



Universiteit
Leiden
The Netherlands

Interleukin-1 genetic polymorphisms in knee osteoarthritis: What do we know? A meta-analysis and systematic review

Budhiparama, N.C.; Lumban-Gaol, I.; Sudoyo, H.; Magetsari, R.; Wibawa, T.

Citation

Budhiparama, N. C., Lumban-Gaol, I., Sudoyo, H., Magetsari, R., & Wibawa, T. (2022). Interleukin-1 genetic polymorphisms in knee osteoarthritis: What do we know? A meta-analysis and systematic review. *Journal Of Orthopaedic Surgery -Hong Kong-*, 30(1). doi:10.1177/23094990221076652

Version: Publisher's Version

License: [Creative Commons CC BY-NC 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/3281395>

Note: To cite this publication please use the final published version (if applicable).

Interleukin-1 genetic polymorphisms in knee osteoarthritis: What do we know? A meta-analysis and systematic review

Journal of Orthopaedic Surgery
30(1) 1–14
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/23094990221076652
journals.sagepub.com/home/osj
 SAGE

Nicolaas C Budhiparama, MD, PhD^{1,2,3} , Imelda Lumban-Gaol, MD³,
Herawati Sudoyo, MD, PhD⁴, Rahadyan Magetsari, MD, PhD¹ and Tri Wibawa, MD, PhD⁵

Abstract

Purpose: Interleukin-1 is the main proinflammatory cytokine in osteoarthritis (OA). Several single-nucleotide polymorphisms (SNPs) within the IL-1 gene cluster (IL-1 β , IL-1RI, and IL-1RN) have been determined, but their associations with knee OA remain poorly understood. The present study aimed to identify the associations between IL-1 SNPs and knee osteoarthritis.

Methods: This meta-analysis and systematic review included all comparative studies published in the MEDLINE/PubMed, Embase, Google Scholar, and Cochrane Library databases. We performed a systematic search to identify relevant studies on the evaluation of the correlation between the IL-1 gene and knee OA published up to February 2020 that met the eligibility criteria. Nine studies on a total of 2256 knees with OA and 3527 healthy knees met the eligibility criteria. Results associated with IL-1A, IL-1B, IL-1RI, and IL-1RN SNPs were extracted and compared between knees with OA and healthy knees. Methodological quality was assessed using the Newcastle–Ottawa scale (NOS). All studies with fair or good quality were included.

Results: The meta-analysis showed that the risk of knee OA is decreased by the IL-1RN*1 and IL-1RN*1/*1 genotypes and increased by the IL-1RN*2 and IL-1RN*1/*2 genotypes. The systematic review revealed only two studies associating the IL-1RN allele, none associating the IL-1B polymorphism, and only one study associating IL-1A and IL-1RI polymorphisms with knee OA.

Conclusions: Several IL-1RN alleles and genotypes play a role in knee OA but other genetic variations in the IL-1 region were still conflicting in its association with knee OA.

Keywords

Knee osteoarthritis, interleukin-1, single-nucleotide polymorphisms

Date received: 25 August 2021; Received revised 2 December 2021; accepted: 12 January 2022

¹Department of Orthopaedic & Traumatology, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

²Department of Orthopaedics, Leiden University Medical Center, Leiden, The Netherlands

³Nicolaas Institute of Constructive Orthopaedic Research & Education Foundation for Arthroplasty & Sports Medicine at Medistra Hospital, Jakarta, Indonesia

⁴Eijkman Institute for Molecular Biology at Cipto Mangunkusumo Hospital, Jakarta, Indonesia

⁵Department of Microbiology, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

Corresponding author:

Nicolaas C Budhiparama, MD, PhD, Department of Orthopaedic & Traumatology, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

Email: n.c.budhiparama@gmail.com, n.c.budhiparama@lumc.nl



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

Introduction

The pathogenesis of osteoarthritis (OA) is not yet fully understood. It was originally thought to result from the failed repair of damaged cartilage.¹ This theory has been expanded to include contributions from the bone and synovial tissue as well as inflammatory factors.¹⁻³ Interleukin-1 (IL-1) is the regulator of inflammation by controlling the innate immune process. IL-1 itself is expressed in a wide range of tissues and cells.⁴ IL-1 is synthesized due to stress response. By binding to its receptors, it will activate other immune response and other hematological changes.⁵ IL-1 also associated with the pathogenesis of knee OA due to the fact that an increased expression of this cytokine correlates with worsening symptoms and more progressive radiological features of knee OA.⁶⁻⁸ Interleukin-1 is regarded as a major proinflammatory cytokine in addition to Tumor Necrosis Factor (TNF) and IL-6, and its biological activity is mediated through specific cell surface receptor known as the IL-1 receptor type I (IL-1R1).⁹ Another natural inhibitor of IL-1 activity, IL-1 receptor antagonist (IL-1RA), is produced by several types of cell including chondrocytes and synovial fibroblasts, and functions as a competitive antagonist in the process of osteoarthritis.^{8,10} Another mechanism is through the binding of IL-1 β to the IL-1 receptor (IL-1R1), which induces a pro-inflammatory reaction resulting in cartilage destruction. Progressive cartilage destruction might be followed by subchondral destruction manifesting as progressive radiological grading. Pro-inflammatory reactions also cause synovial inflammation, that might manifest as pain.¹¹

The latest concept of OA pathogenesis involves a genetic component that might influence inflammation (cytokines), anti-inflammation, and receptor binding processes. Several types of OA are associated with a genetic component,¹²⁻¹⁴ but controversies are also found among different ethnicities.¹⁵ Variations in cytokine levels among individuals become a plausible explanation for differences in disease susceptibility and severity,¹⁵ and this association is particularly true for cytokine gene polymorphisms and OA. The most consistent association involves a broad region on human chromosome 2q13-32, which represents the IL-1 gene cluster.¹⁶ Several DNA variants within the IL-1 gene cluster have been reported, including single-nucleotide polymorphisms (SNPs) in IL-1 β , IL-1R1, and IL-1RN. However, specific genetic factors and polymorphisms associated with these conditions remain poorly understood. Several studies have generated conflicting findings in terms of this association with various OA phenotypes.

The present meta-analysis and systematic review aimed to clarify an association between genetic polymorphisms in the IL-1 gene cluster and the development of knee OA. We hypothesize that there is a correlation between genetic polymorphisms in the IL-1 gene cluster and the development of knee OA.

Material and methods

Search strategy

Based on the Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) guidelines, we performed a systematic review using the MEDLINE/PubMed, Embase, Google Scholar, and Cochrane Library databases to identify relevant studies evaluating the correlation between IL-1 gene and knee OA published up to February 2020 that met the eligibility criteria. We conducted a systematic search using the following medical subject headings (MeSH) and key terms: (((Knee osteoarthritis) AND Single Nucleotide Polymorphism) OR SNP) OR Gene) AND Interleukin-1) OR IL-1))). We limit our search to studies conducted on humans and published in English. Two authors (NCB, ILG) separately reviewed all abstracts for eligibility. We manually-searched the references from the included articles and reviews to avoid missing any relevant studies.

Inclusion and exclusion

The inclusion criteria were (1) studies comparing knee OA patients and normal patients; (2) studies investigating the relationship between the IL-1 gene or polymorphisms and knee OA; (3) studies conducted on human study; (4) studies published in English; (5) studies providing the number subjects for their case and control groups; and (6) studies providing the genotype and/or allele frequency for their case and control groups. The initial search yielded 18,693 references. After the studies were compared against the inclusion criteria, 18,684 studies were excluded due to the following reasons: irrelevant topic (not correlated with IL-1 in knee OA), full text not available, not a comparative study (no control group), no comparison with a healthy control group, incomplete data, and being meta-analyses or systematic review articles. After exclusions and evaluation by two authors, 9 studies met the inclusion criteria. We found 1 cohort study and 8 case-control studies. Using the Newcastle-Ottawa scale (NOS) for quality assessment, we reviewed the 9 articles ([Figure 1](#)). All fair and good-quality studies were included. In each article, we reviewed the comparison between the knee OA group and the healthy control group in terms of the frequency of IL-1 gene polymorphism.

The quality of all articles was assessed by using the Newcastle-Ottawa scale (NOS). Each study is interpreted as having good, fair, and poor quality. The eight case-control and one cohort studies are of good quality. All studies adequately reported a succinct study aim and an appropriate outcome measure. Due to the limitations and wide variation in terms study quality, we were only able to perform meta-analysis for the IL1RN polymorphism while a systematic review was performed for the other IL1 polymorphisms.

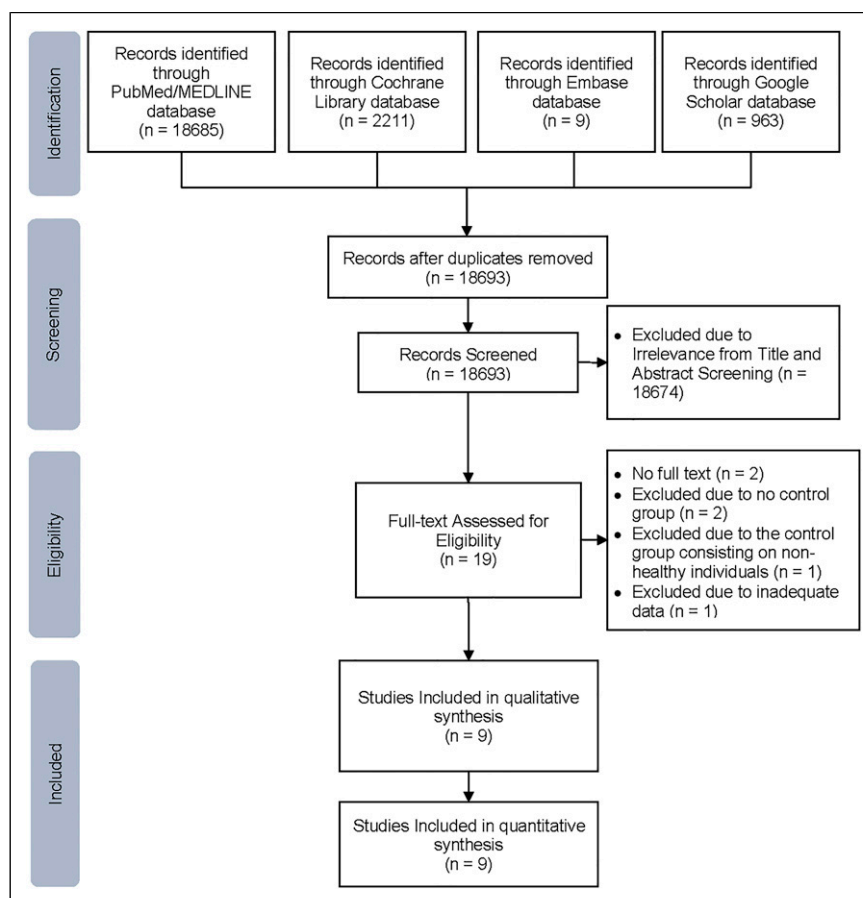


Figure 1. Flowchart shows the numbers of articles initially identified as well as the exclusion and inclusion steps.

Data extraction

In each article, we collected the demographic characteristics, sample size, phenotype information, the number of genotypes in cases and controls, and the results of the study.

Statistical analysis

The distribution of genotypes and alleles is summarized in a data table. The distribution of the genotypes in the control population was assessed using Hardy–Weinberg equilibrium (HWE). p values of <0.05 indicated that the genotype distribution deviated from HWE. General data were evaluated using meta-analysis. Heterogeneity was assessed using chi-squared tests. Random and fixed-effect models were applied when $p < 0.05$ or $p > 0.05$, respectively. Sources of heterogeneity were identified using a meta-regression analysis. Publication bias was assessed using funnel plots, and Begg and Egger tests helped to reach a clear conclusion. After determining the effect model, the strength of the association between the IL-1-RN Variable Number Tandem Repeat (VNTR) polymorphism and the

risk of OA was assessed using odds ratios (OR) and confidence intervals (CI). Two authors independently completed the analysis and obtained the same results. All data were statistically analyzed using Review Manager (Rev-Man) [Computer program] Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. p values of <0.05 were considered significant.

Results

An initial search yielded 18,693 references, but 18,684 were excluded due to irrelevant topics (unrelated to correlations between IL-1 and knee OA), full text unavailability, non-comparative study (without controls), no comparison with healthy controls, inadequate data, and being meta-analysis or systematic reviews. The nine remaining studies comprised of one cohort and eight case-control studies. Two individuals (NCB and ILG) independently assessed the methodological quality of the selected articles and found them to be of fair and good quality according to the Newcastle–Ottawa scale (NOS) (Table 1). We then reviewed the comparisons of IL-1 gene polymorphisms

Table 1. Newcastle–Ottawa scale (NOS) quality assessment of case-control studies.

Study	Type	Selection	Comparability	Exposure	Interpretation
AJP Smith 2004 ²⁷	Case-control	****	**	***	Good quality
Yuyan Na 2017 ²⁸	Case-control	****	**	***	Good quality
Haijian Ni 2009 ²⁹	Case-control	****	**	***	Good quality
Loughlin 2002 ³⁰	Case-control	***	*	***	Good quality
Melek Sezgin 2014 ³¹	Case-control	****	*	***	Good quality
Kaarvatn 2012 ³²	Case-control	****	**	***	Good quality
Menha Swellam 2010 ³³	Case-control	****	**	***	Good quality
Jotanovic 2011 ³⁴	Case-control	****	**	***	Good quality
S. Ruzickova 2008 ³⁵	Cohort	****	*	**	Good quality

frequency between patients with knee OA and healthy controls.

Quantitative synthesis

The allele and haplotype frequencies for cases and controls in each study are presented in Table 2. Pooled analysis of all included studies showed that the IL-1RN*1 and IL-1RN*2 alleles among the IL-1RN (VNTR) (rs419598) polymorphisms were significantly associated with knee OA; IL-1RN*1 and IL-1RN*2, respectively, decreased and increased the risk of knee OA (OR, 0.67; 95% CI, 0.48–0.95; $I^2 = 79$, $p = 0.02$ and OR, 1.38; 95% CI, 1.02–1.85; $I^2 = 71$, $p = 0.04$). One and four studies evaluated Asian and Caucasian cohorts, respectively. The IL-1RN*1 and IL-1RN*2 alleles, respectively, decreased and increased the risk of knee OA in the Caucasian cohort (OR, 0.59; 95% CI, 0.38–0.92; $I^2 = 83$, $p = 0.02$ and OR, 1.50; 95% CI, 1.05–2.14; $I^2 = 74$, $p = 0.03$, respectively; Figure 2).

The meta-analysis revealed that some IL-1RN VNTR genotype polymorphisms were also significantly associated with knee OA. The IL-1RN*1/*1 polymorphism decreased the risk of knee OA (OR, 0.59; 95% CI, 0.37–0.95; $I^2 = 82$, $p = 0.03$). Interleukin-1RN*1/*1 and IL-1RN*1/*2 polymorphisms remained significantly associated with knee OA in Caucasians (OR, 0.50; 95% CI, 0.28–0.89; $I^2 = 84$, $p = 0.02$ and OR, 1.77; 95% CI 1.03–3.06, $I^2 = 86$, $p = 0.04$, respectively). Subgroup analysis revealed a significant association between IL-1RN*1/*2 genotype polymorphism and knee OA in Caucasians (OR, 2.20; 95% CI, 1.10–4.43, $I^2 = 88$, $p = 0.03$). Other IL-1RN VNTR (rs419598) alleles or genotypes polymorphisms were not significantly associated with knee OA (Figure 3).

Heterogeneity tests

The allele contrast model analysis revealed significant heterogeneity ($I^2 = 69$; $p < 0.0001$); therefore, a random effects model was adopted. Subgroup heterogeneity was also high ($I^2 = 68.4$; $p = 0.02$). The genotype model analysis

also indicated significant heterogeneity ($I^2 = 67$; $p < 0.0001$) and the subgroup heterogeneity was $I^2 = 47.1$; $p = 0.08$. Subgroup analysis based on rand type of study did not identify any source of heterogeneity.

Publication bias

Publication bias was evaluated with funnel plots using the IL-1RN*1 allele as a sample. The results showed asymmetry for the IL-1RN*2, IL-1RN*1/*1, and IL-1RN*1/*2 alleles, but not for any other IL-1RN alleles or genotypes (Figure 4).

Systematic review

The IL-1RN allele was evaluated in seven studies, among which, two found an association between knee OA and IL-1RN*1 allele SNP rs419598, and the IL-1RN*2 SNP rs419598. Interleukin-1RN*1 SNP rs419598 decreased the risk, while the IL-1RN*2 polymorphism increased the risk of knee OA in both studies. One study evaluated different IL-1RN SNP, (11,100 known as rs315952), and found no association between these IL-1RN alleles and knee OA. Six studies investigated associations between IL-1RN genotypes and knee OA. Two of these studies associated a decreased and an increased risk for knee OA with IL-1RN*1/*1 SNP rs419598 and IL-1RN*1/*2 SNP rs419598, respectively (Table 2).

Among the nine studies, five that evaluated associations between IL-1B polymorphisms and knee OA found no associations for the IL-1B allele and the IL-1B genotypes, –511C/T (SNP rs16944), +3954 (SNP rs1143634), 5810 (SNP rs1143633), or in +3953. Three studies found an association between IL-1A and knee OA. However, one study found an association between the IL-1A-899 allele (SNP rs1800587) and knee OA but we found no matching association based on gender. Another study found no association between the IL-1A-899 allele with knee OA but associated the IL-1A-899 genotypes CC and CT with knee OA. One study found no association between IL-1A+4845 SNP allele and knee OA.

Table 2. Studies comparing IL-1 gene polymorphisms between knees with OA and healthy knees.

Study	Year	Sample size		Gene	SNP	Type	Outcome			
		Case	Control				Case	Control	OR	p
AJP Smith et al. ²⁷	2004	141	195	IL-1RN VNTR	IL-1A-IL-1B-IL-1RN	Haplotype	28	18	2.44	1.29–4.61
					IL-1B-IL-1RN	CCA-ITT	14	52	0.30	0.16–0.57
	163		195		IL-1A-IL-1B-IL-1RN	Haplotype	30	18	2.22	1.19–4.15
					IL-1B-IL-1RN	CCA-ITT	12	52	0.22	0.11–0.43
	2008	50	170		rs419598	Allele	68*	285*	0.41	0.25–0.68
S. Ruzickova et al. ³⁵							28*	51*	2.20	1.30–3.74
							4*	4*	3.50	0.86–14.25
						Genotype	22	123	0.30	0.16–0.58
							21	35	2.79	1.42–5.48
							3	4	2.65	0.57–12.25
							3	8	1.29	0.33–5.07
							1	0	10.33	0.41–257.66
						MMP-9	50	—	—	ns
							50	—	—	ns
						TIMP-1	50	—	—	ns
							50	—	—	ns
						HA	50	—	—	ns
							50	—	—	ns
						PEN	50	—	—	ns
							50	—	—	ns
						COMP	50	—	—	ns
							50	—	—	ns
						MMP-9	50	—	—	ns
							50	—	—	ns
						TIMP-1	50	—	—	ns
							50	—	—	ns
						HA	50	—	—	ns
							50	—	—	ns
						PEN	50	—	—	ns
							50	—	—	ns
						COMP	50	—	—	ns
							50	—	—	ns
							50	—	—	ns
							50	—	—	ns

(continued)

Table 2. (continued)

Study	Sample size			Gene	SNP	Type	Outcome			
	Year	Case	Control				Case	Control	OR	p
Yuyan Na et al. ²⁸	2017	298	297	IL-IRI	rs10490571 rs12712127 rs956730 rs3917225 rs3917318 rs956730 (G>A)	Allele	61	50	1.27	0.95–1.70
						Allele	74	62	1.25	0.95–1.64
						Allele	63	80	0.74	0.57–0.97
						Allele	123	100	1.38	1.09–1.75
						Allele	131	143	0.85	0.67–1.06
						Genotype	182	158	1.00	
						AG	105	119	0.86	0.60–1.23
						AA	11	20	0.51	0.23–1.15
						Dominant	182	158	1.00	
						AA + AG	116	139	0.81	0.58–1.14
Hailian Ni et al. ²⁹	2009	453 (all)	487 (all)	IL-IRN VNTR	rs3917225 (A>G)	Recessive	287	277	1.00	
						AA	11	20	0.54	0.25–1.21
						Additive	—	—	0.80	0.60–1.06
						Genotype	106	131	1.00	
						AA	138	132	1.32	0.91–1.91
						GA	54	34	2.03	1.20–3.43
						GG	106	131	1.00	
						Dominant	192	166	1.47	1.04–2.07
						GG + GA	244	263	1.00	
						AA + GA	54	34	1.75	1.08–2.85
Hailian Ni et al. ²⁹	2009	453 (all)	487 (all)	IL-IRN VNTR	rs419598	GG	—	—	1.40	1.09–1.79
						Allele	835*	896*	0.98	0.70–1.38
						IL-IRN*1	64*	69*	0.99	0.70–1.41
						IL-IRN*2	0*	3*	0.15	0.01–2.96
						IL-IRN*3	7*	6*	1.25	0.42–3.74
						IL-IRN*4	393	420	1.05	0.72–1.52
						Genotype	56	65	0.92	0.63–1.34
						IL-IRN*1/P2	4	2	2.16	0.39–11.85
						IL-IRN*2/P2	223	249	0.93	0.69–1.25
						Genotype	111	126	0.93	0.72–1.19
Hailian Ni et al. ²⁹	2009	453 (all)	487 (all)	IL-IRN VNTR	rs419598	CT	119	112	1.19	0.89–1.61
						TT	283	268	1.21	0.77–1.915
						Genotype	37	45	0.77	0.49–1.23
						IL-IRN*1/P2	3	1	2.93	0.30–28.36
						IL-IRN*2/P2	79	82	0.92	0.64–1.31
						Genotype	162	164	0.92	0.67–1.26
						CT	82	68	1.23	0.85–1.78
						TT	110	152	0.759	0.393–1.469
						Genotype	19	20	1.309	0.668–2.569
						IL-IRN*1/P2	1	1	1.333	0.083–
Hailian Ni et al. ²⁹	2009	453 (all)	487 (all)	IL-IRN VNTR	rs419598	IL-IRN*2/P2	32	44	0.957	0.566–1.619
						Genotype	61	85	0.915	0.580–1.443
						CT	37	44	1.166	0.699–1.947
						TT	414	463	0.929	0.775–1.113
						Haplotype	31	38	0.873	0.538–1.415
						1_1	428	442	1.078	0.899–1.292
						1_2	33	31	1.150	0.698–1.894
						2_1				
						2_2				
						Genotype	32	44	0.957	0.566–1.619
						CT	61	85	0.915	0.580–1.443
						TT	37	44	1.166	0.699–1.947
						Haplotype	414	463	0.929	0.775–1.113
						1_1	31	38	0.873	0.538–1.415
						1_2	428	442	1.078	0.899–1.292
						2_1	33	31	1.150	0.698–1.894
						2_2				

(continued)

Table 2. (continued)

Study	Year	Sample size		Gene	SNP	Type	Outcome				
		Case	Control				Case	Control	OR	95% CI	P
Loughlin et al. ³⁰	2002	136 (all)	557 (all)	IL-1A	(-899) rs1800587	Allele	167*	763*	0.723	0.546–0.957	0.023
				IL-1B	(+3954) rs143634	Allele	193*	841*	0.817	0.605–1.103	ns
					(5810) rs143633		182*	708*	1.312	0.979–1.757	ns
					(-511) rs16944		182*	747*	0.945	0.712–1.253	ns
				IL-1RN	9589	Allele	65*	315*	0.808	0.594–1.099	ns
					(11100) rs315952		76*	307*	1.019	0.758–1.371	ns
				IL-1A	(-899) rs1800587	Allele	97*	304*	0.759	0.512–1.125	ns
				IL-1B	(+3954)	Allele	115*	325*	0.966	0.627–1.489	ns
					(5810) rs143633		101*	264*	1.360	0.909–2.034	ns
					(-511) rs16944		102*	284*	0.865	0.586–1.277	ns
				IL-1RN	9589	Allele	43*	126*	0.929	0.617–1.398	ns
					(11100) rs315952		43*	113*	1.041	0.689–1.571	ns
				IL-1A	(-899) rs1800587	Allele	70*	459*	0.666	0.444–1.001	ns
				IL-1B	(+3954)	Allele	78*	516*	0.660	0.432–1.010	ns
					(5810) rs143633		81*	444*	1.316	0.852–2.031	ns
Melek Sezgin et al. ³¹	2014	107	67	IL-1RN	(-511) rs16944	Allele	22*	189*	0.624	0.380–1.023	ns
					9589		33*	194*	1.029	0.664–1.594	ns
					(11100) rs315952		28*	19*	0.91	0.49–1.71	ns
				IL-1RN VNTR	rs419598	Allele	2*	1*	1.25	0.11–13.97	ns
							175*	109*	1.03	0.59–1.79	ns
							9*	5*	1.13	0.37–3.45	ns
				Genotypes	IL-1RN [#] 2		74	47	1	(–)	ns
					IL-1RN [#] 4		19	12	0.98	0.32–2.95	ns
					IL-1RN [#] 4 [#] 4		4	3	1.27	0.18–8.63	ns
					IL-1RN [#] 2 [#] 2		7	2	0.75	0.08–6.47	ns
					IL-1RN [#] 5 [#] 4		1	1	0.71	0.04–12.70	ns
					IL-1RN [#] 5 [#] 2		1	1	0.89	0.04–18.53	ns
					IL-1RN [#] 4 [#] 3		0	1	IR	IR	ns
					IL-1RN [#] 5 [#] 5		1	0	IR	IR	ns
					IL-1RN [#] 5 [#] 3		153*	94*	1.092	0.558–2.139	ns
	Allele	C	59*	40*	0.916	0.468–1.793	ns				
		T	53	34	1	(–)	ns				
	Genotypes	CC	47	26	1.16	0.43–3.12	ns				
		CT	6	7	0.39	0.06–2.42	ns				
		TT	168*	104*	1.053	0.504–2.201	ns				
	Allele	C	46*	30*	0.949	0.454–1.983	ns				
		T	68	41	1	(–)	ns				
	Genotypes	CC	32	22	0.77	0.29–2.06	ns				
		CT	7	4	2.15	0.28–16.35	ns				
		TT									

(continued)

Table 2. (continued)

Study	Year	Sample size		Gene	SNP	Type	Outcome					
		Case	Control				Case	Control	OR	95% CI	p	
Kaarvatn et al. ³²	2012	470	1048	IL-1A	(-889) rs1800587	Allele	C	311	739	0.82	0.64–1.04	ns
					T	159	309	1.22	0.96–1.55	ns		
		235	524	IL-1A	(-889) rs1800587	Genotype	CC	101	269	0.71	0.52–0.99	0.033
					CT	109	201	1.39	1.01–1.92	0.038		
	480					TT	25	54	1.04	0.61–1.76	ns	
						Allele	C	365	787	1.11	0.86–1.44	ns
						T	115	275	0.90	0.70–1.17	ns	
						Genotype	CC	138	292	1.11	0.80–1.52	ns
						CT	89	203	0.95	0.69–1.32	ns	
						TT	13	36	0.79	0.39–1.57	ns	
434		1032	IL-IRN VNTR	rs419598	Allele	IL-IRN [#] 1	294*	732*	0.861	0.676–1.096	ns	
					IL-IRN [#] 2	132	276	1.197	0.936–1.532	ns		
					IL-IRN [#] 3	8	23	0.824	0.366–1.856	ns		
					IL-IRN [#] 4	0	1	0.791	0.032–	ns		
Menha Swellam et al. ³³	2010		516	IL-IRN VNTR	rs419598	Genotype	IL-IRN [#] 1/1	101	267	0.812	0.591–1.116	ns
						IL-IRN [#] 1/2	85	182	1.182	0.852–1.639	ns	
						IL-IRN [#] 1/3	7	15	1.113	0.448–2.770	ns	
						IL-IRN [#] 1/4	0	1	0.790	0.032–	ns	
	476					IL-IRN [#] 2/2	23	45	1.241	0.731–2.107	ns	
						IL-IRN [#] 2/3	1	4	0.593	0.066–5.332	ns	
						IL-IRN [#] 3/3	0	2	0.475	0.023–9.934	ns	
						Haplotype	1-2-1-1 (C-T-G-4)	5	32	0.31	0.11–0.84	0.011
						1-2-1-1 (C-T-G-4)	4	15	0.14	0.04–0.47	<0.001	
						Haplotype	1-2-1-1 (C-T-G-4)	37	31	0.14	0.03–0.54	0.001
2010		80	IL-IRN VNTR	rs419598	Haplotype	2-1-1-1 (T-C-G-4)	6	9	3.6	1.12–11.3	0.011	
					Haplotype	1-1-1/1-1-1-2-1 (C-C-G-4/C-C-A-4)	11	48	0.46	0.22–0.94	0.021	
					Allele	IL-IRN [#] 1	5	34	0.30	0.10–0.81	0.008	
					IL-IRN [#] 2	98*	64*	0.26	0.13–0.52	0.040		
Joanovic et al. ³⁴	2011		916	IL-1B	(-511) rs16944	Allele	IL-IRN [#] 1	70*	12*	3.81	1.91–7.58	<0.0001
						IL-IRN [#] 2	0*	0*	0*	0*	0*	0*
						Genotype	IL-IRN [#] 1/1	24	28	0.184	0.080–0.421	0.0001
						IL-IRN [#] 1/2	58	8	10.55	4.215–	0.0001	
	434					IL-IRN [#] 2/2	12	2	3.353	0.713–	ns	
						Allele	G	301	590	0.950	0.755–1.196	ns
						Genotype	GG	175	326	1.052	0.836–1.325	ns
						GA	96	180	1.044	0.758–1.437	ns	
						AA	109	230	0.838	0.612–1.147	ns	
						Allele	IL-IRN [#] 1	294*	685*	0.886	0.694–1.131	ns
217		495	IL-IRN VNTR	rs419598	Genotype	IL-IRN [#] 1/4	101*	248*	0.867	0.630–1.194	ns	
					IL-IRN [#] 4/2	85*	180*	1.127	0.812–1.565	ns		
					IL-IRN [#] 4/5	7*	15*	1.067	0.429–2.655	ns		
					IL-IRN [#] 4/3	0*	1*	0.758	0.031–	ns		
Menha Swellam et al. ³³	2010		80	IL-IRN VNTR	rs419598	Haplotype	2-1-1-1 (T-C-G-4)	6	9	3.6	1.12–11.3	0.011
						Haplotype	1-1-1/1-1-1-2-1 (C-C-G-4/C-C-A-4)	11	48	0.46	0.22–0.94	0.021
						Allele	IL-IRN [#] 1	5	34	0.30	0.10–0.81	0.008
						IL-IRN [#] 2	98*	64*	0.26	0.13–0.52	0.040	
	434					Genotype	IL-IRN [#] 1/1	24	28	0.184	0.080–0.421	0.0001
						IL-IRN [#] 1/2	58	8	10.55	4.215–	0.0001	
						IL-IRN [#] 2/2	12	2	3.353	0.713–	ns	
						Allele	G	301	590	0.950	0.755–1.196	ns
						Genotype	GG	175	326	1.052	0.836–1.325	ns
						GA	96	180	1.044	0.758–1.437	ns	
217		495	IL-IRN VNTR	rs419598	Genotype	IL-IRN [#] 1/4	101*	248*	0.867	0.630–1.194	ns	
					IL-IRN [#] 4/2	85*	180*	1.127	0.812–1.565	ns		
					IL-IRN [#] 4/5	7*	15*	1.067	0.429–2.655	ns		
					IL-IRN [#] 4/3	0*	1*	0.758	0.031–	ns		

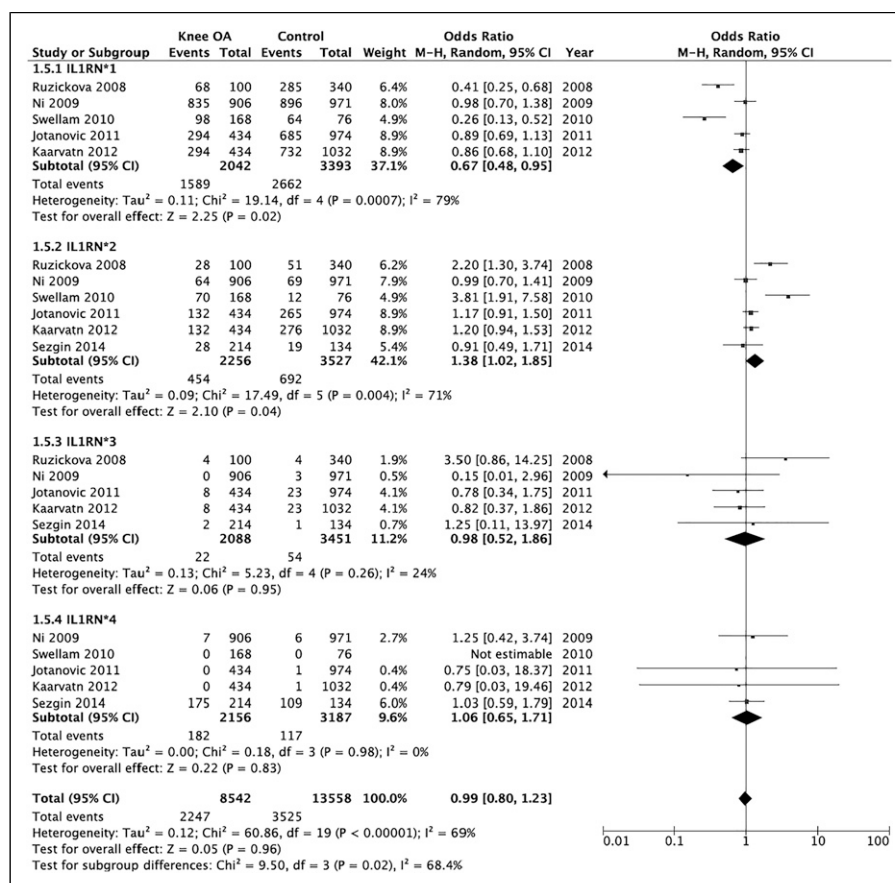


Figure 2. Forest plot of IL1RN VNTR allele.

One of the nine studies evaluated IL-1R1 polymorphisms SNP rs10490571, rs12712127, rs956730, rs3917225, and rs3917318. Among these five SNPs, only two were associated with knee OA: rs956730 decreased the risk (OR, 0.74; 95% CI, 0.57–0.97, $p = 0.028$) while rs3917225 increased the risk of knee OA (OR, 1.38; 95% CI, 1.09–1.75, $p = 0.007$). Interleukin-1R1 rs956730 SNP was associated with a decreased risk of knee OA in an additive model (OR, 0.73; 95% CI, 0.56–0.96; $p = 0.026$); but when the age and sex were matched, no association was found between knee OA and IL-1RN SNP rs956730 regardless of whether it was dominant, recessive, or additive. Interleukin-1RN SNP rs3917225 genotypes GG, dominant GG+GA, recessive GG, and an additive model were associated with an increased risk of knee OA. The correlation persisted in age- and sex-matched dominant (adjusted OR, 1.47; 95% CI, 1.04–2.07, $p = 0.030$), recessive (adjusted OR, 1.75, 95% CI, 1.08–2.85, $p = 0.023$), and additive models (adjusted OR, 1.40; 95% CI, 1.09–1.79; $p = 0.007$).

One study evaluated the associations between the IL-1RN polymorphism and matrix metalloproteinase-9 (MMP-9), tissue inhibitor of matrix metalloproteinases-1 (TIMP-1), as well as hyaluronic acid (HA) and pentosidine

(PEN), which are cartilage oligomeric matrix proteins (COMP) and markers of synovitis and cartilage destruction. They found no associations between IL-1RN and any of these proteins. Some studies also investigated the haplotype of IL-1 family polymorphisms. Interleukin-1B -511C/T-IL-1RN VNTR was not associated with knee OA, but the IL-1A(889)-IL-1B(3954)-IL-1B(511)-IL-1RN VNTR haplotype 1-2-1-1 (C-T-G-4) decreased the risk of knee OA (OR, 0.31; 95% CI, 0.11–0.84, $p = 0.011$). Age- and sex-matched models also found an association between this haplotype and knee OA in women (OR = 0.14, 95% CI = 0.04–0.47, $p < 0.001$). Interleukin-1A(889)-IL-1B(3954)-IL-1B(511)-IL-1RN VNTR haplotype 1-1-1-1/1-1-2-1 (C-C-G-4/C-C-A-4) also decreased the risk of knee OA (OR, 0.46; 95% CI, 0.22–0.94, $p = 0.021$) as did haplotype 1-2-1-1/all (C-T-G-4/all) (OR, 0.30; 95% CI, 0.10–0.81; $p = 0.008$).

One study investigated the associations between IL-1 polymorphisms and patient-reported outcome measurements (PROM), laboratory results, and radiological findings. They evaluated the IL-1RN VNTR (SNP rs419598), IL-1A +4845, and IL-1B +3953 polymorphisms using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) which consists of pain, stiffness, and physical

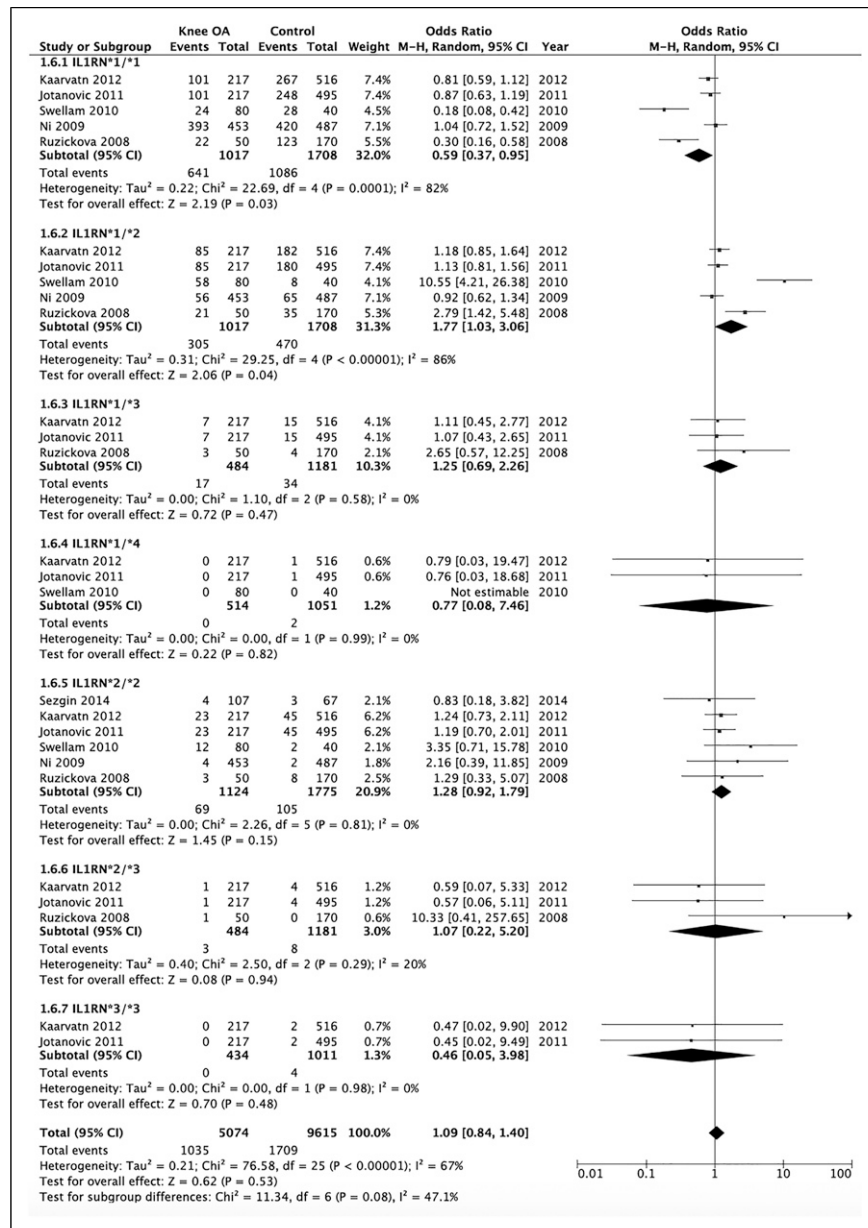


Figure 3. Forest plot of IL1RN VNTR genotype.

function subscales (Table 3). They also compared these polymorphisms with erythrocyte sedimentation rates (ESR) and C-reactive protein (CRP) (Table 3) and radiological OA grades (ROA) on the Kellgren-Lawrence scale (KL) of 1–4 (Table 4). They did not find any associations between IL-1RN, IL-1A, and IL-1B gene polymorphisms and PROM, laboratory results, and radiological findings of knee OA. However, these findings contradicted others showing that the frequency of the IL-1RN*2 allele and IL-1RN*1/*2 and IL-1RN*2/*2 SNP rs419598 genotypes between KL grades 1–2 and 3–4, was higher in more severe knee ROA. They also found differences in the visual analog scale (VAS) that

measures the quality of perceived pain (Table 5). The frequency of IL-1RN*2 allele was lower among patients with mild pain than those with moderate or severe pain. The IL-1RN*1/*1 and IL-1RN*1/*2 genotypes negatively and positively correlated, respectively, with pain.

Discussion

We found that IL-1RN*2 allele and IL-1RN*1/*2 genotype rs419598 increased the risk of knee OA, whereas the IL-1RN*1/*1 allele decreased the risk of knee OA. Furthermore, IL-1RN VNTR was correlated with knee OA in Caucasians.

We were unable to analyze this correlation in Asians because only one study has evaluated this in Asian population. Since only a handful of studies have compared IL-1 gene polymorphisms between knees with OA and healthy knees, only the IL-1RN VNTR could be assessed in a meta-analysis.

Genetic factors are among the many causes of OA, including that of the knee. Although several studies and meta-analyses have assessed various sites of OA, the results have remained inconclusive.^{17–21} The conflicting results among studies were probably due to factors other than genetics, such as the environment, age, gender, ethnicity, and BMI. Combinations of factors and the contributions of individual factors that influence knee OA remain unknown.^{22–24} In

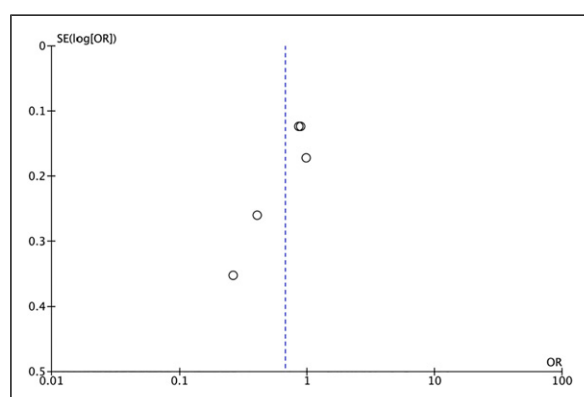


Figure 4. Funnel plot IL1RN*1 allele shows asymmetric funnel plot in IL1RN*1.

addition, the sites of knee OA, whether medial or lateral, affect the risk for severity or progression.^{25,26}

Cytokines play key roles in the pathogenesis of synovitis and cartilage destruction in OA.²⁷ Various differentially expressed cytokines due to polymorphisms in the genes encoding cytokines such as IL-1 also play important roles in cartilage and bone destruction in OA. Interleukin-1 α , IL-1 β , and their naturally occurring antagonist (IL-1RA) are encoded by genes located within the 430-kb region, known as the IL-1 gene family. The IL-1A, IL-1B, and IL-1RN genes produce IL-1 α , IL-1 β , and IL-1Ra, respectively. Interleukin-1Ra counteracts the IL-1 action by binding to the IL-1 receptor without activating it.²⁸

The results of the correlations between IL-1RN VNTR and ROA were inconsistent. They did not significantly differ based on KL grading, but did so when evaluated with dichotomous data; the frequency of IL-1RN VNTR was lower for severe knee OA. Wu et al.²⁹ also found that IL-1RN rs380092 and rs315952 decreased the risk of knee OA, while other specific IL-1RN and IL-1R1 increased the risk of knee OA. Attur et al.³⁰ also found that the IL-1RN SNP rs419598, rs9005, and the haplotype rs419598/rs315952/rs9005 function as protective factors in knee OA. The differences in the results of these studies were probably due to the OA grading on the medial or lateral compartment as revealed by Hunter et al.,³¹ who found that OA in the lateral and medial compartments differs based on risk factors for disease severity and progression. Attur et al.⁸ compared the lateral and medial compartment OA and found a difference in plasma levels of IL-1Ra.

Table 3. Correlation between IL-1 gene polymorphisms and PROM and laboratory findings in knee OA.

Study	Year	Gene	Genotypes	PROM			Laboratory	
				WPS (mean $\pm$ SD)	WSS (mean $\pm$ SD)	WPFS (mean $\pm$ SD)	ESR (mm/h) (mean $\pm$ SEM)	CRP (mg/L) (mean $\pm$ SEM)
Melek Sezgin et al. ³¹	2010	IL-1RN VNTR rs419598	4/4	14.4 $\pm$ 3.5	5.0 $\pm$ 2.1	46.1 $\pm$ 12.8	23.4 $\pm$ 2.2	3.5 $\pm$ 0.4
			4/2	13.5 $\pm$ 4.6	4.5 $\pm$ 2.8	45.3 $\pm$ 15.2	21.6 $\pm$ 4.7	2.9 $\pm$ 0.4
			2/2	13.0 $\pm$ 3.5	4.5 $\pm$ 2.6	55.0 $\pm$ 14.8	13.2 $\pm$ 5.1	1.5 $\pm$ 0.3
			5/4	15.4 $\pm$ 2.6	5.0 $\pm$ 1.7	57.7 $\pm$ 21.5	31.1 $\pm$ 3.3	4.3 $\pm$ 1.5
			5/2	12.0	5.0	52	6.0	0.5
			4/3	16.0	4.0	53	6.2	3.4
			5/3	12.0	3.0	39	5.0	1.2
			p	0.802	0.917	0.373	0.207	0.544
		IL-1A (+4845)	CC	13.9 $\pm$ 3.8	4.6 $\pm$ 0.3	44.4 $\pm$ 14.0	23.2 $\pm$ 2.3	3.1 $\pm$ 0.3
			CT	14.0 $\pm$ 3.2	4.9 $\pm$ 0.2	48.7 $\pm$ 13.1	23.3 $\pm$ 3.0	3.1 $\pm$ 0.4
			TT	16.6 $\pm$ 1.9	5.3 $\pm$ 0.8	53.8 $\pm$ 14.0	26.8 $\pm$ 8.4	7.2 $\pm$ 3.8
			p	0.198	0.683	0.132	0.907	0.519
		IL-1B (+3953)	CC	13.7 $\pm$ 0.4	4.8 $\pm$ 2.2	46.3 $\pm$ 1.5	25.0 $\pm$ 2.3	3.4 $\pm$ 0.4
			CT	14.8 $\pm$ 0.6	4.9 $\pm$ 2.1	48.5 $\pm$ 2.8	19.4 $\pm$ 3.0	2.4 $\pm$ 0.3
			TT	16.5 $\pm$ 1.3	5.1 $\pm$ 3.0	48.2 $\pm$ 6.3	24.1 $\pm$ 8.2	6.7 $\pm$ 3.2
			p	0.085	0.988	0.743	0.384	0.147

WPS = WOMAC pain subscale; WPFS = WOMAC physical function subscale; WSS = WOMAC stiffness subscale.

This systematic review showed that IL-1B polymorphisms were not associated with knee OA in Asian and Caucasian populations. These findings differed from those of Kanoh et al.,²⁰ who evaluated 303 normal knees and 56 ROAs. They found that the rate of ROA was significantly higher for the T/T, than the C/C or CT genotypes. Others have also associated IL-1B SNP with knee OA.^{18,21} Barakat et al. found that the same concentrations of IL-1B in different compartments of the same knee result in different region of cartilage damage.³² Knee joint chondrocytes are more sensitive to stimulation with IL-1B than other joints,³³ but the present systematic review did not found an association between IL-1B polymorphisms and knee OA.

Whether IL-1B polymorphisms are associated with knee OA remains inconclusive.

Moxley et al. found no association between IL-1A SNP, IL-1B SNP, IL-1RN, and knee OA. Evaluations of these three genes using extended haplotypes found no association between genetic variations in the IL-1 region and knee OA.¹⁷ In contrast, others have found that an extended IL-1 region haplotype is associated with knee OA.^{34,35}

This meta-analysis has some limitations. Firstly, the IL-1RN VNTR polymorphisms studies were heterogeneous, although subgroup analysis did not identify any potential sources. This might have resulted in misunderstanding the meta-analysis results. Secondly, the total sample size of the

Table 4. Correlation between IL-1 gene polymorphism and ROA grading in knee OA.

Study	Year	Gene	Genotypes	KL grading				p value
				1 (n, %)	2 (n, %)	3 (n, %)	4 (n, %)	
Melek Sezgin et al. ³¹	2010	IL-1RN VNTR rs419598	4/4	19 (25.7)	26 (35.1)	24 (32.4)	5 (6.8)	0.565
			4/2	3 (15.8)	12 (63.2)	4 (21.1)	0 (0.0)	
			2/2	1 (25.0)	2 (50.0)	0 (0.0)	1 (25.0)	
			5/4	1 (14.3)	2 (28.6)	3 (42.9)	1 (14.3)	
			5/2	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	
			4/3	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	
			5/3	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	
		IL-1A (+4845)	CC	12 (22.6)	23 (43.4)	15 (28.3)	3 (5.7)	0.871
			CT	10 (21.3)	17 (36.2)	17 (36.2)	3 (6.4)	
			TT	1 (16.7)	3 (50.0)	1 (16.7)	1 (16.7)	
		IL-1B (+3953)	CC	13 (19.1)	31 (45.6)	21 (30.9)	3 (4.4)	0.306
			CT	9 (28.1)	8 (25.0)	11 (34.4)	4 (12.5)	
			TT	2 (28.6)	4 (57.1)	1 (14.3)	0 (0.0)	

Table 5. Correlations between IL-1 gene polymorphisms and VAS and ROA grades of knee OA.

Study	Year	Gene	Type	Visual analog scale (VAS) (%)			p value	KL grading		p value
				Mild (N = 18)	Moderate (N = 32)	Severe (N = 30)		KL 1-2 (N = 34)	KL 3-4 (N = 46)	
Menha Swellam et al. ³³	2010	IL-1RN rs419598	Allele							
			1	16 (88.9)	28 (87.5)	30 (100)	0.141	32 (94.1)	42 (91.3)	0.637
			2	2 (11.1)	26 (81.3)	30 (100)	0.0001	19 (55.9)	39 (84.8)	0.004
			Carriage							
			1	16 (88.9)	28 (87.5)	30 (100)	0.141	32 (94.1)	42 (91.3)	0.637
			2	2 (11.1)	26 (81.3)	30 (100)	0.0001	19 (55.9)	39 (84.8)	0.004
			Genotype							
			*1/*1							
			-ve	4 (22.2)	22 (68.8)	30 (100)	0.0001	20 (58.8)	36 (78.3)	0.061
			+ve	14 (77.8)	10 (31.3)			14 (41.2)	10 (21.2)	
			*1/*2							
			-ve	16 (88.9)	6 (18.8)		0.0001	15 (44.1)	7 (15.2)	0.003
			+ve	2 (11.1)	26 (81.3)	30 (100)		19 (55.9)	39 (84.8)	
			*2/*2							
			-ve	18 (100)	28 (87.5)	22 (73.3)	0.038	14 (41.2)	8 (17.4)	0.004
			+ve		4 (12.5)	8 (26.7)		20 (58.8)	38 (82.6)	

eligible studies was insufficient to reach a convincing conclusion. Thirdly, all the samples in this study were taken from peripheral blood which can result in bias. As we know, some SNP of IL-1 β also correlates with heart disease or outcome of other disease. Lastly, our conclusion of the meta-analysis was based on unadjusted estimations. Many factors influence OA, including gender, ethnicity, BMI, lifestyle, and hormones. Since complete data were unavailable, we could not conduct meta-regression analyses, despite the studies included in the analysis being of good qualities.

Conclusion

We concluded that several IL-1RN alleles and genotypes play a role in its severity, but other genetic variations in the IL-1 region were still conflicting in its association with knee OA. Further study is needed to evaluate the association between genetic variations in the IL-1 region and knee OA especially across different ethnicities.

Declaration of conflicting interests

NCB reports personal fees, non-financial support and other from DePuy Synthes, other from Zimmer Biomet, other from Gruppo Bioimpianti, outside the submitted work; and Editorial board/Reviewer: VJSM, CORR, J of Arthroplasty, AJSM, JOS, KSSTA, JISAKOS, BJJ, BJO, Knee Journal, OJSM, JIMR, JSHS, KSRR, CIOs, ANZ Journal of Surgery, JOINTS, Arthroplasty, Arthropeadia, Hip & Knee Journal. The rest of the authors declare no conflict of interest.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Registration

This study was registered in OSF with DOI 10.17605/OSF.IO/W2CY3.

Data availability statement

The data that supports the findings of this study are available within the article [and its supplementary material]

ORCID iD

Nicolaas C. Budhiparama  <https://orcid.org/0000-0002-0801-7400>

Supplemental Material

Supplemental material for this article is available online.

References

1. Kapoor M, Martel-Pelletier J, Lajeunesse D, et al. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol* 2011; 7(1): 33–42.
2. Ajrawat P, Dwyer T and Chahal J. Autologous interleukin 1 receptor antagonist blood-derived products for knee osteoarthritis: A systematic review. *Arthrosc-J Arthrosc Relat Surg* 2019; 35(7): 2211–2221.
3. Martel-Pelletier J, Alaaeddine N and Pelletier JP. Cytokines and their role in the pathophysiology of osteoarthritis. *Front Biosci* 1999; 4: D694–D703.
4. Kaneko N, Kurata M, Yamamoto T, et al. The role of interleukin-1 in general pathology. *Inflamm Regen* 2019; 39(1): 1–16.
5. Epstein FH, Dinarello CA and Wolff SM. The role of interleukin-1 in disease. *N Engl J Med* 1993; 328(2): 106–113.
6. Attur M, Wang H-Y, Kraus VB, et al. Radiographic severity of knee osteoarthritis is conditional on interleukin 1 receptor antagonist gene variations. *Ann Rheum Dis* 2010; 69(5): 856–861.
7. Kerkhof HJM, Doherty M, Arden NK, et al. Large-scale meta-analysis of interleukin-1 beta and interleukin-1 receptor antagonist polymorphisms on risk of radiographic hip and knee osteoarthritis and severity of knee osteoarthritis. *Osteoarthritis Cartil* 2011; 19(3): 265–271.
8. Attur M, Statnikov A, Samuels J, et al. Plasma levels of interleukin-1 receptor antagonist (IL1Ra) predict radiographic progression of symptomatic knee osteoarthritis. *Osteoarthritis Cartil* 2015; 23(11): 1915–1924.
9. Arend WP. Interleukin-1 receptor antagonist. *Immunologist* 1998; 5(6): 197–201.
10. Palmer G, Guerne PA, Mezin F, et al. Production of interleukin-1 receptor antagonist by human articular chondrocytes. *Arthritis Res* 2002; 4(3): 226–231.
11. Sellam J and Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. *Nat Rev Rheumatol* 2010; 6(11): 625–635.
12. Abd-Allah SH, Shalaby SM, Pasha HF, et al. Variation of matrix metalloproteinase 1 and 3 haplotypes and their serum levels in patients with rheumatoid arthritis and osteoarthritis. *Genet Test Mol Biomarkers* 2012; 16(1): 15–20.
13. Ye S, Patodi N, Walker-Bone K, et al. Variation in the matrix metalloproteinase-3, -7, -12 and -13 genes is associated with functional status in rheumatoid arthritis. *Int J Immunogenet* 2007; 34(2): 81–85.
14. Matthey DL, Nixon NB, Dawes PT, et al. Association of matrix metalloproteinase 3 promoter genotype with disease outcome in rheumatoid arthritis. *Genes Immun* 2004; 5(2): 147–149.
15. Honsawek S, Malila S, Yuktanandana P, et al. Association of MMP-3 (-1612 5A/6A) polymorphism with knee osteoarthritis in Thai population. *Rheumatol Int* 2013; 33(2): 435–439.
16. Meulenbelt I, Seymour AB, Nieuwland M, et al. Association of the interleukin-1 gene cluster with radiographic signs of osteoarthritis of the hip. *Arthritis Rheum* 2004; 50(4): 1179–1186.
17. Moxley G, Meulenbelt I, Chapman K, et al. Interleukin-1 region meta-analysis with osteoarthritis phenotypes. *Osteoarthritis Cartil* 2010; 18(2): 200–207.

18. Moos V, Rudwaleit M, Herzog V, et al. Association of genotypes affecting the expression of interleukin-1/ β or interleukin-1 receptor antagonist with osteoarthritis. *Arthritis Rheum* 2000; 43(11): 2417–2422.
19. Meulenbelt I, Bos SD, Kloppenburg M, et al. Interleukin-1 gene cluster variants with innate cytokine production profiles and osteoarthritis in subjects from the genetics, osteoarthritis and progression study. *Arthritis Rheum* 2010; 62(4): 1119–1126.
20. Kanoh T, Hasegawa Y, Masui T, et al. Interleukin-1 β gene polymorphism associated with radiographic signs of osteoarthritis of the knee. *J Orthop Sci* 2008; 13(2): 97–100.
21. Cai H, Sun H-J, Wang Y-H, et al. Relationships of common polymorphisms in IL-6, IL-1A, and IL-1B genes with susceptibility to osteoarthritis: a meta-analysis. *Clin Rheumatol* 2015; 34(8): 1443–1453.
22. Magnusson K, Turkiewicz A and Englund M. Nature vs nurture in knee osteoarthritis – the importance of age, sex and body mass index. *Osteoarthr Cartil* 2019; 27(4): 586–592.
23. Manek NJ, Hart D, Spector TD, et al. The association of body mass index and osteoarthritis of the knee joint: An examination of genetic and environmental influences. *Arthritis Rheum* 2003; 48(4): 1024–1029.
24. Muthuri SG, Doherty S, Zhang W, et al. Gene-environment interaction between body mass index and transforming growth factor beta 1 (TGF β 1) gene in knee and hip osteoarthritis. *Arthritis Res Ther* 2013; 15(2): 1–8.
25. Valdes AM, Hart DJ, Jones KA, et al. Association study of candidate genes for the prevalence and progression of knee osteoarthritis. *Arthritis Rheum* 2004; 50(8): 2497–2507.
26. Valdes AM, Van Oene M, Hart DJ, et al. Reproducible genetic associations between candidate genes and clinical knee osteoarthritis in men and women. *Arthritis Rheum* 2006; 54(2): 533–539.
27. Goldring SR and Goldring MB. The role of cytokines in cartilage matrix degeneration in osteoarthritis. *Clin Orthop Relat Res* 2004; 427(Suppl): S27–S36.
28. Arend WP and Gabay C. Physiologic role of interleukin-1 receptor antagonist. *Arthritis Res* 2000; 2(4): 245–248.
29. Wu X, Kondragunta V, Kornman KS, et al. IL-1 receptor antagonist gene as a predictive biomarker of progression of knee osteoarthritis in a population cohort. *Osteoarthr Cartil* 2013; 21(7): 930–938.
30. Attur M, Zhou H, Samuels J, et al. Interleukin 1 receptor antagonist (IL1RN) gene variants predict radiographic severity of knee osteoarthritis and risk of incident disease. *Ann Rheum Dis* 2020; 79(3): 400–407.
31. Hunter DJ, Niu J, Felson DT, et al. Knee alignment does not predict incident osteoarthritis: The Framingham osteoarthritis study. *Arthritis Rheum* 2007; 56(4): 1212–1218.
32. Barakat AF, Elson CJ and Westacott CI. Susceptibility to physiological concentrations of IL-1 β varies in cartilage at different anatomical locations on human osteoarthritic knee joints. *Osteoarthr Cartil* 2002; 10(4): 264–269.
33. Cole AA and Kuettner KE. Molecular basis for differences between human joints. *Cell Mol Life Sci* 2002; 59(1): 19–26.
34. Smith AJP, Elson CJ, Perry MJ, et al. Accuracy of haplotype association studies is enhanced by increasing number of polymorphic loci examined: Comment on the article by Meulenbelt et al. *Arthritis Rheum* 2005; 52(2): 675.
35. Meulenbelt I, Slagboom PE and van Duijn CM. Reply to editor: accuracy of haplotype association studies is enhanced by increasing number of polymorphic loci examined: comment on the article by Meulenbelt et al. *Arthritis Rheum* 2005; 52(2): 675–676.