in funnel plots, and the use of Begg and Egger tests (Zhang et al., 2010). All statistical analyses were performed using Review Manager 4.2 and STATA 10.0 softwares.

RESULTS

Literature search

The primary literature search initially identified 61 potentially eligible studies. Thirty-six articles were excluded after screening the titles and abstracts because they were either review articles, editorials, or irrelevant to the current study. Of the remaining 25 full-text articles (Arbustini et al., 1996; Furuya et al., 1996; Császár et al., 1997; Sharma et al., 1997; Tomita et al., 1997; Xu et al., 1997; Garrib et al., 1998; Maliarik et al., 1998; Niimi et al., 1998; Takemoto et al., 1998; Pietinalho et al., 1999; Stokes et al., 1999; Papadopoulos et al., 2000; McGrath et al., 2001; Ruprecht et al., 2001; Schürmann et al., 2001; Planck et al., 2002; Alía et al., 2005; Biller et al., 2006; Kruit et al., 2007; Salobir et al., 2007; Tahir et al., 2007; Biller et al., 2009; Kruit et al., 2010; Yilmaz et al., 2012), 2 lacked controls (Stokes et al., 1999; Schürmann et al., 2001), and 2 did not examine patients with sarcoidosis (Ruprecht et al., 2001; Biller et al., 2006); these 4 articles were thus excluded. An additional 3 articles (Császár et al., 1997; Niimi et al., 1998; Kruit et al., 2007) were also excluded because of incomplete reporting of data. Therefore, a total of 18 articles (20 case-control studies, including 1882 cases and 3066 controls) were included in the current meta-analysis examining the association between the I/D polymorphism of the ACE gene and susceptibility to sarcoidosis (Arbustini et al., 1996; Furuya et al., 1996; Sharma et al., 1997; Tomita et al., 1997; Xu et al., 1997; Garrib et al., 1998; Maliarik et al., 1998; Takemoto et al., 1998; Pietinalho et al., 1999; Papadopoulos et al., 2000; McGrath et al., 2001; Planck et al., 2002; Alía et al., 2005; Salobir et al., 2007; Tahir et al., 2007; Biller et al., 2009; Kruit et al., 2010; Yilmaz et al., 2012) (Figure 1). The characteristics of each case-control study are listed in Table 1, and the genotype and allele distributions for each study are detailed in Table 2. With regard to the ethnicities of the participants, 6 studies were in Asian subjects (Furuya et al., 1996; Tomita et al., 1997; Xu et al., 1997; Takemoto et al., 1998; Tahir et al., 2007; Yilmaz et al., 2012), 13 in Caucasian subjects (Arbustini et al., 1996; Sharma et al., 1997; Garrib et al., 1998; Maliarik et al., 1998; Pietinalho et al., 1999; Papadopoulos et al., 2000; McGrath et al., 2001 (one from UK, one from Czech Republic); Planck et al., 2002; Alía et al., 2005; Salobir et al., 2007; Biller et al., 2009; Kruit et al., 2010), and 1 in African-American subjects (Maliarik et al., 1998). The genotypic distributions of the control groups in each study were in Hardy-Weinberg equilibrium, with $\chi^2 < 3.84$ (P > 0.05).
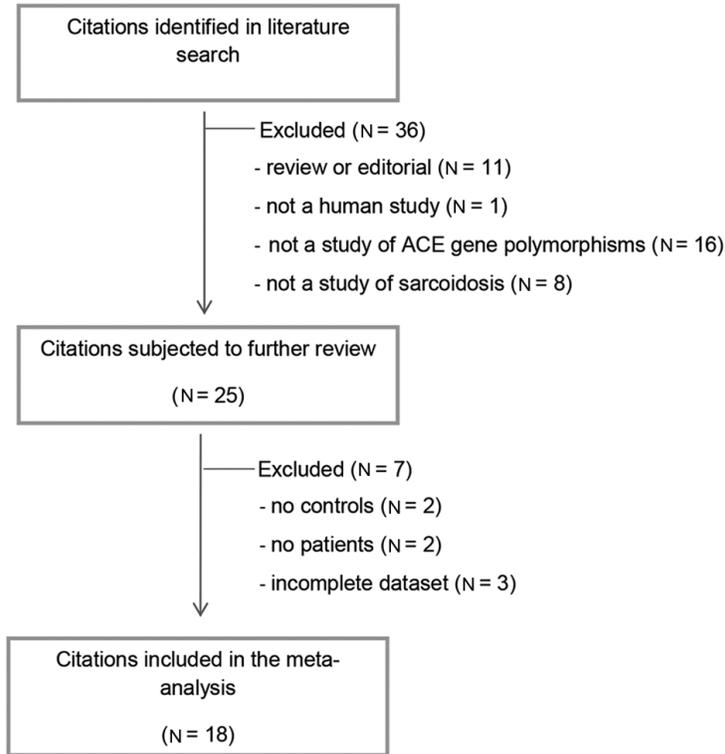
Figure 1. Studies included in the meta-analysis of the association between *ACE* gene polymorphisms and sarcoidosis.

Table 1. Characteristics of the 20 case-control studies (18 publications) included in the meta-analysis.

First author	Year	Ethnicity (country)	Case age (years)	No. of cases	No. of controls	Genotyping method	Diagnostic criteria
Arbustini	1996	Caucasian (Italy)	35.4 ± 10.7	61	80	PCR	Clinical and histological
Furuya	1996	Asian (Japan)	39.5 ± 16.4	103	341	PCR	Clinical and histological
Xu	1997	Asian (China)	?	49	85	PCR	Clinical and histological
Tomita	1997	Asian (Japan)	47.9 ± 16.1	207	314	PCR	Clinical and histological
Sharma	1997	Caucasian (UK)	47.0 ± 10.8	47	146	PCR	Histological
Takemoto	1998	Asian (Japan)	49.4 ± 12.7	100	96	PCR	Histological
Garrib	1998	Caucasian (UK)	?	54	100	PCR	Histological
Maliarik-1	1998	Caucasian (USA)	47.1 ± 10.1	60	48	PCR	Histological
Maliarik-2	1998	African-American (USA)	47.2 ± 10.1	183	111	PCR	Histological
Pietinalho	1999	Caucasian (Finland)	?	59	70	PCR	Not stated
Papadopoulos	2000	Caucasian (Sweden)	44.5 ± ?	32	107	PCR	Clinical and histological
McGrath-1	2001	Caucasian (UK)	40.0 ± 9.0	180	386	PCR	Clinical and histological
McGrath-2	2001	Caucasian (Czech Rep.)	46.0 ± 9.0	56	179	PCR	Clinical and histological
Planck	2002	Caucasian (Scandinavia)	38.0 ± ?	73	65	PCR	Clinical and histological
Alía	2005	Caucasian (Spain)	51.0 ± ?	177	104	PCR	Clinical and histological
Salobir	2007	Caucasian (Slovenia)	41.0 ± 1.0	105	80	PCR	Clinical and histological
Tahir	2007	Asian (India)	44.6 ± 9.5	72	96	PCR	Clinical and histological
Biller	2009	Caucasian (Germany)	43.0 ± 13.0	95	262	PCR	Clinical
Kruit	2010	Caucasian (Netherlands)	37.0 ± 11.0	99	327	PCR	Clinical and histological
Yilmaz	2012	Asian (Turkey)	46.6 ± 10.5	70	69	PCR	Histological

PCR, polymerase chain reaction; ?, data not available.

Table 2. Distribution of ACE genotypes in the patients with sarcoidosis and controls included in the meta-analysis

First author	Sarcoidosis			Control			Hardy-Weinberg equilibrium
	II	DI	DD	II	DI	DD	
Arbustini	10	24	27	10	44	26	0.19
Furuya	36	53	14	158	138	45	0.09
Xu	15	6	28	25	41	19	0.78
Tomita	77	101	29	136	139	39	0.71
Sharma	10	22	15	39	63	44	0.10
Takemoto	38	50	12	39	39	18	0.15
Garrib	14	28	12	11	52	37	0.25
Maliarik-1	13	32	15	7	26	15	0.43
Maliarik-2	32	95	56	29	66	16	0.06
Pietinalho	9	32	18	17	34	19	0.82
Papadopoulos	10	14	8	22	58	27	0.37
McGrath-1	45	84	51	89	180	117	0.22
McGrath-2	17	25	14	47	94	38	0.48
Planck	18	38	17	19	32	14	0.94
Alia	28	81	65	19	51	34	0.99
Salobir	24	42	39	21	42	17	0.64
Tahir	6	39	27	35	45	16	0.81
Biller	44	21	30	55	130	77	0.99
Kruit	25	49	25	68	182	77	0.06
Yilmaz	8	30	32	13	37	19	0.50

All-studies synthesis

As shown in Figure 2, we analyzed the heterogeneity of the recessive model (DD vs DI + II) for all 20 studies using a random-effect model, and determined that the χ^2 value was 43.83, with 19 degrees of freedom and P = 0.001. The I^2 value, used as another index of heterogeneity, was 56.7%, suggesting moderate heterogeneity. Therefore, we selected a random-effect model to synthesize the data. For the recessive model (DD vs DI + II), the OR was 1.28 (95%CI = 1.03-1.60) and the Z value for an overall effect was 2.22 (P = 0.03; Figure 2). Thus, there was a small but significant association between the DD genotype and sarcoidosis susceptibility. The data for the dominant model (DD + DI vs II) are presented in Figure 3: the OR was found to be 1.09 (95%CI = 0.84-1.41) (P > 0.05), indicating a lack of significant association.
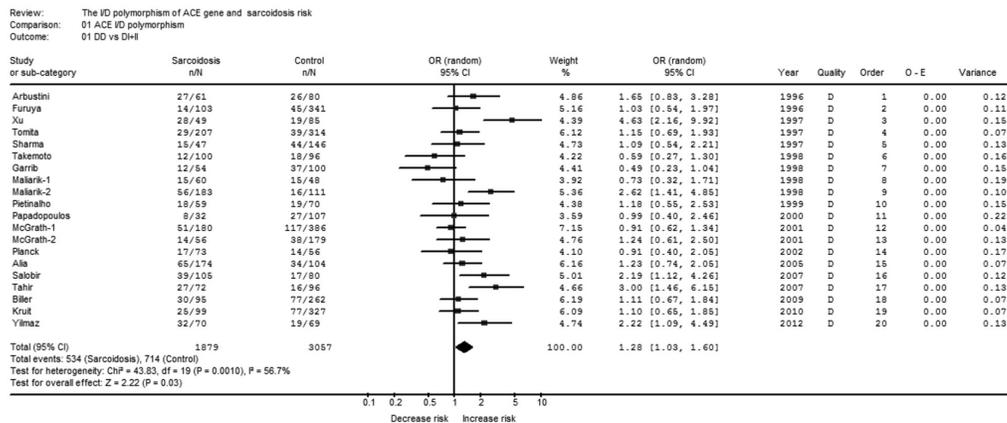
Figure 2. Meta-analysis using a random-effect model of the association between sarcoidosis risk and *ACE* insertion/deletion polymorphism in the recessive model (DD vs II + DI).
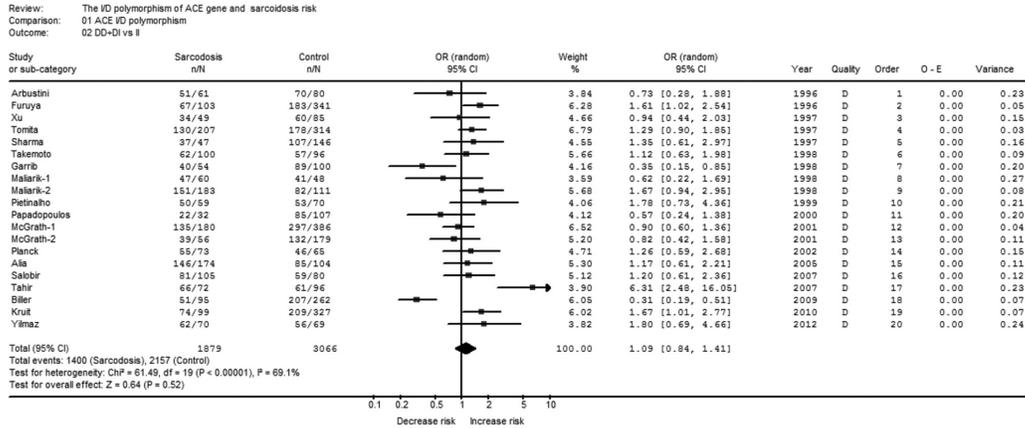
Figure 3. Meta-analysis using a random-effect model of the association between sarcoidosis risk and *ACE* insertion/deletion polymorphism in the dominant model (DI + DD *vs* II).

Subgroup analysis

In subgroup analysis by ethnicity, no significant increased risks were found in Asian (OR = 1.65; 95%CI = 0.94-2.91; P = 0.08) or Caucasian (OR = 1.10; 95%CI = 0.90-1.33; P = 0.35) subjects in the recessive model (DD *vs* DI + II) (Figure 4). It therefore appears that the DD *ACE* gene polymorphism does not increase the risk of sarcoidosis in Caucasian or Asian populations.
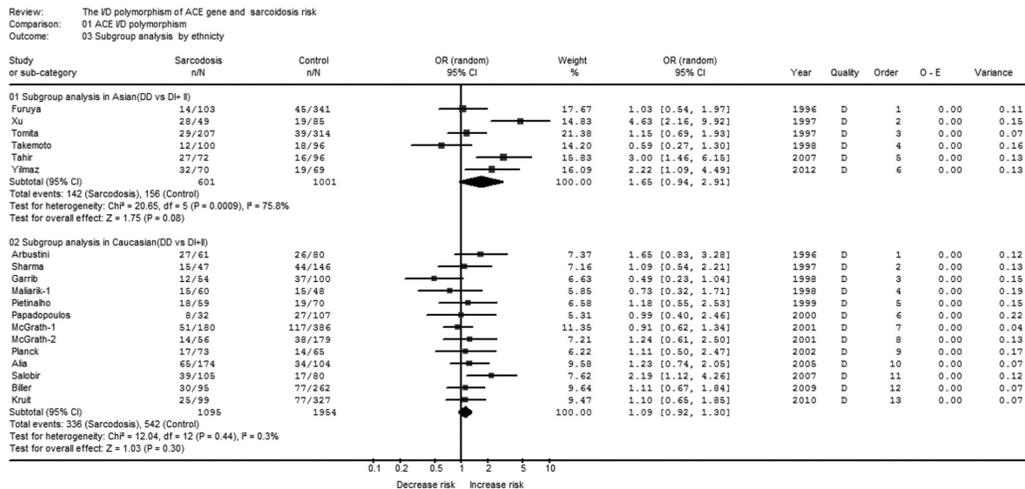
Figure 4. Meta-analysis using a random-effect model of the association between sarcoidosis risk and *ACE* insertion/deletion polymorphism (DD *vs* II + DI): subgroup analysis by ethnicity.

Publication bias

Publication bias was assessed using Begg's funnel plot and the Egger test. The shape of the funnel plots appeared symmetrical for the recessive model (DD *vs* DI + II) comparison,

suggesting an absence of publication bias. The Egger test, used to determine statistical evidence of funnel plot asymmetry, also indicated a lack of publication bias in the current meta-analysis (t = 0.6048, degrees of freedom = 18, P = 0.55; Figure 5).
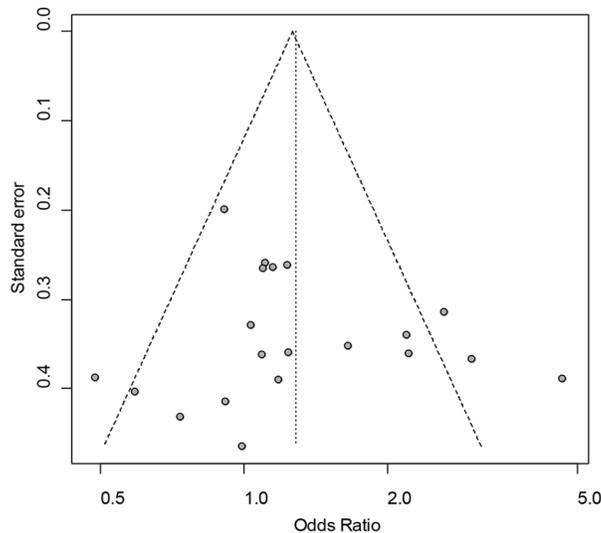

Figure 5. Funnel plot with 95% confidence interval (Begg test: z = -0.3893, P = 0.697).

Sensitivity analysis

To assess the stability of the results of the current meta-analysis, sensitivity analysis was conducted by sequentially excluding each study. Statistically similar results were obtained after sequential exclusion of each study, indicating stability.

DISCUSSION

ACE is expressed in numerous different tissues of the body, including the vascular endothelium, and through the synthesis of angiotensin II from angiotensin I, it plays an important role in regulating vascular smooth muscle and thus blood pressure (Bernstein et al., 2013). ACE is also expressed by the epithelioid cells of granulomas, and its levels reflect sarcoidosis activity. Although *ACE* polymorphisms are known to influence ACE levels, previous studies have provided inconsistent conclusions regarding whether an association exists between these polymorphisms and sarcoidosis. Numerous studies conducted in the United Kingdom, United States, Finland, Sweden, Czech Republic, Spain, Germany, and the Netherlands have reported no differences in the distribution of *ACE* genotypes between patients with sarcoidosis and healthy controls (Sharma et al., 1997; Garrib et al., 1998; Maliarik et al., 1998; Pietinalho et al., 1999; Papadopoulos et al., 2000; McGrath et al., 2001; Planck et al., 2002; Alía et al., 2005; Biller et al., 2009; Kruit et al., 2010). In contrast, several other studies found that *ACE* D/I gene polymorphisms may increase the risk of sarcoidosis, including a study of female Japanese patients with sarcoidosis (Furuya et al., 1996), as well as studies in Chinese (Xu et al., 1997), Slovenian (Salobir et al., 2007), Asian Indian (Tahir et al.,

2007), and Turkish populations (Yilmaz et al., 2012). In the USA, the incidence of sarcoidosis is higher in African-Americans than in Caucasians (Rybicki et al., 1997b, 1998; Maliarik et al., 1998), and the *ACE* genotype may play a more important role in the susceptibility to and progression of sarcoidosis in African-Americans. This implies that ethnicity may modulate the influence of *ACE* gene polymorphisms on the pathophysiology of sarcoidosis. The variation between studies examining the relationship between *ACE* gene polymorphisms and sarcoidosis susceptibility may have arisen from ethnic differences or from small sample sizes that lacked sufficient statistical power to detect a modest effect.

The meta-analysis of Medica et al. (2007) concluded that there was no association between *ACE* gene polymorphisms and sarcoidosis. However, these authors did not conduct subgroup analysis by ethnicity, and the number of articles included was small. In contrast, a more recent meta-analysis (Song et al., 2013) that included a greater number of studies and carried out subgroup analysis by ethnicity yielded conflicting results: the dominant model (DD + DI *vs* II) revealed an association with sarcoidosis in East Asians (OR = 1.342), while the recessive model (DD *vs* DI + II) showed an association both overall (OR = 1.342) and in Europeans (OR = 1.215).

The present meta-analysis included 20 studies (1882 cases and 3066 controls), and the results of the all-studies synthesis were consistent with those of Song et al. (2013). The summary ORs for the dominant genetic model did not show a significant association between *ACE* gene I/D polymorphisms and sarcoidosis risk, whereas a significant association was found for the recessive model. Subgroup analysis to assess the effects of ethnicity revealed that in both Asian and Caucasian populations, DD homozygote carriers did not exhibit a statistically significant increased risk of sarcoidosis. This contrasts with the data presented by Song et al. (2013). Because our meta-analysis included only 1 study carried out in an African-American population, additional research is warranted in this cohort to establish whether as association exists between the *ACE* genotype and sarcoidosis. Possible gender differences should also be further examined, as it has been reported that ACE2 may be involved in the progression of pulmonary sarcoidosis, and that this may depend on gender (Kruit et al., 2005).

Our meta-analysis has some limitations. First, a key potential limitation to any literature-based review and meta-analysis is reporting bias; although no obvious publication bias was observed in our study, it is not possible to rule this out entirely. Second, the number of patients with Asian or African-American ethnicities included in our analysis was relatively small, limiting the conclusions that may be drawn in these populations. Third, only published studies identified in the selected electronic databases were included in this study; this may also bias the results, as the exclusion of additional relevant data available from other sources may have occurred.

In conclusion, this meta-analysis supports the hypothesis that the *ACE* I/D polymorphism is not an important susceptibility marker in Caucasian and Asian individuals. However, the role of *ACE* polymorphisms in African-Americans remains unclear because of the small number of studies available for this ethnic group. Additional case-control studies should be conducted in large-scale cohorts to further investigate the association between *ACE* I/D polymorphisms and sarcoidosis risk in different ethnic groups.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

REFERENCES

American Thoracic Society (ATS) (1999). Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am. J. Respir. Crit. Care Med*. 160: 736-755.

Alía P, Mañá J, Capdevila O, Alvarez A, et al. (2005). Association between ACE gene I/D polymorphism and clinical presentation and prognosis of sarcoidosis. *Scand. J. Clin. Lab. Invest*. 65: 691-697.

Arbustini E, Grasso M, Leo G, Tinelli C, et al. (1996). Polymorphism of angiotensin-converting enzyme gene in sarcoidosis. *Am. J. Respir. Crit. Care Med*. 153: 851-854.

Bernstein KE, Ong FS, Blackwell WL, Shah KH, et al. (2013). A modern understanding of the traditional and nontraditional biological functions of angiotensin-converting enzyme. *Pharmacol. Rev*. 65: 1-46.

Biller H, Zissel G, Ruprecht B, Nauck M, et al. (2006). Genotype-corrected reference values for serum angiotensin-converting enzyme. *Eur. Respir. J*. 28: 1085-1090.

Biller H, Ruprecht B, Gaede KI, Müller-Quernheim J, et al. (2009). Gene polymorphisms of ACE and the angiotensin receptor AT2R1 influence serum ACE levels in sarcoidosis. *Sarcoidosis Vasc. Diffuse Lung Dis*. 26: 139-146.

Császár A, Halmos B, Palicz T, Szalai C, et al. (1997). Interpopulation effect of ACE I/D polymorphism on serum concentration of ACE in diagnosis of sarcoidosis. *Lancet* 350: 518.

Furuya K, Yamaguchi E, Itoh A, Hizawa N, et al. (1996). Deletion polymorphism in the angiotensin I converting enzyme (ACE) gene as a genetic risk factor for sarcoidosis. *Thorax* 51: 777-780.

Garrib A, Zhou W, Sherwood R and Peters TJ (1998). Angiotensin-converting enzyme (ACE) gene polymorphism in patients with sarcoidosis. *Biochem. Soc. Trans*. 26: S137.

Iannuzzi MC (2007). Advances in the genetics of sarcoidosis. *Proc. Am. Thorac. Soc*. 4: 457-460.

Kieszko R, Krawczyk P, Chocholska S, Dmoszyńska A, et al. (2010). TNF-alpha and TNF-beta gene polymorphisms in Polish patients with sarcoidosis. Connection with the susceptibility and prognosis. *Sarcoidosis Vasc. Diffuse Lung Dis*. 27: 131-137.

Kruit A, Ruven HJ, Grutters JC and van den Bosch JM (2005). Angiotensin-converting enzyme 2 (ACE2) haplotypes are associated with pulmonary disease phenotypes in sarcoidosis patients. *Sarcoidosis Vasc. Diffuse Lung Dis*. 22: 195-203.

Kruit A, Grutters JC, Gerritsen WB, Kos S, et al. (2007). ACE I/D-corrected Z-scores to identify normal and elevated ACE activity in sarcoidosis. *Resp. Med*. 101: 510-515.

Kruit A, Ruven HJ, Grutters JC and van den Bosch JM (2010). Angiotensin II receptor type 1 1166 A/C and angiotensin converting enzyme I/D gene polymorphisms in a Dutch sarcoidosis cohort. *Sarcoidosis Vasc. Diffuse Lung Dis*. 27: 147-152.

Maliarik MJ, Rybicki BA, Malvitz E, Sheffer RG, et al. (1998). Angiotensin-converting enzyme gene polymorphism and risk of sarcoidosis. *Am. J. Respir. Crit. Care Med*. 158: 1566-1570.

McGrath DS, Foley PJ, Petrek M, Izakovicova-Holla L, et al. (2001). Ace gene I/D polymorphism and sarcoidosis pulmonary disease severity. *Am. J. Respir. Crit. Care Med*. 164: 197-201.

Medica I, Kastrin A, Maver A and Peterlin B (2007). Role of genetic polymorphisms in ACE and TNF-alpha gene in sarcoidosis: a meta-analysis. *J. Hum. Genet*. 52: 836-847.

Newman LS, Rose CS and Maier LA (1997). Sarcoidosis. *N. Engl. J. Med*. 336: 1224-1234.

Niimi T, Tomita H, Sato S, Mori T, et al. (1998). Bronchial responsiveness and angiotensin-converting enzyme gene polymorphism in sarcoidosis patients. *Chest* 114: 495-499.

Pabst S, Bradler O, Gillissen A, Nickenig G, et al. (2013). Toll-like receptor-9 polymorphisms in sarcoidosis and chronic obstructive pulmonary disease. *Adv. Exp. Med. Biol*. 756: 239-245.

Papadopoulos KI, Melander O, Orho-Melander M, Groop LC, et al. (2000). Angiotensin converting enzyme (ACE) gene polymorphism in sarcoidosis in relation to associated autoimmune diseases. *J. Intern. Med*. 247: 71-77.

Pietinalho A, Furuya K, Yamaguchi E, Kawakami Y, et al. (1999). The angiotensin-converting enzyme DD gene is associated with poor prognosis in Finnish sarcoidosis patients. *Eur. Respir. J*. 13: 723-726.

Planck A, Eklund A, Yamaguchi E and Grunewald J (2002). Angiotensin-converting enzyme gene polymorphism in relation to HLA-DR in sarcoidosis. *J. Intern. Med*. 251: 217-222.

Ruprecht B, Schürmann M, Ziegenhagen MW, vom Bauer E, et al. (2001). Corrected normal values for serum ACE by genotyping the deletion-/insertion-polymorphism of the ACE gene. *Pneumologie* 55: 326-332.

Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, et al. (1997a). Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am. J. Epidemiol*. 145: 234-241.

Rybicki BA, Maliarik MJ, Major M, Popovich J Jr, et al. (1997b). Genetics of sarcoidosis. *Clin. Chest Med*. 18: 707-717.

Rybicki BA, Maliarik MJ, Major M, Popovich J Jr, et al. (1998). Epidemiology, demographics, and genetics of sarcoidosis. *Semin. Respir. Infect*. 13: 166-173.

Saidha S, Sotirchos ES and Eckstein C (2012). Etiology of sarcoidosis: does infection play a role? *Yale J. Biol. Med*. 85: 133-141.

Salobir B, Medica I, Tercelj M, Kastrin A, et al. (2007). Association of angiotensin-converting enzyme/DD genotype with sarcoidosis susceptibility in Slovenian patients. *Med. Sci. Monit*. 13: CR538-CR542.

Schürmann M, Reichel P, Müller-Myhsok B, Dieringer T, et al. (2001). Angiotensin-converting enzyme (ACE) gene polymorphisms and familial occurrence of sarcoidosis. *J. Intern. Med*. 249: 77-83.

Sharma P, Smith I, Maguire G, Stewart S, et al. (1997). Clinical value of ACE genotyping in diagnosis of sarcoidosis. *Lancet* 349: 1602-1603.

Song GG, Kim JH and Lee YH (2013). Associations between the angiotensin-converting enzyme insertion/deletion polymorphism and susceptibility to sarcoidosis: a meta-analysis. *J. Renin Angiotensin Aldosterone Syst*. [Epub ahead of print].

Stokes GS, Monaghan JC, Schrader AP, Glenn CL, et al. (1999). Influence of angiotensin converting enzyme (ACE) genotype on interpretation of diagnostic tests for serum ACE activity. *Aust. N. Z. J. Med*. 29: 315-318.

Suzuki H, Ota M, Meguro A, Katsuyama Y, et al. (2012). Genetic characterization and susceptibility for sarcoidosis in Japanese patients: risk factors of BTNL2 gene polymorphisms and HLA class II alleles. *Invest. Ophthalmol. Vis. Sci*. 53: 7109-7115.

Tahir M, Sharma SK, Ashraf S and Mishra HK (2007). Angiotensin converting enzyme genotype affects development and course of sarcoidosis in Asian Indians. *Sarcoidosis Vasc. Diffuse Lung Dis*. 24: 106-112.

Takemoto Y, Sakatani M, Takami S, Tachibana T, et al. (1998). Association between angiotensin II receptor gene polymorphism and serum angiotensin converting enzyme (SACE) activity in patients with sarcoidosis. *Thorax* 53: 459-462.

Tomita H, Ina Y, Sugiura Y, Sato S, et al. (1997). Polymorphism in the angiotensin-converting enzyme (ACE) gene and sarcoidosis. *Am. J. Respir. Crit. Care Med*. 156: 255-259.

Xu ZJ, Luo RC and Qiu CC (1997). The tentative exploration of ACE gene polymorphism in sarcoidosis. *Chin. J. Tuberc. Respir. Dis*. 20: 376-377.

Yılmaz D, Karkucak M, Coşkun F, Yakut T, et al. (2012). ACE gene I/D polymorphism and risk of sarcoidosis development in Turkish patients. *Tuberk. Toraks* 60: 201-206.

Zhang Y, Zhang J, Huang J, Li X, et al. (2010). Polymorphisms in the transforming growth factor-beta1 gene and the risk of asthma: a meta-analysis. *Respirology* 15: 643-650.