The correlation of endoplasmic reticulum aminopeptidase 1 polymorphisms with Behçet's disease: a meta-analysis

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Abstract

Objective

Substantial evidence has highlighted the mediation of endoplasmic reticulum aminopeptidase 1 (ERAP1) in the onset of Behçet's disease (BD), which can be differentially converted by ERAP1 variants. To comprehensively elaborate this issue, we undertook the meta-analysis to estimate the liaison of ERAP1 polymorphisms with BD risk.

Methods

Literatures were retrieved in a standardised fashion and data underwent multi-perspective analyses utilising STATA Statistical Software. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) of manifold comparisons between BD sufferers and healthy masses were exploited to evaluate the extent of relevance.

Results

*Overall analyses suggested that the meanings of ERAP1 polymorphisms in BD susceptibility varied among plentiful variations, where rs10050860, rs17482078, rs2287987, rs1065407 and rs72773968 presented pathogenic influence and rs26618 acted out beneficial function, while rs27044, rs26653, rs27895 and rs3734016 had no pronounced biological significance. Additionally, the effect of rs30187 is not yet determined. Moreover, race appeared a crucial ingredient as Mongolian were more susceptible to suffering from BD than Caucasian, while the diagnostic criteria of BD exerted a relative inconspicuous role, where the International Study Group criteria slightly attenuated the pathogenicity of ERAP1 polymorphisms compared with the International Criteria for Behçet's Disease. Finally, an exceeding importance was attached to the proceeding analysis based on disparities in BD symptoms, ERAP1 haplotypes and HLA-B*51 in computing the hazard zonation of ERAP1 polymorphisms on BD tendency.*

Conclusion

The present meta-analysis prompted the heterogeneous influences of ERAP1 polymorphisms on BD development, which were malleable under the discrepancies in genetic grounds and disease diagnoses.

Key words

Behçet's disease, ERAP1, polymorphism, meta-analysis

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Introduction

As a relapsing vasculitic condition, Behçet's disease (BD) is typically presented with clinical manifestations of multiple system involvement, including uveitis, dermatological lesions, and oral and genital aphthosis (1). Initially, BD predominantly occurs among young people aged 30-40 years in the Middle East and Far East area, and the geographic aggregation is gradually being slashed with the progression of globalization (2-4). However, what should also be paid attention to is that the discrepancy in diagnostic references is likely to yield a certain impact on the estimation of the prevalence of BD (5). Furthermore, despite the elusive aetiology of BD, it has been well-accepted that genetic factors, like HLA-B*51, IL10, and IL23R-IL12RB2, count much in the onset and development of BD (6, 7). The important thing to note here is that the relationship between inflammatory genes and BD susceptibility not only demonstrates the potential actions of non-HLA genes in BD, but also implies the possible involvement of cytokines imbalance in the pathogenesis of BD.

Endoplasmic reticulum aminopeptidase 1 (ERAP1) is a pleiotropic zinc-metallopeptidase. It is reported that ERAP1 is concerned with the cleavage of endogenous and exogenous proteins, the presentation of peptides to the MHC-I molecules, and the irritation of the immune reactivity (8). Also, it can suppress the activity of such pro-inflammatory molecule receptors as TNFR1 by disintegrating their extracellular domains (9). Clinical literatures have found that the decrease of ERAP1 expression is related to the risk of BD (10), which emphasises the critical role of ERAP1 during the pathogenesis of BD. A multitude of testimonies have attested that there is an enormous latitude of genetic variants in the gene locus of ERAP1, which may lead to the alteration of catalytic activity and/or the amount of ERAP1 protein (11-13). Hence, numerous studies have engaged in clarifying the association of ERAP1 single nucleotide polymorphisms (SNPs) and the tendency of BD, results of which appear contradictory, however.

On account of the dilemma above, we performed the meta-analysis to discuss the link of ERAP1 polymorphisms with BD and the potential confounding compositions.

Methods

Meta-analysis protocol

The meta-analysis, designed to specify the relationship of ERAP1 polymorphisms with BD susceptibility, was raised complying with the guideline composed of population, exposure, comparator, and outcomes, which was proposed by Morgan *et al*. (14), and then was carried out following the framework of the preferred reporting items for systematic reviews and meta-analysis (15). Besides, the study was registered in the Prospero Website as CRD42022337666.

Retrieval strategy

A thorough literature collection was performed in the databases of PubMed, Embase, Web of science, Cochrane Library and the China National Knowledge Internet (CNKI) (to May 24th, 2022) through the retrieval formula ('Behçet's disease' OR 'Behçet disease' OR 'Behçet diseases' OR 'Behcet's disease' OR 'Behçet disease' OR 'Behçet's syndrome' OR 'Behçet syndrome' OR 'triple-symptom complex' OR 'triple symptom complex' OR 'symptom complex, triple' OR 'triple symptom complices' OR 'Adamantiades-Behçet disease' OR 'Adamantiades Behcet disease' OR 'Adamantiades-Behçet diseases' OR 'Behçet triple symptom complex' OR 'old silk route disease') AND ('endoplasmic reticulum aminopeptidase 1' OR 'endoplasmic-reticulum aminopeptidase-1' OR 'ERAP1' OR 'ERAP-1' OR 'adipocyte-derived leucine aminopeptidase' OR 'A-LAP' OR 'ALAP' OR 'type 1 tumour necrosis factor receptor shedding aminopeptidase regulator' OR 'ARTS-1' OR 'ARTS1' OR 'puromycin-insensitive leucyl-specific aminopeptidase' OR 'PILS-AP' OR 'aminopeptidase PILS' OR 'APPILS' OR 'KIAA0525') AND ('polymorphism, single nucleotide' OR 'nucleotide polymorphism, single' OR 'nucleotide polymorphisms, single' OR 'polymorphisms, single nucleotide' OR

'single nucleotide polymorphism' OR 'single nucleotide polymorphisms' OR 'SNP' OR 'SNPs' OR 'polymorphism' OR 'polymorphisms' OR 'genotype' OR 'genotypes' OR 'variant' OR 'variants' OR 'variation' OR 'variations' OR 'allele' OR 'alleles' OR 'mutation' OR 'mutations') to obtain genetic researches studying the correlation between ERAP1 SNPs and the risk of BD as thoroughly as possible. No restrict in language was set. Besides, references of relative studies concerning this theme were also searched to have an access to incidental data.

Inclusion and exclusion criteria

Articles were screened for inclusion or exclusion by two authors with minimal disturbance and divergences were arbitrated by consulting with the third author. Only case-control studies reporting the relationship between ERAP1 polymorphisms and BD were included, and when several theses corresponded to the same batch of participants, the most integral or rigorous evidence was picked. However, research that did not explicitly point out the detected sites of ERAP1 variants or ERAP1 genotypes that had less than 2 relevant reports would not be included for further analysis.

Data extraction

For each qualified article, details listed below were extracted: the first author, the publication time, the country of authors, the race of subjects, the diagnostic criteria of BD, genotyping methods, sample size, sex ratio, age, and the genotypes distribution of each ERAP1 SNP. Races were sorted into the Caucasian and the Mongolian, and the diagnostic criteria were divided into the International Study Group criteria (ISG) and the International Criteria for Behçet's Disease (ICBD). The unavailable data were acquired via liaising directly with the first author or the corresponding author. Two investigators gleaned the aforementioned material independently, eliminated divisions jointly, and reached an agreement ultimately.

Quality evaluation

The Newcastle-Ottawa Scale (NOS) questionnaire was employed to assess the methodological quality of eligible literatures, where studies were respectively categorised as low-, intermediate- or high-quality articles based on the points of 1-3, 4-6 and 7-9. Disagreement was settled by the third author.

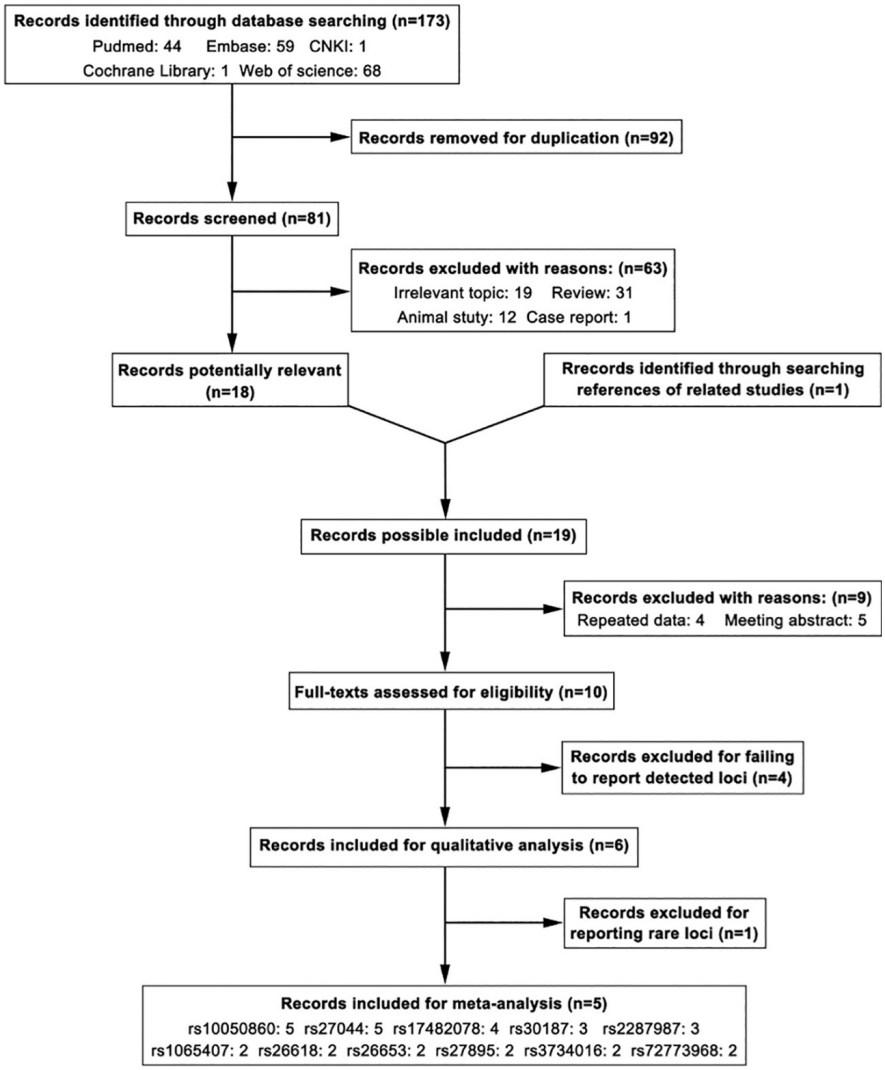

Fig. 1. Flowchart of included studies.

Statistical assessment

The STATA Statistical Software (v.12.0; StataCorp, LP, College Station, TX) was used to evaluate the link intensity between ERAP1 polymorphisms and BD propensity by computing the incorporated odds ratios (ORs) with 95% confidence intervals (CIs). When details of SNPs were from the same data set, Bonferroni correction was applied. Five genetic models, encompassing the codominant model (A2A2 *vs*. A1A1; A1A2 *vs*. A1A1), the dominant model [(A1A2+A2A2) *vs*. A1A1], the recessive model [A2A2 *vs*. (A1A1+A1A2)] and the allelic model (A2 *vs*. A1), were employed, where A1 and A2 represented the major allele and the minor allele, respectively. The control groups in all included studies were examined by the Hardy-Weinberg equilibrium (HWE) with the chi-square test. If the distribution of genotypes showed significant deviation from HWE, the sensitivity analysis would be undertaken, otherwise, it was not. Heterogeneity among various evidence was checked by the I2 statistic, during which an incompatible heterogeneity was considered if I2 >50% and the random-effects model was adopted, if not, the fixed-effects model would be the substitute. The subgroup analyses were executed in terms of race and the diagnostic criteria of BD. Begg's test were implemented to estimate publica-

Table I. Major features of case-control studies included in the meta-analysis.

SNP(A_1/ A_2)	First author (year)	Country	Race	Diagnostic criteria	Genotyping methods	Sample size (M/F)	Age (mean ±SD)	Distribution of genotypes					HWE	NOS score
								A_1A_1	A_1A_2	A_2A_2	A_1	A_2		
rs10050860 (C/T)	Mahmoudi, 2018 (17)	Iran	Caucasian	ICBD	Taqman-ADA	748 (448,300) 776 (476,300)	40.26 ± 10.88 38.88 ± 11.54	581 627	147 141	1309 8	1309 1395	187 157	0.98	8
	Kang, 2017 (18)	Korea	Mongolian	ISG	GWAS	379 (191,188) 2000 (-,-)	41.6 ± 10.1 Matched	- -	- -	- -	- -	- -	-	9
	Takeuchi, 2016 (19)	Turkey	Caucasian	ISG	Immunochip	1900 (1015,885) 1779 (-,-)	38.7 ± 11.6 Matched	1348 1299	465 446	87 34	3161 3044	639 514	0.55	9
	Zhang, 2015 (20)	China	Mongolian	ICBD	PCR-RFLP	930 (781,149) # 1704 (955,749)	34.1 ± 9.2 Matched	797# 1563	127# 139	6# 2	1721# 3265	139# 143	0.55	8
	Sousa, 2015 (21)	Iran	Caucasian	ICBD	TOF-MS	958 (-,-) 821 (-,-)	39.1 ± 10.9* 40.4 ± 11.9*	725 651	197 159	36 11	1647 1461	269 81	0.72	8
				ISG		737 (-,-) 821 (-,-)	39.1 ± 10.9* 40.4 ± 11.9*	562 651	146 159	29 11	1270 1461	204 81		8
	Conde-Jaldón, 2014 (22)	Spain	Caucasian	ISG	Taqman-ADA	361 (-,-) 458 (-,-)	35.1 ± 11.2* Matched	234 298	110 148	17 12	578 744	144 172	0.20	6
rs27044 (C/G)	Padula, 2019a (16)[1]	Italy	Caucasian	ISG	Sequencing	55 (33,22) 65 (36,29)	45.81 ± 11.94 44.52 ± 12.04	26 18	18 25	11 22	70 61	40 69	0.07	9
	Padula, 2019b (11)	Italy	Caucasian	ISG	Sequencing	50 (29,21) 50 (28,22)	46.10 ± 12.19 44.31 ± -	- -	- -	- -	- -	- -	-	9
	Mahmoudi, 2018 (17)	Iran	Caucasian	ICBD	Taqman-ADA	748 (448,300) 776 (476,300)	40.26 ± 10.88 38.88 ± 11.54	373 366	323 369	52 41	1069 1101	427 451	1.94E-5	8
	Takeuchi, 2 016 (19)	Turkey	Caucasian	ISG	Immunochip	1878 (1003,875)* 1766 (-,-)	38.7 ± 11.6* Matched	1139 974	626 701	113 91	2904 2649	852 883	0.01	8
	Zhang, 2015 (20)	China	Mongolian	ICBD	PCR-RFLP	382 (-,-)# 570 (-,-)	- -	102# 154	210# 298	70# 118	414# 606	350# 534	0.23	8
	Conde-Jaldón, 2014 (22)	Spain	Caucasian	ISG	Taqman-ADA	362 (148,214) 460 (230,230)	35.1 ± 11.2 Matched	154 206	162 203	46 51	470 615	254 305	0.93	7
rs17482078 (C/T)	Padula, 2019a (16)	Italy	Caucasian	ISG	Sequencing	55 (33,22) 65 (36,29)	45.81 ± 11.94 44.52 ± 12.04	29 42	16 23	10 0	74 107	36 23	0.08	9
	Padula, 2019b (11)	Italy	Caucasian	ISG	Sequencing	50 (29,21) 50 (28,22)	46.10 ± 12.19 44.31 ± -	- -	- -	- -	- -	- -	-	9
	Mahmoudi, 2018 (17)	Iran	Caucasian	ICBD	Taqman-ADA	748 (448,300) 776 (476,300)	40.26 ± 10.88 38.88 ± 11.54	581 624	146 144	21 8	1308 1392	188 160	0.92	8
	Kang, 2017 (18)	Korea	Mongolian	ISG	GWAS	379 (191,188) 2000 (-,-)	41.6 ± 10.1 Matched	- -	- -	- -	- -	- -	-	9
	Takeuchi, 2016 (19)	Turkey	Caucasian	ISG	Immunochip	1900 (1015,885) 1779(-,-)	38.7 ± 11.6 Matched	1354 1305	459 440	87 34	3167 3050	633 508	0.66	9
	Conde-Jaldón, 2014 (22)	Spain	Caucasian	ISG	Taqman-ADA	361 (-,-) 458 (-,-)	35.1 ± 11.2* Matched	236 299	108 147	17 12	580 745	142 171	0.22	6
rs30187 (C/T)	Padula, 2019b (11)	Italy	Caucasian	ISG	Sequencing	50 (29,21) 50 (28,22)	46.10 ± 12.19 44.31 ± -	- -	- -	- -	- -	- -	-	9
	Mahmoudi, 2018 (17)	Iran	Caucasian	ICBD	Taqman-ADA	748 (448,300) 776 (476,300)	40.26 ± 10.88 38.88 ± 11.54	283 279	330 379	135 118	896 937	600 615	0.56	8
	Takeuchi, 2016 (19)	Turkey	Caucasian	ISG	Immunochip	1900 (1015,885) 1779 (-,-)	38.7 ± 11.6 Matched	801 669	806 864	293 246	2408 2202	1392 1356	0.21	9
	Conde-Jaldón, 2014) (22)	Spain	Caucasian	ISG	Taqman-ADA	362 (148,214) 459 (-,-)	35.1 ± 11.2 Matched	118 155	174 231	70 73	410 541	314 377	0.39	6
rs2287987 (T/C)	Mahmoudi, 2018 (17)	Iran	Caucasian	ICBD	Taqman-ADA	748 (448,300) 776 (476,300)	40.26 ± 10.88 38.88 ± 11.54	580 626	149 142	19 8	1309 1394	187 158	0.99	8
	Takeuchi, 2016 (19)	Turkey	Caucasian	ISG	Immunochip	1899 (-,-) 1763 (-,-)	38.7 ± 11.6* Matched	1350 1300	452 430	87 33	3152 3030	626 496	0.71	8
	Conde-Jaldón, 2014 (22)	Spain	Caucasian	ISG	Taqman-ADA	361 (-,-) 458 (-,-)	35.1 ± 11.2* Matched	234 298	110 148	17 12	578 744	144 172	0.20	6
rs1065407 (T/G)	Mahmoudi, 2018 (17)	Iran	Caucasian	ICBD	Taqman-ADA	748 (448,300) 776 (476,300)	40.26 ± 10.88 38.88 ± 11.54	301 360	345 326	102 90	947 1046	549 506	0.23	8
	Zhang, 2015 (20)	China	Mongolian	ICBD	PCR-RFLP	930 (781,149) # 1704 (955,749)	34.1 ± 9.2 Matched	775# 1548	147# 152	8# 4	1697# 3248	163# 160	0.89	8
rs26618 (T/C)	Mahmoudi, 2018 (17)	Iran	Caucasian	ICBD	Taqman-ADA	748 (448,300) 776 (476,300)	40.26 ± 10.88 38.88 ± 11.54	480 461	235 274	33 41	1195 1196	301 356	0.97	8
	Takeuchi, 2016 (19)	Turkey	Caucasian	ISG	Immunochip	1900 (1015,885) 1779 (-,-)	38.7 ± 11.6 Matched	1207 1028	593 656	100 95	3007 2712	793 846	0.47	9

SNP(A_1/ A_2)	First author (year)	Country	Race	Diagnostic criteria	Genotyping methods	Sample size (M/F)	Age (mean ±SD)	Distribution of genotypes					HWE	NOS score
								A_1A_1	A_1A_2	A_2A_2	A_1	A_2		
rs26653 (G/C)	Mahmoudi, 2018 (17)	Iran	Caucasian	ICBD	Taqman-ADA	748 (448,300) 776 (476,300)	40.26 ± 10.88 38.88 ± 11.54	267 279	360 379	121 118	894 937	602 615	0.56	8
	Takeuchi, 2016 (19)	Turkey	Caucasian	ISG	Immunochip	1900 (1015,885) 1779 (-,-)	38.7 ± 11.6 Matched	827 739	807 799	266 241	2461 2277	1339 1281	0.28	9
rs27895 (C/T)	Mahmoudi, 2018 (17)	Iran	Caucasian	ICBD	Taqman-ADA	748 (448,300) 776 (476,300)	40.26 ± 10.88 38.88 ± 11.54	612 629	125 141	11 6	1349 1399	147 153	0.53	8
	Takeuchi, 2016 (29)	Turkey	Caucasian	ISG	Immunochip	1871 (-,-) 1755 (-,-)	38.7 ± 11.6* Matched	1563 1472	287 269	21 14	3413 3213	329 297	0.66	8
rs3734016 (C/T)	Mahmoudi, 2018 (17)	Iran	Caucasian	ICBD	Taqman-ADA	748 (448,300) 776 (476,300)	40.26 ± 10.88 38.88 ± 11.54	720 739	27 37	1 0	1467 1515	29 37	0.50	8
	Takeuchi, 2016 (19)	Turkey	Caucasian	ISG	Immunochip	1870 (-,-) 1757 (-,-)	38.7 ± 11.6* Matched	1765 1673	104 82	1 2	3634 3428	106 86	0.34	8
rs72773968 (G/A)	Mahmoudi, 2018 (17)	Iran	Caucasian	ICBD	Taqman-ADA	748 (448,300) 776 (476,300)	40.26 ± 10.88 38.88 ± 11.54	610 626	130 146	8 4	1350 1398	146 154	0.14	8
	Takeuchi, 2016 (19)	Turkey	Caucasian	ISG	Immunochip	1900 (1015,885) 1779 (-,-)	38.7 ± 11.6 Matched	1525 1400	349 365	26 14	3399 3165	401 393	0.06	9

In each study, the data in the upper and lower rows represent the cases and controls, respectively.
SNP: single nucleotide polymorphism; A_1: major allele; A_2: minor allele; ISG: International Study Group criteria; ICBD: International Criteria for Behçet's Disease; ADA: allelic discrimination assay; GWAS: genome-wide association study; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism assay; TOF-MS: time of flight mass spectrometry; M: male; F: female; SD: standard deviation; BD: Behçet's disease; HWE: Hardy-Weinberg equilibrium; NOS: Newcastle-Ottawa quality assessment Scale; - inaccessible data; *approximate value.

tion bias, and $p<0.05$ was regarded as being significant difference.

Results

Eligible studies

A tree of literatures retrieval and screening was displayed in Figure 1. In all, 8 case-control researches were selected in the study, which mainly consisted of rs10050860, rs27044, rs17482078, rs30187, rs2287987, rs1065407, rs26618, rs26653, rs27895, rs3734016, and rs72773968 (16-21, 12, 22), and due to the failure to acquire genotypes distribution of ERAP1 SNPs in some reports, 6 discoveries involving 4,952 cases and 5,603 controls were finally included in this meta-analysis (16-19, 21, 22).

Features of qualified literatures

The basic information of included explorations were exhibited in Table I. First, the results of NOS quality assessment indicated that all articles were of high quality, except the one conducted by Conde-Jaldón *et al*. (16) in 2014 which had intermediate quality. Secondly, the genotyping techniques applied were quite variable, which consisted of taqman, immunochip, polymerase chain reaction-restriction fragment length polymorphism method, time of flight mass spectrometry, and DNA sequencing. Thirdly, while volunteers in 5 studies were Caucasian, those in 1 study were Mongolian, and it was likely to add uncertainty to the reliability of results. Fourthly, there were 2 papers following the International Criteria for Behçet's Disease (ICBD), 3 articles complying with the International Study Group criteria (ISG), and 1 research referring to both ICBD and ISG among the included studies. Finally, discoveries published by Takeuchi *et al*. (19) in 2016 and Mahmoudi *et al*. (21) in 2018 deviated from HWE when talking about the rs27044, which suggested the necessity of sensitivity analysis.

Meta-analysis

The major findings of our meta-analysis were shown in Table II. Collectively, there were four scenarios for the connection between ERAP1 SNPs and BD propensity, which were harmful, rewarding, paradoxical and insignificant, respectively. Specifically, while examinees who carried SNPs including rs10050860, rs17482078, rs2287987, rs1065407 or rs72773968 took on munity to BD, rs26618 carriers were less likely to suffer from BD (for A1A2 *vs*. A1A1: OR 0.79, 95% CI 0.70 to 0.88; for (A1A2 + A2A2) *vs*. A1A1: OR 0.80, 95% CI 0.71 to 0.90; for A2 *vs*. A1: OR 0.85, 95% CI 0.77 to 0.93), in comparison with the masses without those mutations. Note that there existed some conflicting aspects in respect of the conjunction of rs30187 with BD proclivity. Statistics from the codominant model (A1A2 *vs*. A1A1: OR 0.82, 95% CI 0.74 to 0.92) and the dominant model [(A1A2 + A2A2) *vs*. A1A1: OR 0.88, 95% CI 0.79 to 0.97)] showed the protective effect of rs30187 to the development of BD, whereas that from the recessive model [A2A2 *vs*. (A1A1 + A1A2): OR 1.18, 95% CI 1.03 to 1.36] revealed a marginally damaging role. And the specious link between rs72773968 and the possibility of BD was erased after Bonferroni correction (data not shown). Additionally, no significant connection was detected for rs27044, rs26653, rs27895 and rs3734016 in the pathogenesis of BD.

Subgroup analysis

As shown in Table II, there was quite a high extent of heterogeneity among studies concerned with rs10050860, rs27044, rs1065407 and rs3734016, and certain relevance might be concealed by the integration of different investigations. Therefore, the subgroup analysis was conducted to seek potential sources of heterogeneity and to uncover the functions of ERAP1 SNPs in BD risk as thoroughly as possible.

Taken as a whole, racial differences of

participants exerted a more meaningful impact on the correlation between ERAP1 SNPs and BD proclivity, in contrast with the variable of diagnostic criteria which brought about a mild influence on the conclusion. Above all, the factor of races accounted for the bulk of heterogeneity among evidence related with rs10050860, and although the codominant model of A1A2 *versus* A1A1 supported the independence between rs10050860 and BD on the whole (OR 1.16, 95% CI 0.94 to 1.43), the stratified analysis by races pointed out the pathogenicity of it to BD in Mongolian (OR 1.79, 95% CI 1.39 to 2.31). At the same time, despite the failure to explain the source of heterogeneity among discoveries looking into rs1065407 owing to insufficient relevant reports, results of the subgroup analysis put forward a more remarkable connection between rs1065407 and the hazard of BD in Mongolian, which was weaker in Caucasian. But neither Mongolian nor Caucasian were testified any association when the conjunction between rs27044 and BD predisposition was discussed. Furthermore, since all subjects were Caucasian in research discussing rs17482078, rs30187, rs2287987, rs26618, rs26653, rs27895, rs3734016 and rs72773968, the stratified analyses according to races were not implemented. Next, although diagnostic criteria had no significant action on the heterogeneity among studies relevant with rs10050860, the results of dominant model (A1A2+A2A2) *versus* A1A1 showed the mitigation of ISG on the promotion of rs10050860 to BD (OR 1.09, 95% CI 0.96 to 1.24). And while no noticeable bond was found when ICBD served as the diagnostic reference, rs30187 and rs26618 were manifested as the possible antagonistic effects on BD based on ISG. In addition, the slim tie between rs72773968 and BD tendency could be eliminated by the factor of diagnostic criteria. What is more, the disparity of diagnostic criteria had nothing to do with the tendency of BD among carriers with rs27044, rs17482078, rs2287987, rs26653, rs27895 or rs3734016. Lasty, because ICBD was the exclusive diagnostic basis in articles investigating rs1065407, the separate analysis based on diagnostic criteria was not carried out.

Sensitivity analysis

Given there were several researches not abiding by the HWE in rs27044 and existed excessively obvious inconsistency among studies involving rs10050860 and rs27044, which had not been well explained, we proceeded to the sensitivity analysis. Noted that even though there was prominent discrimination between studies bound up with rs1065407 and rs3734016, it was unnecessary to execute the sensitivity analysis as a result of limited reports.

With regards to rs10050860, there was not any qualitative change about the crude ORs with 95% CIs in all comparison models after investigations included being omitted individually. Similarly, as for rs27044, results also did not have any substantial alteration when relevant explorations were removed one by one (Fig. 2). Briefly, findings above indicated the fairly good stability and reliability of conclusions in the meta-analysis about rs10050860 and rs27044.

Publication bias

As Table II shows, the *p*-values of Begg's test were evidently greater than 0.05 for all analysis models in rs10050860, rs27044, rs17482078, rs30187 and rs2287987, which did not state enough evidence of publication bias in them. Besides, the analyses of publication bias were not fulfilled in rs1065407, rs26618, rs26653, rs27895, rs3734016, and rs72773968 given the lack of adequate research.

Discussion

By searching pertinent publications in generous databases to extensively obtain research data, the text was designed to calculate liaisons between ERAP1 polymorphisms and the possibility of developing BD among distinct publics as accurately as possible. And then multiple analyses, containing the heterogeneity detection, grouping analysis and sensitivity test, were also undertaken to identify components that were probable to disturb the outcomes.

Simply put, achievements of diverse projects differed from each other visibly. As early as 2014, the works of Conde-Jaldón *et al*. (16) had argued rs10050860, rs27044, rs17482078, rs30187 and rs2287987 as risk candidates for BD developing, especially in the crowds positive for HLA-B*51, although no compelling statistical weight had been achieved, yet. Afterwards, Sousa *et al*. (17) and Zhang *et al*. (18) testified the higher odds of BD in the recruited carrying rs10050860 in Iranian and Chinese Han demographics, respectively. Particularly, in the former study, the increased hazard was verified by applying the diagnostic criteria of both ISG and ICBD and kept unchanged in those positive for HLA-B*51, and the virulence of rs1065407 to BD prevalence was also unveiled in the latter. Then, Takeuchi *et al*. (19) surveyed total ERAP1 SNPs discussed in our study except rs1065407 and identified a strong linkage disequilibrium among them. Studies had declared that ERAP1 haplotypes modulated the alterations in immunodominance patterns via regulating their catalytic efficiencies or affinities to substrates, or the epitope repertoire of $CD8^+$ T cells, and thus controlled the variation of immune reactivity and the preferentialism of chronic diseases (23, 24). Accordingly, the interaction analyses according to haplotypes instead of SNPs were executed, and results implicated Hap10, which covers rs10050860, rs27044, rs17482078, rs30187 and rs2287987, as susceptible genes for the inclination of BD, which underlined the importance of haplotypes in BD risk (19). By comparison, nothing of any substantial contribution was derived in the Korean undertaking dealing with 43 ERAP1 SNPs comprised of rs10050860 and rs17482078 (20). However, the situation soon appeared a turning point again. The pathogenicity of rs10050860, rs17482078, rs2287987, and rs1065407 in the occurrence of BD was reiterated among the Iranian public, which was radically reversed by the differential analysis on the ground that whether carrying HLA-B*51 or not (21), however. That is, rs30187, rs26618 and rs26653, rather than the 4 SNPs mentioned above, were related with BD onset, and rs26618 was a promising resistant gene for suffering from BD. Unfortunately,

Table II. Relevance of various ERAP1 SNPs loci with Behçet's disease risk.

SNP	Comparison model	Grouping factors		Studies included	Subjects included (Case/Control)	I^2 (%)	OR (95% CI)	Begg's test (z/p)
rs10050860	A_2A_2 *vs.* A_1A_1	Race	Total	5	8,356 (3,851/4,505)	0.0	2.55 (1.91, 3.40)	0.73/0.46
				5	8,186 (3,681/4,505)	0.0	2.56 (1.91, 3.42)	0.73/0.46
			Caucasian	4	5,988 (3,048/2,940)	0.0	2.47 (1.84, 3.32)	
				4	5,818 (2,878/2,940)	0.0	2.48 (1.85, 3.34)	
			Mongolian	1	2,368 (803/1,565)	-	5.88 (1.19, 29.22)	
				1	2,368 (803/1,565)	-	5.88 (1.19. 29.22)	
		Diagnosis	Total	5	8,356 (3,851/4,505)	0.0	2.55 (1.91, 3.40)	
				5	8,186 (3,681/4,505)	0.0	2.56 (1.91, 3.42)	
			ICBD	3	5,027 (2,165/2,862)	0.0	3.05 (1.85, 5.02)	
				2	3,604 (1,404/2,200)	0.0	3.18 (1.53, 6.62)	
			ISG	2	3,329 (1,686/1,643)	0.0	2.31 (1.62, 3.30)	
				3	4,582 (2,277/2,305)	0.0	2.45 (1.79, 3.36)	
	A_1A_2 *vs.* A_1A_1	Race	Total	5	10,202 (4,731/5,471)	75.3	1.16 (0.94, 1.43)	0.24/0.81
				5	9,988 (4,517/5,471)	75.6	1.15 (0.93, 1.42)	0.24/0.81
			Caucasian	4	7,576 (3,807/3,769)	0	1.04 (0.93, 1.16)	
				4	7,362 (3,593/3,769)	0	1.03 (0.92, 1.15)	
			Mongolian	1	2,626 (924/1,702)	-	1.79 (1.39, 2.31)	
				1	2,626 (924/1,702)	-	1.79 (1.39, 2.31)	
		Diagnosis	Total	5	10,202 (4,731/5,471)	75.3	1.16 (0.94, 1.43)	
				5	9,988 (4,517/5,471)	75.6	1.15 (0.93, 1.42)	
			ICBD	3	5,854 (2,574/3,280)	77.7	1.31 (0.96, 1.77)	
				2	4,122 (1,652/2,470)	84.2	1.42 (0.90, 2.24)	
			ISG	2	4,348 (2,157/2,191)	0	0.99 (0.87, 1.14)	
				3	5,866 (2,865/3,001)	0	1.01 (0.90, 1.14)	
	(A_1A_2+A_2A_2) *vs.* A_1A_1	Race	Total	5	10,435 (4,897/5,538)	71.1	1.25 (1.04, 1.50)	0.24/0.81
				5	10,214 (4,676/5,538)	71.1	1.24 (1.03, 1.50)	0.24/0.81
			Caucasian	4	7,801 (3,967/3,834)	0	1.14 (1.03, 1.26)	
				4	7,580 (3,746/3,834)	0	1.13 (1.02, 1.25)	
			Mongolian	1	2,634 (930/1,704)	-	1.85 (1.44, 2.38)	
				1	2,634 (930/1,704)	-	1.85 (1.44, 2.38)	
		Diagnosis	Total	5	10,435 (4,897/5,538)	71.1	1.25 (1.04, 1.50)	
				5	10,214 (4,676/5,538)	71.1	1.24 (1.03, 1.50)	
			ICBD	3	5,937 (2,636/3,301)	72.6	1.40 (1.07, 1.82)	
				2	4,158 (1,678/2,480)	82.0	1.50 (0.99, 2.27)	
			ISG	2	4,498 (2,261/2,237)	0	1.09 (0.96, 1.24)	
				3	6,056 (2,998/3,058)	0	1.11 (0.99, 1.24)	
	A_2A_2 *vs.* (A_1A_1+A_1A_2)	Race	Total	5	10,435 (4,897/5,538)	0	2.53 (1.89, 3.37)	0.73/0.46
				5	10,214 (4,676/5,538)	0	2.54 (1.90, 3.39)	0.73/0.46
			Caucasian	4	7,801 (3,967/3,834)	0	2.46 (1.83, 3.30)	
				4	7,580 (3,746/3,834)	0	2.47 (1.84, 3.32)	
			Mongolian	1	2,634 (930/1,704)	-	5.53 (1.11, 27.43)	
				1	2,634 (930/1,704)	-	5.53 (1.11, 27.43)	
		Diagnosis	Total	5	10,435 (4,897/5,538)	0	2.53 (1.89, 3.37)	
				5	10,214 (4,676/5,538)	0	2.54 (1.90, 3.39)	
			ICBD	3	5,937 (2,636/3,301)	0	2.97 (1.80, 4.89)	
				2	4,158 (1,678/2,480)	0	3.09 (1.48, 6.42)	
			ISG	2	4,498 (2,261/2,237)	0	2.32 (1.63, 3.30)	
				3	6,056 (2,998/3,058)	0	2.45 (1.79, 3.36)	
	A_2 *vs.* A_1	Race	Total	5	20,770 (9,794/10,976)	91.7	1.54 (1.11, 2.13)	1.22/0.22
				5	19,644 (8,668/10,976)	92.2	1.58 (1.12, 2.23)	1.22/0.22
			Caucasian	4	15,502 (7,934/7,568)	92.9	1.47 (1.00, 2.17)	
				4	14,376 (6,808/7,568)	93.4	1.52 (1.01, 2.30)	
			Mongolian	1	5,268 (1,860/3,408)	-	1.84 1.45, 2.35)	
				1	5,268 (1,860/3,408)	-	1.84 (1.45, 2.35)	
		Diagnosis	Total	5	20,770 (9,794/10,976)	91.7	1.54 (1.11, 2.13)	
				5	19,644 (8,668/10,976)	92.2	1.58 (1.12, 2.23)	
			ICBD	3	11,774 (5,272/6,502)	91.4	1.90 (1.18, 3.05)	
				2	8,316 (3,356/4,960)	79.7	1.53 (1.06, 2.20)	
			ISG	2	8,996 (4,522/4,474)	0	1.17 (1.05, 1.31)	
				3	11,328 (5,312/6,016)	95.6	1.62 (0.90, 2.94)	

SNP	Comparison model	Grouping factors		Studies included	Subjects included (Case/Control)	I^2 (%)	OR (95% CI)	Begg's test (z/p)
rs27044	A_2A_2 *vs.* A_1A_1	Race	Total	5	4,127 (2,086/2,041)	42.1	1.03 (0.86, 1.23)	0.24/0.81
			Caucasian	4	3,683 (1,914/1,769)	52.2	1.07 (0.87, 1.31)	
			Mongolian	1	444 (172/272)	-	0.90 (0.611, 1.32)	
		Diagnosis	Total	5	4,127 (2,086/2,041)	42.1	1.03 (0.86, 1.23)	
			ICBD	2	1,276 (597/679)	18.6	1.04 (0.78, 1.38)	
			ISG	3	2,851 (1,489/1,362)	64.8	1.02 (0.81, 1.29)	
	A_1A_2 *vs.* A_1A_1	Race	Total	5	6,447 (3,133/3,314)	51.0	0.88 (0.74, 1.04)	0.24/0.81
			Caucasian	4	5,683 (2,821/2,862)	46.6	0.84 (0.71, 1.00)	
			Mongolian	1	764 (312/452)	-	1.06 (0.78, 1.45)	
		Diagnosis	Total	5	6,447 (3,133/3,314)	51.0	0.88 (0.74, 1.04)	
			ICBD	2	2,195 (1,008/1,187)	22.2	0.93 (0.76, 1.13)	
			ISG	3	4,252 (2,125/2,127)	62.4	0.83 (0.61, 1.12)	
	(A_1A_2+A_2A_2) *vs.* A_1A_1	Race	Total	5	7,062 (3,425/3,637)	54.7	0.89 (0.75, 1.05)	-0.24/1.00
			Caucasian	4	6,110 (3,043/3,067)	60.1	0.86 (0.71, 1.05)	
			Mongolian	1	952 (382/570)	-	1.02 (0.76, 1.36)	
		Diagnosis	Total	5	7,062 (3,425/3,637)	54.7	0.89 (0.75, 1.05)	
			ICBD	2	2,476 (1,130/1,346)	0	0.93 (0.79, 1.10)	
			ISG	3	4,586 (2,295/2,291)	71.9	0.83 (0.59, 1.15)	
	A_2A_2 *vs.* (A_1A_1+A_1A_2)	Race	Total	5	7,062 (3,425/3,637)	40.8	1.06 (0.90, 1.26)	0.73/0.46
			Caucasian	4	6,110 (3,043/3,067)	34.1	1.15 (0.94, 1.40)	
			Mongolian	1	952 (382/570)	-	0.86 (0.62, 1.19)	
		Diagnosis	Total	5	7,062 (3,425/3,637)	40.8	1.06 (0.90, 1.26)	
			ICBD	2	2,476 (1,130/1,346)	62.1	1.02 (0.79, 1.32)	
			ISG	3	4,586 (2,295/2,291)	48.9	1.10 (0.88, 1.38)	
	A_2 *vs.* A_1	Race	Total	5	14,124 (6,850/7,274)	55.8	0.93 (0.82, 1.06)	-0.24/1.00
			Caucasian	4	12,220 (6,086/6,134)	66.3	0.92 (0.78, 1.08)	
			Mongolian	1	1,904 (764/1,140)	-	0.96 (0.80, 1.15)	
		Diagnosis	Total	5	14,124 (6,850/7,274)	55.8	0.93 (0.82, 1.06)	
			ICBD	2	4,952 (2,260/2,692)	0	0.97 (0.86, 1.09)	
			ISG	3	9,172 (4,590/4,582)	75.7	0.87 (0.67, 1.13)	
rs17482078	A_2A_2 *vs.* A_1A_1	Diagnosis	Total	4	4,659 2,335/2,324)	20.8	2.58 (1.87, 3.55)	1.02/0.31
			ICBD	1	1,234 (602/632)	-	2.82 (1.24, 6.42)	
			ISG	3	3,425 (1,733/1,692)	45.6	2.54 (1.79, 3.59)	
	A_1A_2 *vs.* A_1A_1	Diagnosis	Total	4	5,953 (2,929/3,024)	0	1.01 (0.90, 1.14)	-0.34/1.00
			ICBD	1	1,495 (727/768)	-	1.09 (0.84, 1.41)	
			ISG	3	4,458 (2,202/2,256)	0	0.99 (0.87, 1.13)	
	(A_1A_2+A_2A_2) *vs.* A_1A_1	Diagnosis	Total	4	6,142 (3,064/3,078)	0	1.12 (1.00, 1.25)	0.34/0.73
			ICBD	1	1,524 (748/776)	-	1.18 (0.92, 1.51)	
			ISG	3	4,618 (2,316/2,302)	0	1.10 (0.97, 1.25)	
	A_2A_2 *vs.* (A_1A_1+A_1A_2)	Diagnosis	Total	4	6,142 (3,064/3,078)	19.3	2.59 (1.88, 3.56)	1.02/0.31
			ICBD	1	1,524 (748/776)	-	2.77 (1.22, 6.30)	
			ISG	3	4,618 (2,316/2,302)	45.0	2.56 (1.81, 3.61)	
	A_2 *vs.* A_1	Diagnosis	Total	4	12,284 (6,128/6,156)	43.0	1.20 (1.09, 1.33)	0.34/0.73
			ICBD	1	3,048 (1.496/1,552)	-	1.25 (1.00, 1.56)	
			ISG	3	9,236 (4,632/4,604)	61.1	1.20 (1.07, 1.34)	
rs30187	A_2A_2 *vs.* A_1A_1	Diagnosis	Total	3	3,240 (1,700/1,540)	0	1.06 (0.91, 1.24)	1.03/0.30
			ICBD	1	815 (418/397)	-	1.13 (0.84, 1.52)	
			ISG	2	2,425 (1,282/1,143)	4.6	1.04 (0.87, 1.24)	
	A_1A_2 *vs.* A_1A_1	Diagnosis	Total	3	5,089 (2,512/2,577)	3.8	0.82 (0.74, 0.92)	1.04/0.30
			ICBD	1	1,271 (613/658)	-	0.86 (0.69, 1.07)	
	(A_1A_2+A_2A_2) *vs.* A_1A_1	Diagnosis	Total	3	6,024 (3,010/3,014)	20.1	0.88 (0.79, 0.97)	1.04/0.30
			ICBD	1	1,524 (748/776)	-	0.92 (0.75, 1.14)	
			ISG	2	4,500 (2,262/2,238)	54.5	0.86 (0.76, 0.97)	
	A_2A_2 *vs.* (A_1A_1+A_1A_2)	Diagnosis	Total	3	6,024 (3,010/3,014)	0	1.18 (1.03, 1.36)	1.04/0.30
			ICBD	1	1,524 (748/776)	-	1.23 (0.94, 1.61)	
			ISG	2	4,500 (2,262/2,238)	0	1.16 (0.99, 1.37)	
	A_2 *vs.* A_1	Diagnosis	Total	3	12,048 (6,020/6,028)	16.3	0.98 (0.91, 1.06)	1.04/0.30
			ICBD	1	3,048 (1,496/1,552)	-	1.02 (0.88, 1.18)	
			ISG	2	9,000 (4,524/4,476)	49.9	0.97 (0.89, 1.05)	

SNP	Comparison model	Grouping factors		Studies included	Subjects included (Case/Control)	I^2 (%)	OR (95% CI)	Begg's test (z/p)
rs2287987	A_2A_2 *vs.* A_1A_1	Diagnosis	Total	3	4,564 (2,287/2,277)	0	2.39 (1.72, 3.33)	0.00/1.00
			ICBD	1	1,233 (599/634)	-	2.56 (1.11, 5.90)	
			ISG	2	3,331 (1,688/1,643)	0	2.36 (1.65, 3.38)	
	A_1A_2 *vs.* A_1A_1	Diagnosis	Total	3	5,819 (2,875/2,944)	0	1.03 (0.91, 1.16)	0.00/1.00
			ICBD	1	1,497 (729/768)	-	1.13 (0.88, 1.46)	
			ISG	2	4,322 (2,146/2,176)	0	1.00 (0.87, 1.14)	
	(A_1A_2+A_2A_2) *vs.* A_1A_1	Diagnosis	Total	3	5,995 (2,998/2,997)	0	1.12 (1.00, 1.26)	0.00/1.00
			ICBD	1	1,524 (748/776)	-	1.21 (0.94, 1.55)	
			ISG	2	4,471 (2,250/2,221)	0	1.10 (0.96, 1.25)	
	A_2A_2 *vs.* (A_1A_1+A_1A_2)	Diagnosis	Total	3	5,995 (2,998/2,997)	0	2.39 (1.72, 3.31)	0.00/1.00
			ICBD	1	1,524 (748/776)	-	2.50 (1.09, 5.75)	
			ISG	2	4,471 (2,250/2,221)	0	2.37 (1.66, 3.38)	
	A_2 *vs.* A_1	Diagnosis	Total	3	11,990 (5,996/5,994)	0	1.20 (1.08, 1.33)	0.00/1.00
			ICBD	1	3,048 (1,496/1,552)	-	1.26 (1.01, 1.58)	
			ISG	2	8,942 (4,500/4,442)	0	1.18 (1.06, 1.33)	
rs1065407	A_2A_2 *vs.* A_1A_1	Race	Total	2	3,188 (1,186/2,002)	65.4	1.98 (0.72, 5.44)	-
			Caucasian	1	853 (403/450)	-	1.36 (0.98, 1.87)	
			Mongolian	1	2,335 (783/1,552)	-	4.00 (1.20, 13.31)	
	A_1A_2 *vs.* A_1A_1	Race	Total	2	3,954 (1,568/2,386)	84.7	1.56 (1.03, 2.36)	-
			Caucasian	1	1,332 (646/686)	-	1.27 (1.02, 1.57)	
			Mongolian	1	2,622 (922/1,700)	-	1.93 (1.52, 2.46)	
	(A_1A_2+A_2A_2) *vs.* A_1A_1	Race	Total	2	4,158 (1,678/2,480)	86.5	1.59 (1.04, 2.43)	-
			Caucasian	1	1,524 (748/776)	-	1.29 (1.05, 1.58)	
			Mongolian	1	2,634 (930/1,704)	-	1.99 (1.56, 2.52)	
	A_2A_2 *vs.* (A_1A_1+A_1A_2)	Race	Total	2	4,158 (1,678/2,480)	68.1	1.80 (0.63, 5.16)	-
			Caucasian	1	1,524 (748/776)	-	1.20 (0.89, 1.63)	
			Mongolian	1	2,634 (930/1,704)	-	3.69 (1.11, 12.28)	
	A_2 *vs.* A_1	Race	Total	2	8,316 (3,356/4,960)	91.9	1.52 (0.94, 2.44)	-
			Caucasian	1	3,048 (1,496/1,552)	-	1.20 (1.03, 1.39)	
			Mongolian	1	5,268 (1,860/3,408)	-	1.95 (1.56, 2.44)	
rs26618	A_2A_2 *vs.* A_1A_1	Diagnosis	Total	2	3,445 (1,820/1,625)	0	0.86 (0.67, 1.10)	-
			ICBD	1	1,015 (513/502)	-	0.77 (0.48, 1.24)	
			ISG	1	2,430 (1,307/1,123)	-	0.90 (0.67, 1.20)	
	A_1A_2 *vs.* A_1A_1	Diagnosis	Total	2	4,934 (2,515/2,419)	0	0.79 (0.70, 0.88)	-
			ICBD	1	1,450 (715/735)	-	0.82 (0.66, 1.02)	
			ISG	1	3,484 (1,800/1,684)	-	0.77 (0.67, 0.89)	
	(A_1A_2+A_2A_2) *vs.* A_1A_1	Diagnosis	Total	2	5,203 (2,648/2,555)	0	0.80 (0.71, 0.90)	-
			ICBD	1	1,524 (748/776)	-	0.82 (0.66, 1.01)	
			ISG	1	3,679 (1,900/1,779)	-	0.79 (0.69, 0.90)	
	A_2A_2 *vs.* (A_1A_1+A_1A_2)	Diagnosis	Total	2	5,203 (2,648/2,555)	0	0.94 (0.73, 1.20)	-
			ICBD	1	1,524 (748/776)	-	0.83 (0.52, 1.32)	
			ISG	1	3,679 (1,900/1,779)	-	0.99 (0.74, 1.31)	
	A_2 *vs.* A_1	Diagnosis	Total	2	10,406 (5,296/5,110)	0	0.85 (0.77, 0.93)	-
			ICBD	1	3,048 (1,496/1,552)	-	0.85 (0.71, 1.01)	
			ISG	1	7,358 (3,800/3,558)	-	0.85 (0.76, 0.94)	
rs26653	A_2A_2 *vs.* A_1A_1	Diagnosis	Total	2	2,858 (1,481/1,377)	0	1.01 (0.86, 1.20)	-
			ICBD	1	785 (388/397)	-	1.07 (0.79, 1.45)	
			ISG	1	2,073 (1,093/980)	-	0.99 (0.81, 1.21)	
	A_1A_2 *vs.* A_1A_1	Diagnosis	Total	2	4,457 (2,261/2,196)	0	0.93 (0.82, 1.04)	-
			ICBD	1	1,285 (627/658)	-	0.99 (0.80, 1.24)	
			ISG	1	3,172 (1,634/1,538)	-	0.90 (0.79, 1.04)	
	(A_1A_2+A_2A_2) *vs.* A_1A_1	Diagnosis	Total	2	5,203 (2,648/2,555)	0	0.95 (0.85, 1.06)	-
			ICBD	1	1,524 (748/776)	-	1.01 (0.82, 1.25)	
			ISG	1	3,679 (1,900/1,779)	-	0.92 (0.81, 1.05)	
	A_2A_2 *vs.* (A_1A_1+A_1A_2)	Diagnosis	Total	2	5,203 (2,648/2,555)	0	1.05 (0.90, 1.23)	-
			ICBD	1	1,524 (748/776)	-	1.08 (0.82, 1.42)	
			ISG	1	3,679 (1,900/1,779)	-	1.04 (0.86, 1.26)	
	A_2 *vs.* A_1	Diagnosis	Total	2	10,406 (5,296/5,110)	0	0.99 (0.91, 1.07)	-
			ICBD	1	3,048 (1,496/1,552)	-	1.03 (0.89, 1.19)	
			ISG	1	7,358 (3,800/3,558)	-	0.97 (0.88, 1.06)	

SNP	Comparison model	Grouping factors		Studies included	Subjects included (Case/Control)	I^2 (%)	OR (95% CI)	Begg's test (z/p)
rs27895	A_2A_2 *vs.* A_1A_1	Diagnosis	Total	2	4,328 (2,207/2,121)	0	1.55 (0.88, 2.72)	-
			ICBD	1	1,258 (623/635)	-	1.88 (0.69, 5.13)	
			ISG	1	3,070 (1,584/1,486)	-	1.41 (0.72, 2.79)	
	A_1A_2 *vs.* A_1A_1	Diagnosis	Total	2	5,098 (2,587/2,511)	0	0.97 (0.84, 1.13)	-
			ICBD	1	1,507 (737/770)	-	0.91 (0.70, 1.19)	
			ISG	1	3,591 (1,850/1,741)	-	1.01 (0.84, 1.20)	
	(A_1A_2+A_2A_2) *vs.* A_1A_1	Diagnosis	Total	2	5,150 (2,619/2,531)	0	1.00 (0.87, 1.16)	-
			ICBD	1	1,524 (748/776)	-	0.95 (0.73, 1.23)	
			ISG	1	3,626 (1,871/1,755)	-	1.03 (0.86, 1.22)	
	A_2A_2 *vs.* (A_1A_1+A_1A_2)	Diagnosis	Total	2	5,150 (2,619/2,531)	0	1.56 (0.89, 2.73)	-
			ICBD	1	1,524 (748/776)	-	1.92 (0.71, 5.21)	
			ISG	1	3,626 (1,871/1,755)	-	1.41 (0.72, 2.79)	
	A_2 *vs.* A_1	Diagnosis	Total	2	10,300 (5,238/5,062)	0	1.03 (0.90, 1.18)	-
			ICBD	1	3,048 (1,496/1,552)	-	1.00 (0.79, 1.27)	
			ISG	1	7,252 (3,742/3,510)	-	1.04 (0.89, 1.23)	
rs3734016	A_2A_2 *vs.* A_1A_1	Diagnosis	Total	2	4,901 (2,487/2,414)	0	0.98 (0.17, 5.61)	-
			ICBD	1	1,460 (721/739)	-	3.08 (0.13, 75.71)	
			ISG	1	3,441 (1,766/1,675)	-	0.47 (0.04, 5.23)	
	A_1A_2 *vs.*A_1A_1	Diagnosis	Total	2	5,147 (2,616/2,531)	59.9	0.99 (0.63, 1.57)	-
			ICBD	1	1,523 (747/776)	-	0.75 (0.45, 1.24)	
			ISG	1	3,624 (1,869/1,755)	-	1.20 (0.89, 1.62)	
	(A_1A_2+A_2A_2) *vs.* A_1A_1	Diagnosis	Total	2	5,151 (2,618/2,533)	50.6	1.01 (0.68, 1.51)	-
			ICBD	1	1,524 (748/776)	-	0.78 (0.47, 1.28)	
			ISG	1	3,627 (1,870/1,757)	-	1.19 (0.88, 1.59)	
	A_2A_2 *vs.* (A_1A_1+A_1A_2)	Diagnosis	Total	2	5,151 (2,618/2,533)	0	0.98 (0.17, 5.60)	-
			ICBD	1	1,524 (748/776)	-	3.12 (0.13, 76.62)	
			ISG	1	3,627 (1,870/1,757)	-	0.47 (0.04, 5.18)	
	A_2 *vs.* A_1	Diagnosis	Total	2	10,302 (5,236/5,066)	35.6	1.06 (0.83, 1.36)	-
			ICBD	1	3,048 (1,496/1,552)	-	0.81 (0.50, 1.32)	
			ISG	1	7,254 (3,740/3,514)	-	1.16 (0.87, 1.55)	
rs72773968	A_2A_2 *vs.* A_1A_1	Diagnosis	Total	2	4,213 (2,169/2,044)	0	1.78 (1.00, 3.16)	-
			ICBD	1	1,248 (618/630)	-	2.05 (0.62, 6.85)	
			ISG	1	2,965 (1,551/1,414)	-	1.71 (0.89, 3.28)	
	A_1A_2 *vs.* A_1A_1	Diagnosis	Total	2	5,151 (2,614/2,537)	0	0.89 (0.77, 1.02)	-
			ICBD	1	1,512 (740/772)	-	0.91 (0.70, 1.19)	
			ISG	1	3,639 (1,874/1,765)	-	0.88 (0.75, 1.03)	
	(A_1A_2+A_2A_2) *vs.* A_1A_1	Diagnosis	Total	2	5,203 (2,648/2,555)	0	0.92 (0.80, 1.05)	-
			ICBD	1	1,524 (748/776)	-	0.94 (0.73, 1.22)	
			ISG	1	3,679 (1,900/1,779)	-	0.91 (0.77, 1.07)	
	A_2A_2 *vs.* (A_1A_1+A_1A_2)	Diagnosis	Total	2	5,203 (2,648/2,555)	0	1.82 (1.03, 3.23)	-
			ICBD	1	1,524 (748/776)	-	2.09 (0.63, 6.96)	
			ISG	1	3,679 (1,900/1,779)	-	1.75 (0.91, 3.36)	
	A_2 *vs.* A_1	Diagnosis	Total	2	10.406 (5,296/5,110)	0	0.96 (0.85, 1.09)	-
			ICBD	1	3,048 (1,496/1,552)	-	0.98 (0.77, 1.25)	
			ISG	1	7,358 (3,800/3,558)	-	0.95 (0.82, 1.10)	

For rs10050860, the data located at the upper and lower rows in each subgroup represent the included subjects in the study by Sousa *et al*. in 2015 were diagnosed by ICBD and ISG, respectively.

the magnitude of all conjunctions was diminished to the span of statistical insignificance after undergoing the Bonferroni correction. In addition, rs27044, rs27895, rs3734016 and rs72773968 were meaningless mutations either in the overall crowds or subjects with HLA-B*51 (21). Meanwhile, what the most pity was the absence of comparisons on the basis of linkage disequilibrium among these SNPs. Ultimately, Padula *et al*. (12, 22) conducted 2 studies with a sprinkle of sample sizes, the preliminary outcomes of which stated that the synergistic effect of rs17482078 to BD prevalence was not sharply affected by gender and HLA-B*51, rs30187 was a benign variant, and rs27044 played a neutral or palliative role in BD susceptibility. To sum up, one of enlightenments those findings provided with us was a ravenous necessity to take into account the presence of HLA-B*51 and haplotypes in the process of inspecting the roles of ERAP1 polymorphisms. Unfortunately, however, as a result of the status that most documents did not specify the genotypes' distribution of subjects according to whether the recruited carried HLA-B*51, we failed to further inspect functions of HLA-B*51 in the connection of ERAP1 SNPs with BD susceptibility.

As we all know, BD is a condition encompassing a wide spectrum of clinical features such as oral ulcers, uveitis, pseudofolliculitis and epididymitis, which do not always arise in parallel. Genetic polymorphisms may partially

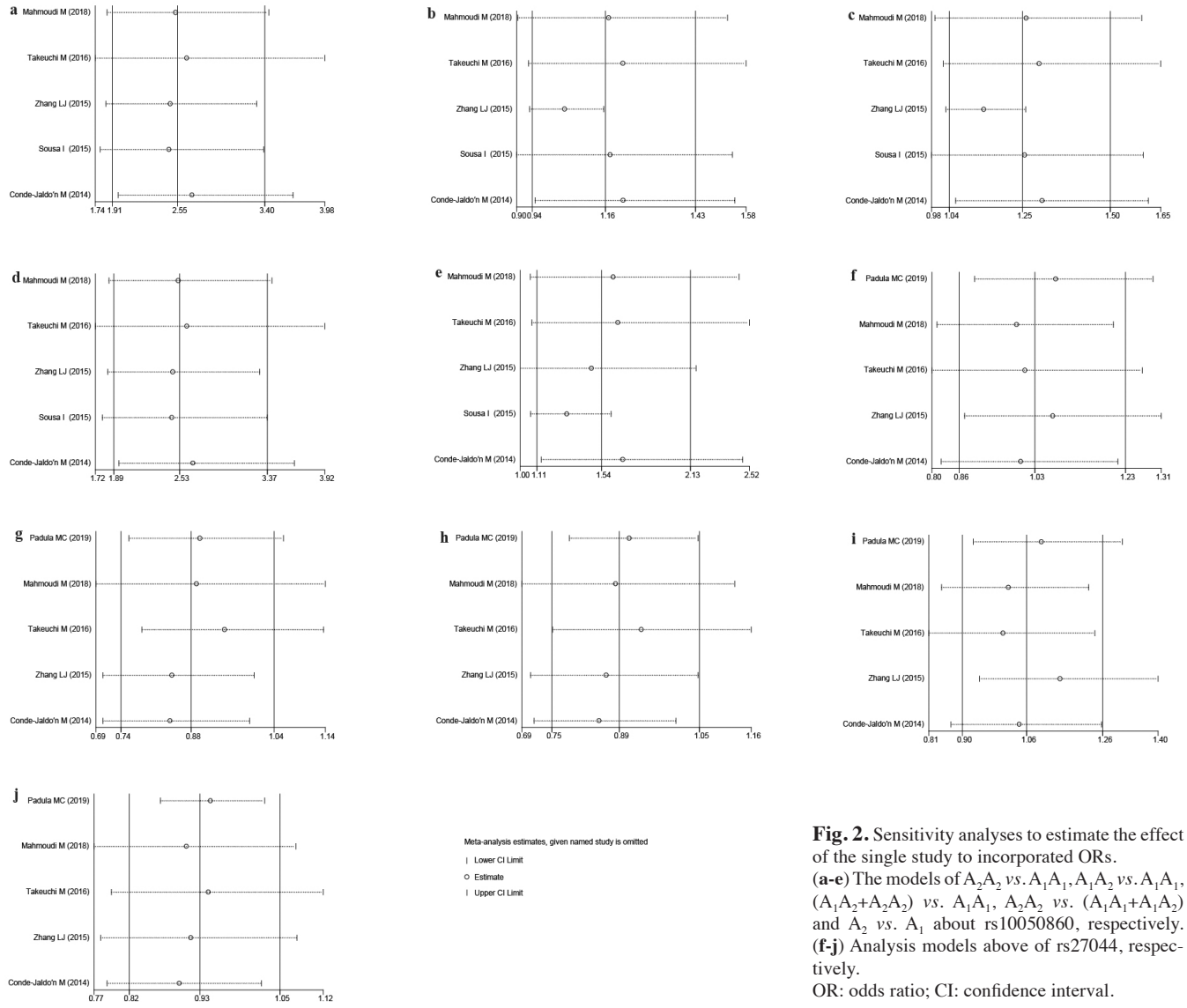

Fig. 2. Sensitivity analyses to estimate the effect of the single study to incorporated ORs.
(**a-e**) The models of A_2A_2 *vs.* A_1A_1, A_1A_2 *vs.* A_1A_1, (A_1A_2+A_2A_2) *vs.* A_1A_1, A_2A_2 *vs.* (A_1A_1+A_1A_2) and A_2 *vs.* A_1 about rs10050860, respectively. (**f-j**) Analysis models above of rs27044, respectively.
OR: odds ratio; CI: confidence interval.

underlie those discriminations in phenotypes of BD. For example, in BD patients, rs30187 promoted the involvement of heart on the whole, which became insignificant in HLA-B*51 carriers (21). Comparatively, the incidence of arthritis was apparently enhanced in HLA-B*51 carriers but lost statistical difference on the whole (21). Moreover, tissues of eyes, skin and mucosa had a disposition to be attacked in sufferers with HLA-B*51 (25). Thus, it is obliged to deeply illustrate the susceptible genes of BD according to the discrepancy of clinical characteristics. In particular, we were desperate to comprehend those potential ERAP1 variations that determined the presence or absence of uveitis in BD sufferers. Several investigations had highlighted the pivotal significance of rs10050860 in facilitating the occurrence of uveitis in BD invalids, especially among those carrying HLA-B*51 (26, 17, 18), and so did rs17482078 (26) and rs1065407 (18). And results had also proved the impartial influence of rs30187 on eye symptoms either on the whole or in crowds with HLA-B*51 (21). Nevertheless, proofs concerning the role of ERAP1 polymorphisms on uveitis in BD were still too sporadic and inadequate to arrive at a convincing conclusion, and that threw a more meticulous and momentous issue for the future study.

Moreover, the theme has also been discussed in some rare ERAP1 SNPs. For instance, rs13154629 emerged a deleterious function in the development of BD and the presence of uveitis (17), and SNPs incorporating rs13167972, rs149481, rs27038, rs27980 and rs771156 probably did not yield any notable role on the incidence of uveitis in BD (27, 18). At present, some investigators have been engaging in seeking novel SNPs to elucidate the relationship between ERAP1 polymorphisms and the prevalence of BD, such as the predicted nosogenic loci named NG_027839.1:g.18169A >T, NG_027839.1:g.18217 T >C (12) and NG_027839.1:g.25637T >G (13). In consideration of the convenient available of increasing advanced technologies, it is rational to hypothesise that we will be able to shed light on the roles of ERAP1 polymorphism in BD more entirely in the future.

Finally, there were still inevitably several drawbacks in our study. To start

with, the analysis failed to adequately figure out the possible origins of heterogeneity among some SNPs, which crippled the reliability of our results, although the distinguishment in genotyping might partly be culpable of it. Next, it was necessary to revise the acquired results in the light of HLA-B*51 and ERAP1 haplotypes through gathering more concrete and extensive data. Then, we did not further analyse the correlation between ERAP1 polymorphisms and the involvement of different organs in BD due to the lack of specific details. At last, the sample sizes were too small to derive a sufficient statistical power, which hindered us from draw a more felicitous verdict, especially for rs1065407 and rs3734016.

Conclusions

Taken together, this study manifests that diverse ERAP1 SNPs may exert divergent roles in BD risk, embodying as the synergetic effect of rs10050860, rs17482078, rs2287987, rs1065407 and rs72773968, the profitable function of rs26618, the meaninglessness of rs27044, rs26653, rs27895 and rs3734016, and the controversial value of rs30187. Further, Mongolian were more likely to suffer from BD compared with Caucasian, and ISG may help to reduce the predictive values of ERAP1 SNPs on the pathogenicity of BD while ICBD is the opposite. Because of limitations of the study, some larger and more exhaustive explorations should be performed to optimise our findings.

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