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ORIGINAL ARTICLE

Associations between *ERAP1* polymorphisms and susceptibility to ankylosing spondylitis: a meta-analysis

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Abstract The aim of this study was to determine whether 11 polymorphisms of endoplasmic reticulum aminopeptidase 1 *(ERAP1)* confer susceptibility to ankylosing spondylitis (AS). The authors conducted meta-analyses on associations between *ERAP1* polymorphisms and AS susceptibility by using fixed and random effects models. A total of 19 articles were included in this meta-analysis, which comprised a total of 19,902 AS patients and 39,750 controls. The meta-analysis revealed a significant association between AS and the minor alleles of the *rs30187* polymorphism in all study subjects (OR = 1.255, 95 % CI = 1.147–1.373, $P = 8.0 \times 10^{-8}$). Stratification by ethnicity led to the identification of a significant association between this polymorphism and AS in European patients (OR = 1.283, 95 % CI = 1.237–1.331, $P < 1.0 \times 10^{-9}$). Meta-analyses of the results for the *rs27044*, *rs10050860*, *rs2287987*, *rs17482078*, and *rs26653* polymorphisms showed the same pattern that was found for *rs30187*. Interestingly, the *rs27037* polymorphism was significantly associated with AS susceptibility in both European and Asian patients. Meta-analysis showed a significant association between AS and the minor alleles of the *rs27980* and *rs27582* polymorphisms in the East Asian patients (OR = 0.904, 95 % CI = 0.818–0.999, $P = 0.047$; OR = 0.871, 95 % CI = 0.772–0.982, $P = 0.024$, respectively) (Table 2). However, these polymorphisms have not been studied in Europeans. This meta-analysis shows that the *ERAP1* polymorphisms are associated with the development of AS in Europeans and East Asians.

Keywords Ankylosing spondylitis · *ERAP1* · Meta-analysis · Polymorphism

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disorder characterized by the inflammation of the spinal and sacroiliac joints, which initially causes bone and joint erosion and leads to ankylosis [1]. Strong genetic factors have been implicated in the etiology of AS. Human leukocyte antigen *(HLA) B27* was the first genetic factor to be associated with AS, and it confers the greatest susceptibility to this disease. However, increasing evidence indicates that genes other than *HLA-B27* also contribute to AS susceptibility [2].

Genome-wide association studies suggest that endoplasmic reticulum aminopeptidase 1 (*ERAP1*, a known aminopeptidase regulator of tumor necrosis factor receptor 1 [TNFR1] shedding), also known as *ARTS1*, is a potential candidate (for contributing to AS susceptibility) that is not an HLA gene [3]. *ERAP1*, which is located on chromosome 5q15, trims peptides for class I HLA presentation and cleaves cell-surface cytokine receptors. ERAP1 was recently found to be a key determinant of the repertoire of peptides that are presented by class I HLA molecules and initiate T-cell responses [4]. A genome-wide association study revealed that two single-nucleotide polymorphisms (SNPs) (rs27044, rs30187) of ERAP1 were significantly associated with AS, and demonstrated that rs17482078, rs10050860, and rs2287987 polymorphisms also trended toward association with AS [3]. Although some studies have demonstrated that SNPs of *ERAP1* are associated with AS susceptibility, others disagree [5–23]. It would appear

that allelic frequencies often differ substantially between populations, and ethnicity-specific association studies are needed to confirm genetic associations in different populations. Meta-analysis provides a powerful means of summarizing the results produced by different studies [24–26], and in the present study, we performed a meta-analysis to investigate whether *ERAP1* polymorphisms are associated with susceptibility to AS in different ethnic populations.

Methods

Identification of eligible studies and data extraction

A search was performed using MEDLINE and EMBASE for studies that examined associations between the polymorphisms of *ERAP1* and AS to identify articles in which the *ERAP1* polymorphisms were determined in AS patients and controls (up to June 2014). Combinations of keywords such as "endoplasmic reticulum aminopeptidase 1," "*ERAP1*," "polymorphism," "ankylosing spondylitis," and "AS" were used as Medical Subject Heading (MeSH) and text words. References cited in the resulting studies were also investigated to identify additional studies not indexed by MEDLINE and EMBASE. Genetic association studies that determined the distributions of *ERAP1* alleles in AS patients and controls were eligible for inclusion. Studies were included in the analysis if (1) they were case control studies, (2) contained original data, and (3) had sufficient data to calculate odds ratios (ORs). Studies were excluded if (1) they contained data obtained from other studies, (2) the number of alleles could not be ascertained, or (3) family members were included in the study, because such analyses are based on linkage considerations. The following information was extracted from each study: first author, year of publication, ethnic make-up of the study population, numbers of cases and controls, and the allele frequencies of the *ERAP1* polymorphisms.

Evaluation of statistical associations

The allelic frequencies of the *ERAP1* polymorphisms from the respective studies were determined using the allele counting method. We examined the difference between the effect of the minor allele, designated as 2, and that of the common allele, designated as 1, of each *ERAP1* polymorphism. Point estimates of risk, ORs, and 95 % confidence intervals (CIs) were estimated for each study. Cochran's Q statistic was used to assess variations or heterogeneities within each study and between studies [21]. This heterogeneity test was conducted with the null hypothesis that all the studies were analyzing the same effect. In addition, we quantified the effect of heterogeneity using $I^2 = 100\,\% \times (Q - df)/Q$ [22]. I^2 ranges between 0 and 100 % and represents the proportion of variability attributable to heterogeneity rather than chance between the studies. I^2 values of 25, 50, and 75 % were assigned as low, moderate, and high estimates, respectively. A fixed effects model assumes that the effects of individual genetic factors on AS susceptibility are similar for all the included studies and that observed variations between studies are caused by chance alone [23]. The random effects model assumes that different studies show substantial diversity and assesses both within-study sampling errors and between-study variances [24]. If study groups show no heterogeneity, the fixed and random effects models produce similar results, and if not, the random effects model usually produces wider CIs than does the fixed effects model. Accordingly, the random effects model was used to evaluate polymorphisms that had significant between-study heterogeneity. Statistical manipulations were performed using a Comprehensive Meta-Analysis computer program (Biostatics, Englewood, NJ, USA).

Results

Studies included in the meta-analysis

Electronic and manual literature searches resulted in the identification of 87 studies, and 22 of these studies were selected for a full-text review based on their titles and abstracts [9–16, 25–28]. Two studies were excluded because one used the data analyzed in another study and another did not have extractable allele data. Thus, 20 studies met the inclusion criteria (Table 1) [5–23, 27]. However, one of these studies contained data on three groups [13] and two studies had data on two different groups [17]. These groups were treated independently. Thus, for this meta-analysis, we considered 22 separate comparisons, which comprised, in total, 19,902 AS patients and 39,750 controls. Due to the limited number of studies on polymorphisms, 11 types of meta-analyses were performed (Table 2). Selected characteristics of the 21 studies are summarized in Table 1.

Meta-analysis of the association between *rs30187*, *rs27044*, *rs10050860*, *rs2287987*, *rs17482078*, and *rs26653* polymorphisms and AS susceptibility

The meta-analysis identified a significant association between AS and the minor alleles of the *rs30187* polymorphism in the overall population (OR = 1.255, 95 % CI = 1.147–1.373, $P = 8.0 \times 10^{-8}$) (Table 2, Fig. 1). Stratification by ethnicity led to the identification of a significant association between this polymorphism and AS in Europeans (OR = 1.283, 95 % CI = 1.237–1.331, $P < 1.0 \times 10^{-9}$), but not in East Asians and Middle Easterners (Table 2, Fig. 1). Meta-analyses of results of the studies on *rs27044*, *rs10050860*, *rs2287987*, *rs17482078*, and *rs26653* polymorphisms showed that these

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

Study (ref)	Country	Ethnicity	Numbers		*ERAP1* polymorphisms	Major associations
			AS	Control		
Zhang 2014 [5]	China	East Asian	602	619	*rs27037, rs27980, rs27582, rs27434*	*rs27037, rs27980, rs27582* (NS), *rs27434* ($P=0.0499$)
Betterncourt 2013 [6]	Portugal	European	200	559	*rs27044, rs17482078, rs10050860, rs30187, rs2287987*	All SNPs ($P<0.05$)
Cinar 2013 [7]	Turkey	Middle Eastern	150	150	*rs30187, rs27044, rs26653, rs27037, rs2287987, rs1343151, rs10050860, rs17482078, rs27980, rs27529*	*rs26653* ($P=0.004$), others (NS)
Cherciu 2013 [8]	Romania	European	137	139	*rs30187, rs27044*	*rs30187* ($P=0.008$), *rs27044* (NS)
Mahmoudi 2012 [9]	Iran	Middle Eastern	387	316	*rs30187, rs27434*	*rs30187* ($P=1.51\times10^{-5}$), *rs27434* ($P=5\times10^{-3}$)
Wang 2012 [10]	Taiwan	East Asian	797	1150	*rs27037, rs27980, rs27044, rs30187*	*All SNPs* ($P<0.05$)
Wu 2012 [11]	China	East Asian	328	627	*rs27044*	*rs27044* ($P<0.0001$)
Szczypiorska 2011 [12]	Spain	European	300	300	*rs30187, rs27044, rs26653, rs2287987, rs10050860, rs17482078*	*rs27044* (NS), *other SNPs* ($P<0.05$)
Evans-1 2011 [13]	UK	European	1787	4800	*rs30187, rs10050860*	*rs30187* ($P=0.0017$), *rs10050860* ($P=0.026$)
Evans-2 2011 [13]	UK	European	3023	8779	*rs30187, rs10050860*	*rs30187* ($P=0.0028$), *rs10050860* ($P=0.00033$)
Evans-3 2011 [13]	UK	European	2111	4483	*rs30187, rs10050860*	*rs30187* ($P=1.3\times10^{-3}$), *rs10050860* (NS)
Li 2011 [14]	China	East Asian	471	456	*rs26653, rs27434, rs27529, rs27582*	*rs26653* (NS), *rs27434* ($P=0.00039$), *rs27529* ($P=0.0083$), *rs27582*(NS)
Bang 2011 [15]	Korea	East Asian	1164	752	*rs27037, rs27434*	*rs27037* ($P=1.3\times10^{-4}$), *rs27434* ($P=4.6\times10^{-6}$)
Zvyagin 2010 [16]	Russia	European	84	77	*rs30187, rs27044, rs2287987, rs10050860, rs17482078*	*rs2287987, rs10050860, rs17482078* ($P<0.05$), *rs30187, rs27044* (NS)
Reveille-1 2010 [17]	USA	European	2053	5140	*rs27037, rs27434*	*rs27037* ($P=2.5\times10^{-6}$), *rs27434* ($P=2.2\times10^{-8}$)
Reveille-2 2010 [17]	USA	European	898	1,518	*rs27037, rs27434*	*rs27037* ($P=2.7\times10^{-6}$), *rs27434* ($P=5.0\times10^{-5}$)
Pazar 2010 [18]	Hungary	European	297	200	*rs30187, rs27044, rs2287987, rs10050860, rs17482078*	*rs30187* (NS), *other SNPs* ($P<0.05$)
Choi 2010 [19]	Korea	East Asian	872	403	*rs30187, rs27044, rs2287987, rs10050860, rs17482078*	*rs30187* ($P=9.37\times10^{-7}$), *rs27044*($P=7.16\times10^{-6}$), *other SNPs* (NS)
Wen 2010 [27]	Taiwan	East Asian	475	527	*rs27434*	*NS*
Davidson 2009 [20]	China	East Asian	527	945	*rs27037, rs27434*	*rs27037* ($P=0.012$), *rs27434* ($P=0.14$)
Harvey 2009 [21]	UK	European	1730	5400	*rs27044, rs2287987*	*rs27044* ($P=1.1\times10^{-9}$), *rs2287987* ($P=5.4\times10^{-8}$)
Maksymowych 2009 [22]	Canada	European	992	1437	*rs30187, rs27044, rs26653, rs10050860*	*rs27044* (NS), *other SNPs* ($P<0.05$)
Burton 2007 [23]	UK	European	992	1500	*rs27044, rs2287987, rs17482078*	*rs27044* ($P=1.0\times10^{-6}$), *rs2287987* ($P=1.6\times10^{-4}$), *rs17482078* ($P=2.3\times10^{-4}$)

USA United States of America, *UK* United Kingdom, *AS* ankylosing spondylitis, *ref* reference, *NS* not significant, *SNP* single-nucleotide polymorphism

polymorphisms had the same pattern as *rs30187* in the overall population and in the European group. All of these polymorphisms were associated with AS susceptibility in Europeans (Table 2).

Meta-analysis of the relationship between the *rs27434*, *rs27037*, *rs27980*, and *rs27582* polymorphisms and AS susceptibility

Meta-analysis revealed a significant association between the minor alleles of the *rs27434* and *rs27037* polymorphisms and the susceptibility to AS in Europeans (OR = 1.214, 95 % CI = 1.131–1.304, $P<1.0\times10^{-9}$; OR = 1.238, 95 % CI = 1.159–1.323, $P<1.0\times10^{-9}$, respectively) (Table 2, Fig. 2). The *rs27037* polymorphism was significantly associated with AS susceptibility in both European and Asian patients (Table 2). Meta-analysis showed a significant association between susceptibility to AS and the minor alleles of the *rs27980* and *rs27582* polymorphisms in East Asians (OR = 0.904, 95 % CI = 0.818–0.999, $P=0.047$; OR = 0.871, 95 % CI = 0.772–0.982, $P=0.024$, respectively) (Table 2). However, these polymorphisms had not been studied in Europeans.

Meta-analysis of the relationship between *rs27529* and AS susceptibility

No association was found between the *rs27529* polymorphism and AS susceptibility by meta-analysis (OR = 1.007, 95 % CI = 0.644–1.573, $P=0.977$) in the overall population

Table 2 Meta-analysis of associations between *ERAP1* polymorphisms and AS

Polymorphism	Population	Number		No. of studies	Test of association			Test of heterogeneity		
		AS	Control		OR	95 % CI	*P* value	Model	*P* value	I^2
Rs30187	Overall	11,137	22,793	13	1.255	1.147–1.373	8.0×10^{-8}	R	0.000	80.0
2 vs. 1 allele	European	8931	20,774	9	1.283	1.237–1.331	$<1.0 \times 10^{-9}$	F	0.694	0
	East Asian	1669	1553	2	1.099	0.625–1.995	0.756	R	0.000	96.8
	Middle Eastern	537	466	2	1.311	0.890–1.932	0.170	R	0.043	75.5
rs27044	Overall	6879	11,942	12	1.542	1.186–2.005	0.001	R	0.000	96.3
	European	4732	9612	8	1.546	1.189–2.010	0.001	R	0.000	94.2
	East Asian	1997	2180	3	1.673	0.685–4.088	0.259	R	0.000	98.8
rs10050860	Overall	9816	21,188	10	0.771	0.737–2.807	$<1.0 \times 10^{-9}$	F	0.322	13.1
	European	8794	20,635	8	0.772	0.738–0.808	$<1.0 \times 10^{-9}$	F	0.179	31.2
rs2287987	Overall	4625	8589	8	0.707	0.659–0.760	$<1.0 \times 10^{-9}$	F	0.454	0
	European	3603	8,036	6	0.708	0.658–0.762	$<1.0 \times 10^{-9}$	F	0.265	22.5
rs27434	Overall	6577	10,273	8	1.175	1.058–1.305	0.003	R	0.000	75.8
	European	2951	6658	2	1.214	1.131–1.304	$<1.0 \times 10^{-9}$	F	0.160	49.4
	East Asian	3239	3299	5	1.114	0.940–1.321	0.213	R	0.000	82.7
rs27037	Overall	6191	10,274	7	1.252	1.193–1.314	$<1.0 \times 10^{-9}$	F	0.403	2.90
	European	2951	6658	2	1.238	1.159–1.323	$<1.0 \times 10^{-9}$	F	0.208	36.8
	East Asian	3090	3466	4	1.268	1.181–1.363	$<1.0 \times 10^{-9}$	F	0.225	31.1
rs17482078	Overall	2895	3189	7	0.701	0.630–0.779	$<1.0 \times 10^{-9}$	F	0.902	0
	European	1873	2636	5	0.702	0.628–0.785	$<1.0 \times 10^{-9}$	F	0.967	0
rs26653	Overall	1913	2343	4	1.187	0.936–1.504	0.157	R	0.001	81.5
	European	1292	1737	2	1.229	1.101–1.371	2.4×10^{-5}	F	0.547	0
rs27980	Overall	1549	1919	3	0.907	0.824–0.999	0.047	F	0.587	0
	East Asian	1399	1769	2	0.904	0.818–0.999	0.047	F	0.331	0
rs27529	Overall	621	606	2	1.007	0.644–1.573	0.977	R	0.016	82.8
rs27582	East Asian	1073	1075	2	0.871	0.772–0.982	0.024	F	0.720	0

AS ankylosing spondylitis, *F* fixed effects model, *R* random effects model

(Table 2). Due to the limited number of available studies, stratification by ethnicity was not performed for this meta-analysis.

Heterogeneity and publication bias

Heterogeneity was found between the studies during the meta-analyses for the association between AS susceptibility and some *ERAP1* polymorphisms. However, heterogeneity was not found during the meta-analyses of the *rs10050860*, *rs27037*, *rs17482078*, *rs27980*, and *rs27582* polymorphisms. Publication bias causes a disproportionate number of positive studies and poses a problem for meta-analyses. However, we found no evidence of publication bias for all study subjects (Egger's regression test *P* values >0.1).

Discussion

AS is strongly associated with *HLA-B27*, but only 1–5 % of *HLA-B27*-positive individuals develop AS, which suggests that other genes contribute to the risk of AS development [2]. A previous genome-wide association study revealed that *ERAP1* polymorphisms are associated with AS at a high level of statistical significance [3], but more recent studies, in different ethnic groups, have produced mixed results [5–23].

In our previous meta-analysis, we found that the *rs27044*, *rs17482078*, *rs10050860*, *rs30187*, and *rs2287987* polymorphisms of *ERAP1* were associated with the development of AS in Europeans [28]. In the present study, we updated our meta-analysis on the association between *ERAP1* polymorphisms and AS. We undertook an ethnicity-specific meta-analysis of the associations between the *ERAP1* polymorphisms and AS susceptibility in European, East Asian, and Middle Eastern populations. Our meta-analysis revealed a significant association between AS and the *rs30187* polymorphism in the group containing all study subjects and in the group containing Europeans. Meta-analyses of results for the *rs27044*, *rs10050860*, *rs2287987*, *rs17482078*, and *rs26653* polymorphisms showed the same pattern as *rs30187*. Our findings support associations between AS susceptibility in East Asians and the *ERAP1* polymorphisms *rs27037*, *rs27980*, and *rs27582*, but not the *rs30187*, *rs27434*, and *rs27044* polymorphisms. The *rs27037* polymorphisms were significantly associated with AS susceptibility in both Europeans and Asians. In addition, meta-analysis showed a significant association between AS and the *rs27980* and *rs27582* polymorphisms in East Asians. However, these

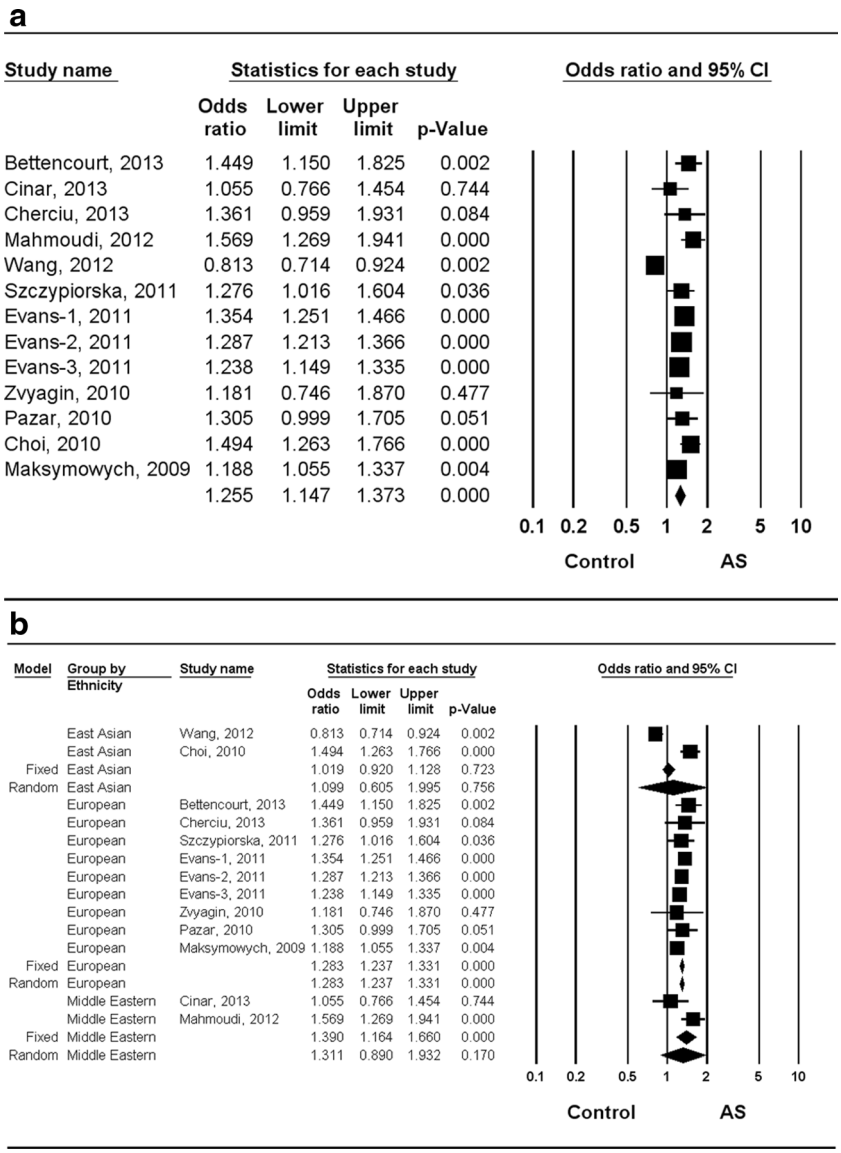

Fig. 1 ORs and 95 % CIs of individual studies and pooled data for the minor allele versus the common allele of the *ERAP1 rs30187* polymorphism for susceptibility to AS overall (**a**) and each ethnic group (**b**)

polymorphisms had not been studied in Europeans. The minor alleles of the rs27980 and rs27582 polymorphisms in East Asians were protective for developing AS unlike other ERAP1 polymorphisms. The reason for the difference remains unclear but may be in part explained by different linkage disequilibrium with causative polymorphisms or gene of AS. These findings suggest that *ERAP1* polymorphisms are associated with the development of AS in Europeans as well as Asians. The allelic frequencies of genes may often differ substantially between populations, and an association between the polymorphisms and a particular disease may depend on ethnicity. Therefore, ethnicity-specific association studies are required to confirm genetic associations in different populations. The ORs for all associations were a little above 1 and small, while the OR for HLA B27 and the susceptibility of AS has been known as very high. However, most associations of polymorphisms in complex diseases refer to small odds ratios [29]. Our finding suggests that ERAP1 is one of the associated genes with AS susceptibility, although the associations had small effect and were not strong as much as HLA-B27.

The role of ERAP1 in the pathogenesis of AS has yet to be fully understood. ERAP1 is known to be an important determinant of the repertoire of peptides that are presented by class I HLA molecules and, consequently, initiate T cell responses. *ERAP1* encodes an endoplasmic reticulum aminopeptidase that is involved in trimming peptides to optimal lengths for class I HLA presentation [4]. Thus, *ERAP1* variants that may affect the aminopeptidase function could perturb peptide presentation. AS is primarily an HLA class I-mediated autoimmune disease, and more than 90 % of patients carry the *HLA-B27* gene. The association between *ERAP1* and AS supports the arthritogenic peptide hypothesis, which suggests that the

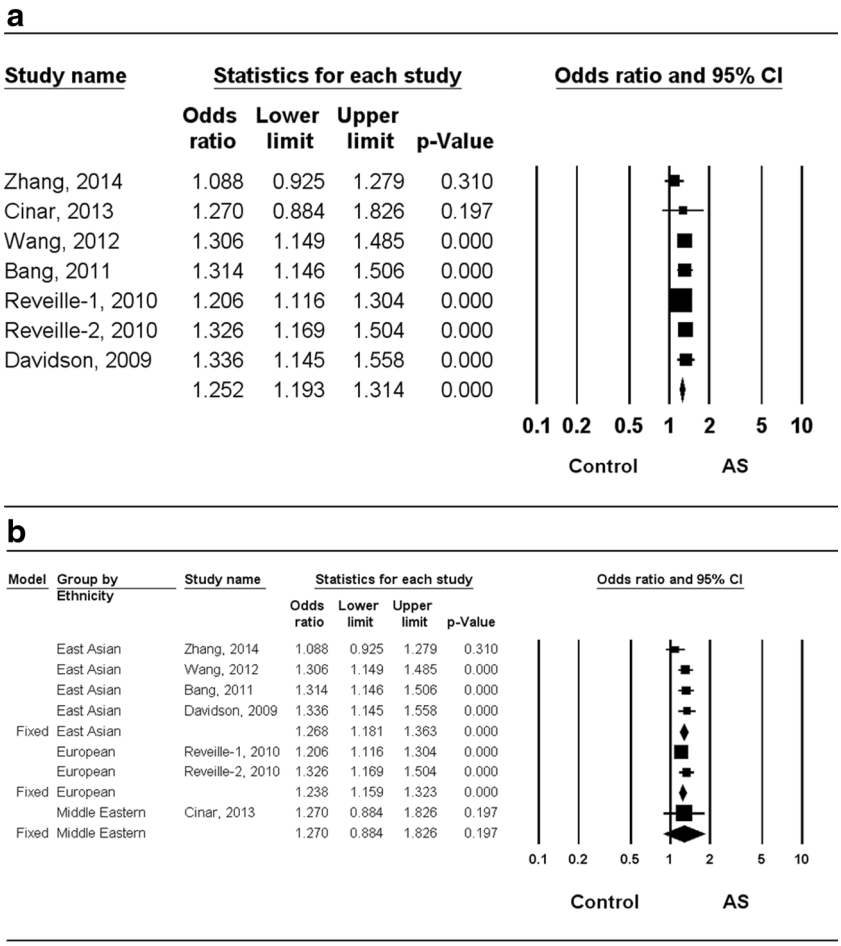

Fig. 2 ORs and 95 % CIs of individual studies and pooled data for the minor allele versus the common allele of the *ERAP1 rs27037* polymorphism for susceptibility to AS in the overall population (**a**) and in each ethnic group (**b**)

disease is triggered by the presentation of a peptidase, on HLA-B27 molecules at the surface of antigen-presenting cells, to cytotoxic CD8-positive cells. ERAP1 cleaves cell surface receptors for pro-inflammatory cytokines, which downregulates their signaling [30]. Thus, genetic variants that alter this function of ERAP1 could have proinflammatory effects. Furthermore, ERAP1 binds directly to the extracellular domain of TNFR1 and promotes the IL-1β-mediated cleavage of its ectodomain, to generate soluble TNFR1. This ERAP1-assisted generation of extracellular TNFR1 could be crucial for regulating the bioactivity of TNF, which plays a key role in the regulation of inflammation [30]. However, it is not known whether *ERAP1* polymorphisms affect the clinical manifestations of AS. Further studies are required to determine the natures of the associations between *ERAP1* polymorphisms and disease severity.

The present study has some limitations that should be considered. First, publication bias, heterogeneity, and confounding factors may have distorted the meta-analysis. Second, our ethnicity-specific meta-analysis included data mainly from European and East Asian populations, and thus, our results are applicable only to these ethnic groups. Third, the majority of these studies were performed on populations of European descent, and only two to four studies were conducted on East Asians, which might mean that our investigations using the East Asian group were underpowered. Fourth, the possibility of contributions to AS susceptibility by *ERAP1* haplotypes also needs to be examined by meta-analysis. Unfortunately, in the present study, we could not conduct meta-analysis on AS susceptibility and *ERAP1* haplotypes due to limited data. Fifth, it would have been interesting to determine if an association exists between *ERAP1* polymorphisms and *HLA-B27* status, HLA-B27 activity, or the clinical features of AS, but this was not possible because the available data was limited.

In conclusion, this meta-analysis of published data confirms that the *ERAP1* polymorphisms are associated with AS susceptibility in Europeans and East Asians. The allelic frequencies of genes often differ substantially between populations, and thus, further ethnicity-specific association studies are required to confirm genetic associations with AS susceptibility in different populations. This meta-analysis demonstrates the need for further studies to determine whether *ERAP1* polymorphisms contribute to AS susceptibility in various ethnic groups.

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Compliance with ethical standards

Conflict of interest The authors have no financial or non-financial conflicts of interest to declare.

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