Association of *IL-1Ra* Ser133Ser Variant with Susceptibility to Immune-Mediated and Inflammatory Diseases: A Meta-Analysis of 2622 Cases and 3854 Controls

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Abstract

Background: The rs315952 (Ser133Ser) has been reported to influence the risk for immune-mediated as well as inflammatory diseases in many studies; however, the results remain inconsistent. The current meta-analysis was performed to give a more precise estimation for the relationship between this *IL-1Ra* missense variant and the risk of both types of diseases.

Methods: Relevant publications were retrieved through a literature search in Web of Science, Medline, Pub-Med, Scopus, EMBASE, and Google scholar search engines, between 2000 and 2019. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of the association.

Results: Twenty-two studies, including 2622 cases with and 3854 controls were identified. The *IL-1Ra* Ser133Ser variant does not confer an increased overall risk for immune-mediated and inflammatory diseases. This variant was statistically associated with decreased risk of systemic lupus erythematosus (under allelic, co-dominant heterozygous, and dominant models) or ankylosing spondylitis (in allelic and recessive models)(OR<1). Moreover, alleles, as well as genotypes of the *IL-1Ra* Ser133Ser variant, may confer an increased risk of immune-mediated and inflammatory diseases in Hispanics. However, this variant was not associated with susceptibility to immune-mediated and inflammatory diseases in both Asians and Arabs.

Conclusion: The pooled results fail to support the hypothesis that the *IL-1Ra Ser133Ser* variant is associated with the overall risk of immune-mediated and inflammatory diseases. Performing large scale replication and meta-analysis of functional variants within this gene is encouraged to further investigate the influence of *IL-1Ra* SNPs on overall disease susceptibility.

Keywords: Polymorphism; Inflammation; Autoimmunity; Meta-analysis

Introduction

Interactions between various environmental and genetic factors may cause different inflammatory and immune-mediated diseases (1). These diseases have an unknown progression mechanism and

share genetic backgrounds since their co-occurrence was reported in some families (2, 3). Pro-inflammatory and anti-inflammatory mediators are produced during the inflammatory and immune-mediated processes (4, 5).

Interleukin 1 (IL-1), as a well-studied pro-inflammatory cytokine, serves essential functions in the inflammatory pathways and its involvement in the pathophysiology of rheumatoid arthritis, periodontitis, ankylosing spondylitis, and osteoarthritis (6-9). The IL-1 receptor/toll-like receptor superfamily comprises two agonists (IL-1α and IL-1β), a specific receptor antagonist (IL-1Ra), and two receptors (IL-1/Toll-like receptor and IL-1RII) (10). Cytokine imbalance between IL-1 and IL-1Ra, as its competitive antagonist, contributes to the susceptibility to and severity of such diseases (11-13). *IL-1Ra* is an acute-phase protein with primary anti-inflammatory functions, which competitively inhibits IL1A and IL1B signaling (14).

The *IL-1Ra* gene, also known as *IL-1RN*, is a conserved gene with five transcript variants located on chromosome 2q14.1. *IL-1Ra* is predominantly expressed in human macrophages (15). A missense variant (T/C Mspa-I 11100, Ser133Ser) within exon 7 of the *IL-1Ra* gene has presumed to have significant associations with multiple human diseases originated from endothelial or epithelial cells (10). A large number of population-based studies have been conducted to determine if this single nucleotide polymorphism (SNP) contributes to inflammation-associated conditions (16). However, these results were inconsistent due to ethnic diversities or limited sample sizes. In this regard, meta-analyses tools could give convincible estimates to identify gene variants in such underpowered studies (17).

In the current work, we pooled the data from individual association studies to provide quantitative summaries of the link between *IL-1Ra* Ser133Ser variant and the susceptibility to immune-mediated and inflammatory diseases, aiming to enhance the statistical power for comprehensive analysis of such genetic effects.

Materials and Methods

Literature search

A comprehensive search for relevant studies focusing on T/C Mspa-I 11100 polymorphism was carried out in Web of Knowledge, PubMed, Scopus, EMBASE, and Google Scholar databases between 2000 and 2020. The searched queries were 'rs315952 or Ser133Ser or Mspa-I 11100 or IL-1Ra-Mspa- I11100 or IL-1RN-Mspa- I11100' and 'polymorphism or variation or variant or mutation or SNP or single nucleotide polymorphism or association or genetic association' and 'immunity or autoimmunity or immune-mediated or immune-mediated disease or immune-mediated disorder or inflammation or inflammatory.' Moreover, additional eligible studies were identified by the use of hand searching of retrieved articles. Articles were included in the meta-analysis if they met the following inclusion criteria: 1) original case-control population-based studies determining the link between *IL-1Ra* variant and human immune-mediated and inflammatory diseases; 2) studies that contain sufficient data of the allelic and genotypic frequencies of the *IL-1Ra* Ser133Ser variant in both studied groups. Case reports, meta-analyses, review articles, conference abstracts, and duplicated data were excluded.

Data extraction

Two independent investigators (Sargazi S and Haratisadegh M) extracted the data from articles meeting the mentioned criteria. A third investigator (Sheervalilou R) rechecked the results. Information regarding the first author's name, year of publication, genotyping method, country, ethnicity, disease type, sample size, and the available genotypic and allelic distributions in participants were extracted from each relevant article.

Statistical analysis

After extracting the quantity information of each included study, the odds ratio (OR) and standard error of OR (SE) were calculated to evaluate the

correlation between diseases and the *IL-1Ra* Ser133Ser variant. The I² statistics were calculated to assess heterogeneity using a random-effect model (I² > 50%) or a fixed-effect model (I² < 50%) when appropriate. Otherwise, a fixed-effect model was used. To assess sources of clinical heterogeneity, subgroup analysis was used to compare effect sizes (OR). Statistical test for funnel-plot asymmetry was performed using Egger's test. The Sensitivity analysis was carried out to assess the robustness of pooled ORs. All analysis was carried out using both MetaGenyo web tool (18) and STATA v.11 software.

Results

Study characteristics

Upon primary search through scientific databases, 49 results were obtained. After two steps of exclusion, 22 case-control studies (published between the years 2000 to 2019) with a total of 2622 cases and 3854 controls were selected and further investigated in this meta-analysis (19-40). A flowchart of the study selection process is shown in Fig. 1. The elaborated characteristics of all included studies are summarized in Table 1.
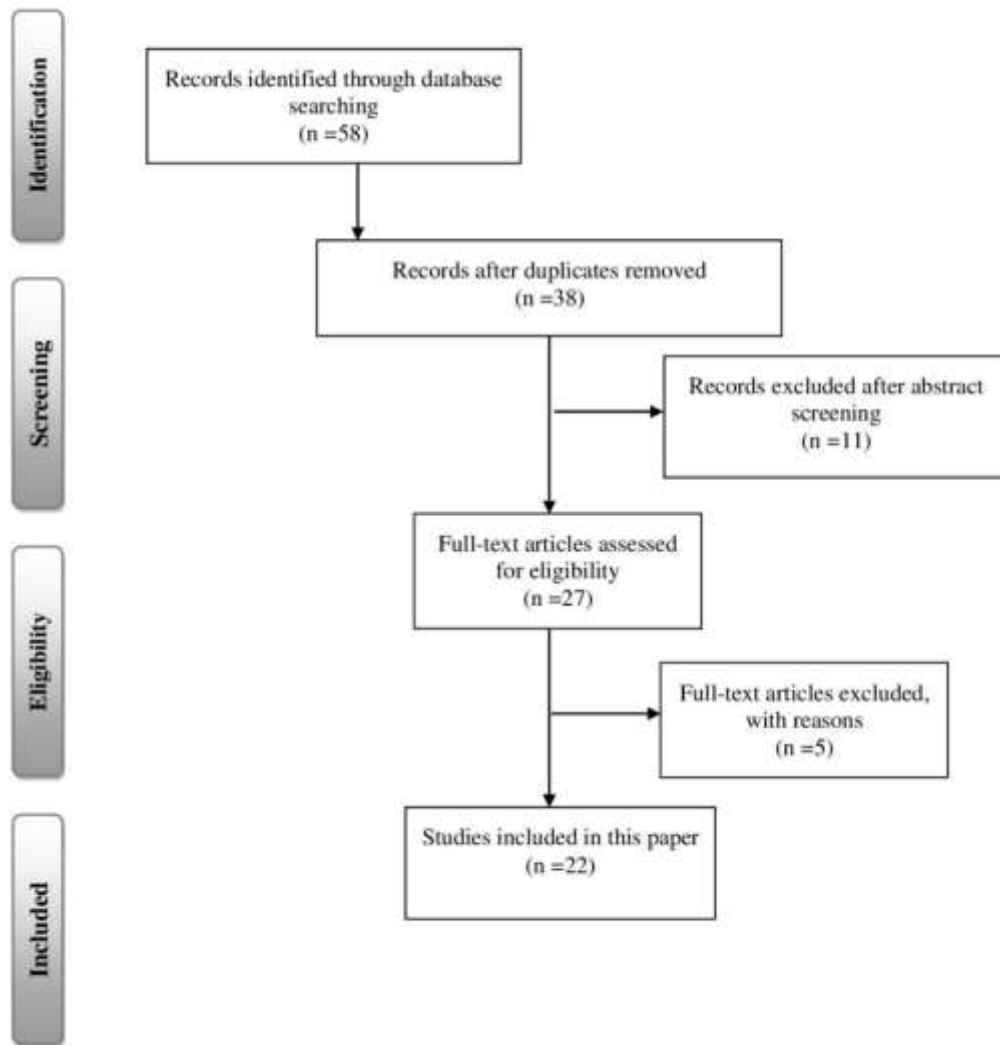

Fig. 1: Flow diagram indicating the study selection process for Meta-analysis.

Table 1: Characteristics of all studies included in the meta-analysis

Study	Genotyping method	Ethnicity	Disease	Case	Control	P_{HWE}
Chou (2006)(19)	Mass Array	Asian	AS	192	185	0.29
Tsai (2006)(35)	PCR-RFLP	Asian	SLE	104	97	0.20
Mahdaviani (2009)(29)	PCR-SSP	Asian	Asthma	36	140	0.11
Guo (2010)(23)	PCR-RFLP	Asian	AS	238	222	0.75
Jung (2010)(24)	ISM Array	Asian	RA	299	462	0.87
Khalilzadeh (2010)(26)	PCR-SSP	Asian	GD	107	140	0.11
Yamamoto-Furusho (2010)(37)	TaqMan	Hispanic	UC	199	248	0
Karasneh (2011)(25)	PCR-RFLP	Arab	Periodontitis	180	80	0.45
Kim (2011)(27)	PCR-RFLP	Asian	Kawasaki	107	287	0.82
Schulz (2011)(33)	PCR-SSP	Caucasian	Periodontitis	159	88	0.46
Mahmoudi (2011)(30)	PCR-SSP	Asian	AS	99	216	0
Loʹpez (2013)(28)	TaqMan	Hispanic	TA	58	248	0
Nasiri (2013)(31)	PCR-SSP	Asian	AR	93	140	0.11
Tahmasebi (2013)(34)	PCR-SSP	Asian	SLE	205	212	0.002
Wu (2013)(36)	Multiplex PCR	American	OA	88	66	0.99
Behniafard (2014)(22)	PCR-SSP	Asian	AD	86	140	0.11
Ziaee (2014)(39)	PCR-SSP	Asian	SLE	57	140	0.11
Osman (2015)(32)	TaqMan	Arab	AHO	52	103	0.49
Ziaee (2016)(40)	PCR-SSP	Asian	JIA	53	140	0.11
Assari (2018)(21)	PCR-SSP	Asian	Kawasaki	55	140	0.11
Yousefi (2018)(38)	PCR-SSP	Asian	AIH	55	140	0.11
Ad'hiah (2019)(20)	PCR-SSP	Arab	IBD	100	220	0

SLE: Systemic lupus erythematosus; AIH: Immune-mediated hepatitis; AD: Atopic dermatitis; IBD: Inflammatory bowel disease; AHO: Hematogenous osteomyelitis; OA: Osteoarthritis; AR: Allergic Rhinitis; RA: Rheumatoid arthritis; TA: Takayasu's arteritis; UC: Ulcerative colitis; JIA: Juvenile idiopathic arthritis; AS: Ankylosing spondylitis; GD: Graves' disease; UAE: United Arab Emirates; US: United States.

Main analysis results

Table 2 summarizes the results of the association test, heterogeneity, and publication bias under codominant (TC vs. TT and CC vs. TT), dominant (CC+TC vs. TT), recessive (CC vs. TC+TT), and allele contrast (C vs. T) models. Our findings revealed that the *IL-1Ra* Ser133Ser variant was not associated with an increased risk of immune-mediated and inflammatory diseases under any of the assessed contrasted genetic models ($P>0.05$). Forest plots representing the association between the SNP and the risk of immune-mediated and inflammatory diseases under codominant TC vs. TT models are shown in Fig. 2.

### Analysis of heterogeneity and publication bias

As shown in Table 2, we found heterogeneity between studies for *IL-1Ra* rs315952 variant in heterozygous codominant, homozygous codominant, dominant, recessive, and allelic genetic models. Egger's test was applied for detecting publication bias of the included studies (Fig. 3). In this regard, there is no publication bias observed in assessed models concerning this variant.
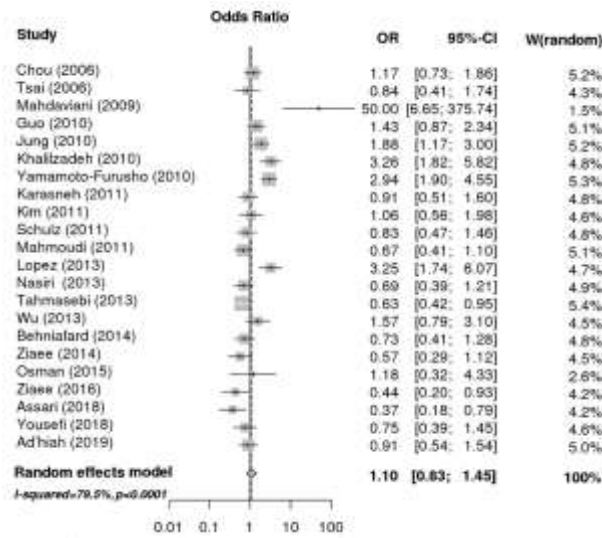
Fig. 2: Forest plot representing the association between *IL-1Ra* Ser133Ser variant and susceptibility to immune-mediated and inflammatory diseases under the codominant CT vs. TT model.

Table 2: The results of the association test, heterogeneity, and publication bias of *IL-1Ra* rs315952 polymorphism on susceptibility to immune-mediated and inflammatory diseases

Excluded study	No.	Type of Genetic model	No.	Association test		Heterogeneity test	Egger' test
				OR(95%CI)	p	I²	p
		T vs. C	22	1.04 (0.86-1.27)	0.64	81.59	0.68
		TC vs. TT	22	1.09 (0.82-1.45)	0.51	79.4	0.75
Mahmoudi M.	1	CC vs. TT	21	1.20(0.84-1.73)	0.31	63.90	0.55
		TC+CC vs. TT	22	1.08 (0.82-1.42)	0.55	80.65	0.71
Mahmoudi M.	1	CC vs. TC+TT	21	1.03 (0.77-1.37)	0.81	59.1	0.55
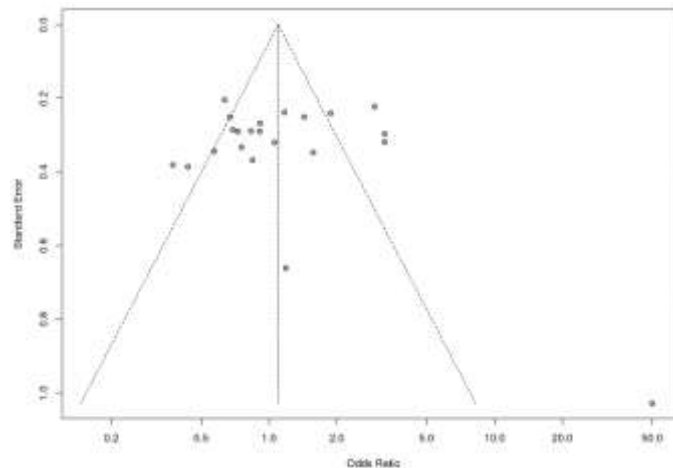
Fig. 3: Funnel plot representing the association between *IL-1Ra* Ser133Ser variant and susceptibility to immune-mediated and inflammatory diseases under the codominant CT vs. TT model.

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Subgroup analysis results

Stratified analysis of *IL-1Ra* Ser133Ser variant by disease type, ethnicity, and genotyping methods was performed (Table 3). The rs315952 variant was associated with decreased risk of ankylosing spondylitis (AS)(*n*=3 studies) regarding allelic [OR=0.83, 95% CI (0.69 - 0.99), *P* =0.003] and recessive [OR=0.59, 95% CI (0.49 - 0.81), *P* =0.001] models. Ser133Ser variant also had protective effect against systemic lupus erythematosus (SLE) susceptibility in allelic [OR=0.77, 95% CI (0.61-0.970), *P*=0.03], codominant heterozygous [OR=0.65, 95% CI (0.4-0.89), *P*=0.007], and dominant [OR=0.67, 95% CI (0.50-0.90), *P*=0.008] genetic models. Moreover, we found an increased risk of immune-mediated and inflammatory diseases (*n*=2 studies) among Hispanics regarding dominant [OR=2.65, 95% CI (1.90 - 3.71), *P*<0.001], codominant heterozygous [OR=3.03, 95% CI (2.12 - 4.34), *P*<0.001], and allelic C vs. T (OR=1.98, 95% CI=1.50 - 2.61, *P*<0.001) inheritance models (Table 3). A significant association was noticed between the genotyping method (Taqman) and *IL-1Ra* Ser133Ser variant in patients affected with these type of diseases (*n*=3 studies).

Table 3: Stratified analysis of *IL-1Ra* rs315952 polymorphism on susceptibility to immune-mediated and inflammatory diseases.

	No.	OR (95% CI)	P	I²%	OR (95% CI)	P	I²%	OR (95% CI)	P	I²%	OR (95% CI)	P	I²%	OR (95% CI)	P	I²%
		C vs. T			TC vs. TT			CC vs. TT			TC+CC vs. TT			CC vs. TC+TT		
Disease type																
AS	3	0.83 (0.69-0.99)	0.003	0	1.04 (0.67-1.61)	0.86	59.28	0.71 (0.47-1.06)	0.10	0	0.93 (0.71-1.22)	0.60	23.63	0.59 (0.42-0.81)	0.001	0
SLE	3	0.77 (0.61-0.97)	0.03	0	0.65 (0.48-0.89)	0.007	0	0.83 (0.45-1.53)	0.55	0	0.67 (0.50-0.90)	0.008	0	0.90 (0.54-1.50)	0.68	0
Kawasaki	2	0.81 (0.61-1.07)	0.14	55.62	0.64 (0.23-1.77)	0.39	77.01	0.87 (0.46-1.61)	0.65	0	0.65 (0.28-1.49)	0.30	69.46	0.85 (0.54-1.33)	0.47	0
periodontitis	2	0.84 (0.63-1.12)	0.24	0	0.87 (0.58-1.30)	0.49	0	0.69 (0.36-1.31)	0.26	0	0.83 (0.57-1.21)	0.33	0	0.75 (0.41-1.38)	0.36	0
Ethnicity																
Asian	14	1.01 (0.78-1.30)	0.94	83.99	0.99 (0.70-1.41)	0.97	79.13	1.36 (0.82-2.27)	0.23	71.14	1.02 (0.70-1.15)	0.93	81.37	1.16 (0.77-1.75)	0.47	69.45
Arab	3	0.80 (0.63-1.02)	0.55	0	0.93 (0.64-1.35)	0.70	0	061 (0.36-1.04)	0.07	0	0.82 (0.58-1.15)	0.25	0	0.70 (0.46-1.08)	0.11	0
Hispanic	2	1.98 (1.50-2.61)	<0.001	0	3.03 (2.12-4.34)	<0.001	0	1.42 (0.71-2.82)	0.31	0	2.65 (1.90-3.71)	<0.001	0	1.02 (0.52-2.01)	0.94	0
Genotyping method																
PCR-SSP	11	0.99 (0.69-1.42)	0.94	85.93	0.87 (0.57-1.31)	0.35	79.13	1.45 (0.67-3.13)	0.34	71.32	0.92 (0.60-1.41)	0.70	82.40	1.40 (0.72-2.71)	0.32	63.64
PCR-RFLP	4	0.85 (0.72-1.00)	0.05	0	1.09 (0.81-1.46)	0.57	0	0.74 (0.52-1.05)	0.09	0	0.96 (0.72-1.26)	0.75	0	0.68 (0.52-0.89)	0.005	0
TaqMan	3	1.64 (1.10-2.45)	0.01	58.94	2.84 (2.01-4.01)	<0.001	0	1.35 (0.74-2.47)	0.33	0	2.5 (1.81-3.46)	<0.001	0	1.00 (0.62-1.61)	0.99	0

SLE: Systemic lupus erythematosus; AS: Ankylosing spondylitis.

Sensitivity analysis

Sensitivity analysis was performed to approximate the effects of individual studies on the reliability and stability of the results. None of the studies substantially impacted pooled OR regarding the assessed genetic models, indicating that all

studies can be included in this meta-analysis. Fig. 4 shows sensitivity analyses for studies on the association of *IL-1Ra* Ser133Ser variant and risk

of immune-mediated and inflammatory diseases under the codominant heterozygous model.
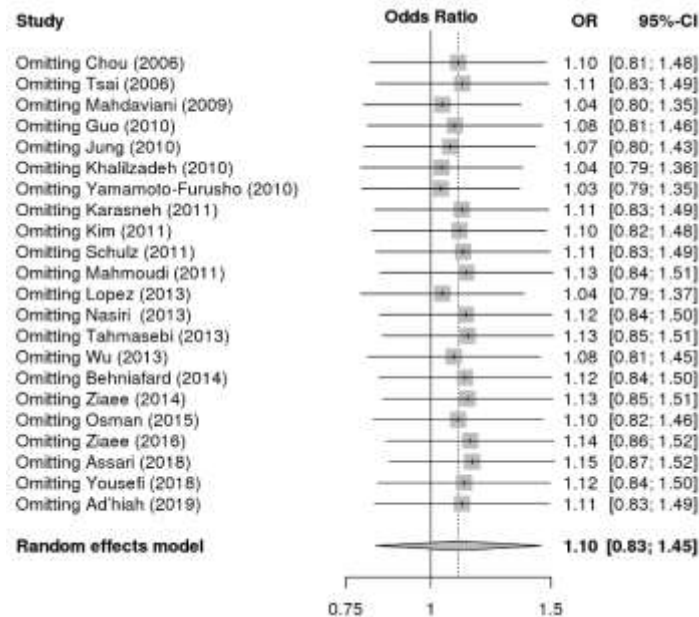
Fig. 4: Sensitivity analyses for studies on the association of *IL-1Ra* Ser133Ser variant and susceptibility to immune-mediated and inflammatory diseases under the codominant CT vs. TT model.

Discussion

Different cytokines delicately regulate the in-flammatory pathways in autoimmune diseases. Previous studies have established a link between SNPs and various inflammatory diseases and even cancers (28, 41). Interleukin-1Ra is considered as one of the crucial controllers of the inflammatory pathways in multiple systems (42). It has been shown in many reports that IL-1Ra inhibits the activity of either IL-1α or IL-1β (43). Due to the distinct roles of Interleukin-1Ra in negative modulation of inflammation, potential variations in the *IL-1Ra* gene might contribute to susceptibility to immune-mediated disorders.

In this meta-analysis, we comprehensively searched eligible studies from 2000 to 2019. We found no association between *IL-1Ra* Ser133Ser variant and overall susceptibility to immune-mediated and inflammatory diseases under co-dominant, dominant, recessive, and allelic con-trasted genetic models (*P*>0.05). Following strati-

fied analysis, it was discovered that this variant is associated with a decreased risk of systemic lupus erythematosus and/or ankylosing spondylitis. Except for the recessive CC vs. TC+TT model, enhanced risk of immune-mediated and inflam-matory diseases were observed in Hispanics un-der all the assessed models. Five studies violated Hardy–Weinberg equilibrium (HWE) in controls (20, 28, 30, 34, 37). However, we exclude this studied and found no significant difference in pooled ORs. Furthermore, a study was excluded from the analysis because zero subjects in cases and controls had carried CC genotype. One ex-planation for the observed insignificant associa-tion might be due to the functional role of the SNP. The rs315952 is a synonymous variation; hence, it does not affect the IL-1Ra protein struc-ture and function.

In a meta-analysis, three *IL-1Ra* SNPs were geno-typed in 2675 patients diagnosed with ankylosing spondylitis and 2592 controls. Their result indi-cated no increased risk of ankylosing spondylitis

regarding the *IL-1Ra* Ser133Ser variant (7). By performing a comprehensive analysis, the carriers of the rs315952 T allele were positively linked to the risk of ankylosing spondylitis (44). No meta-analysis study yet investigated the pooled effects of this variant against inflammatory or immune-mediated diseases rather than ankylosing spondylitis. Moreover, a variable number of tandem repeats (VNTR) within the *IL-1Ra* gene has been conferred an increased risk of inflammatory bowel disease in Northern European people (45). Our study has limitations. First, discrepancies were observed in the presentation of published papers for the *IL-1Ra* Ser133Ser variant. Second, different heterogeneity levels were observed among studies under the assessed models due to the broad range of immune-mediated and inflammatory diseases with different etiologies. Third, the majority of SNPs were studied in Asian populations. Fourth, in eight studies performed on Iranians, 140 controls with similar genotypic frequencies (57% TT, 40% TC, 3% CC) were included. This introduces bias into the pooled data interpretation. Despite these statistical limitations, as a preliminary report, we estimated the summary ORs of available data concerning the association between the *IL-1Ra Ser133Ser* variant and the overall risk of immune-mediated and inflammatory diseases.

Conclusion

The *IL-1Ra* Ser133Ser variant was associated with the overall risk of immune-mediated and inflammatory diseases. Performing large scale replication and meta-analysis of functional variants located in this gene is encouraged to further investigate the influence of *IL-1Ra* SNPs on overall disease susceptibility.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interest

The authors disclose no conflict of interest.

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