

Osteoarthritis and Cartilage



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

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SUMMARY

Objective: To clarify the role of common genetic variation in the Interleukin-1 β (*IL1B*) and Interleukin-1R antagonist (*IL1RN*) genes on risk of knee and hip osteoarthritis (OA) and severity of knee OA by means of large-scale meta-analyses.

Methods: We searched PubMed for articles assessing the role of *IL1B* and *IL1RN* polymorphisms/haplotypes on the risk of hip and/or knee OA. Novel data were included from eight unpublished studies. Meta-analyses were performed using fixed- and random-effects models with a total of 3595 hip OA and 5013 knee OA cases, and 6559 and 9132 controls respectively. The role of *IL1RN* haplotypes on radiographic severity of knee OA was tested in 1918 cases with Kellgren–Lawrence (K/L) 1 or 2 compared to 199 cases with K/L 3 or 4.

Results: The meta-analysis of six published studies retrieved from the literature search and eight unpublished studies showed no evidence of association between common genetic variation in the *IL1B* or *IL1RN* genes and risk of hip OA or knee OA ($P > 0.05$ for rs16944, rs1143634, rs419598 and haplotype C-G-C (rs1143634, rs16944 and rs419598) previously implicated in risk of hip OA). The C-T-A haplotype formed by rs419598, rs315952 and rs9005, previously implicated in radiographic severity of knee OA, was associated with reduced severity of knee OA (odds ratio (OR) = 0.71 95%CI 0.56–0.91; $P = 0.006$,

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$I^2 = 74\%$), and achieved borderline statistical significance in a random-effects model (OR = 0.61 95%CI 0.35–1.06 $P = 0.08$).

Conclusion: Common genetic variation in the Interleukin-1 region is not associated with prevalence of hip or knee OA but our data suggest that *IL1RN* might have a role in severity of knee OA.

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Introduction

Osteoarthritis (OA) is a multifactorial disease of the musculo-skeletal system primarily involving the joints of the knee, hip, hand and spine. The prevalence of OA increases with age and is estimated to affect 40% of people over the age of 70 years¹. There is a large body of evidence that synovial inflammation is implicated in many of the signs and symptoms of OA, including joint swelling and effusion². This synovitis is cytokine-driven and there is convincing evidence that chondrocytes contribute to cytokine production leading to cartilage matrix degradation and in fact a number of variants in genes encoding for cytokines, in particular Interleukin-1 (*IL-1*), *IL-6* and *IL-10* involved in inflammation, have been reported to be associated with risk of OA as shown in a recent review^{3,4}. Chondrocytes are known to respond to IL-1 beta and alpha (*IL1B*, *IL1A*) by decreasing synthesis of matrix components and increasing synthesis of matrix metalloproteinases³. The IL-1 receptor antagonist (*IL1RN* gene) could antagonise the effects of both *IL1A* and *IL1B*. In addition, it was recently shown that carriers of the IL1RN C-T-A haplotype had significantly lower synovial fluid levels of IL-10 and trends towards lower levels of IL-6 and IL1B⁵. It is therefore expected that carriers of this haplotype are able to antagonise the effects of IL-1 and therefore reduce the risk of OA.

Several studies have investigated the role of polymorphisms in the *IL-1* gene on knee and hip OA, in particular *IL1B* C + 3954T (rs1143634), *IL1B* A-511G (rs16944) and the *IL1RN* 86 bp intron two variable number tandem repeat (VNTR) (tagged by rs419598), but results are conflicting^{6–15}. One haplotype, C-G-C (rs1143634, rs16944 and rs419598), was associated with an increased risk of hip OA in two studies (in total 144 cases and 1501 controls)^{10,14}. However, this could not be replicated by another study (370 cases, 544 controls)⁶. Recently, a small meta-analysis ($n = 1238$ hip, knee and hand OA cases and 1260 controls) has been published on the *IL-1* region and OA, but remained inconclusive¹⁶. In that meta-analysis, some studies ($n = 4$) with data available on allele frequencies of single nucleotide polymorphisms (SNPs) rs16944, rs419598 or rs1143634 (or SNPs/VNTR in linkage disequilibrium (LD) with these three SNPs) and knee and/or hip OA data were not included in the final analysis.

In 2009, Attur and colleagues explored the role of *IL1RN* variants on radiographic severity⁵. It was shown in two studies (n total = 130) that carriers of the C-T-A haplotype (rs419598/rs315952/rs9005) had a significantly decreased risk for severe knee OA (odds ratio (OR) 0.14, 95%CI 0.05–0.37, $P < 0.0001$ for the haplotype analysis). The CC/CT genotype at rs419598, was also reported in the same study to be significantly associated with radiographic severity (OR 0.22 95%CI 0.10–0.49).

Our scope was to clarify the role of rs1143634, rs16944 and rs419598 *IL1B* and *IL1RN* polymorphisms on risk of knee and hip OA. To do so, we have carried out a large meta-analysis of both published data ($n = 6$) and unpublished new studies ($n = 8$), comprising a total 3595 hip OA cases and 6559 controls and 5013 knee OA cases and 9132 controls. Because one of these variants has also been implicated in severity of knee OA, a meta-analysis on severity of knee OA with rs419598 was also carried out in eight new studies plus the original report. To detect association between severity of knee OA and the C-T-A haplotype, three studies and the original report were meta-analysed.

Subjects and methods

Study subjects

Unpublished studies with novel data

A full detailed description of each study cohort on recruitment, radiographic and clinical assessment is presented in the **Supplementary methods** section. In this meta-analysis, five studies are available with data on common genetic variation in the IL-1 region for hip OA and eight studies for knee OA. The baseline characteristics and sample size of these studies are shown in **Table 1a**. In total seven cohort studies originating from three countries were included. We included studies from the United Kingdom (UK): the Chingford Study (CS)^{17,18}, TwinsUK¹⁹ and the Hertfordshire Cohort Study (HCS)²⁰, the Netherlands: Rotterdam Study I and III (RSI, RSIII)²¹ and the Genetics osteoArthritis and Progression Study (GARP Study)²² and Estonia: Estonia Cohort Study (ECS)²³. Also, one case-control study from Nottingham (NCCS) (UK) is included²⁴. All studies were approved by the relevant Ethics Committee and informed consent was obtained from all study participants (see **Supplementary methods** section). In addition, severity of knee OA was studied in seven of these studies and in one additional study (CS, GARP, HCS, NCCS, RSI, RSIII, TwinsUK and GOAL).

Published studies

We searched PubMed for relevant articles assessing the relationship between genetic variation in the *IL-1* region and knee and hip OA. In **Table 1b** the baseline characteristics and sample size of six studies identified by our search are given. Since not all studies published allele and/or haplotype counts we contacted the authors if necessary to obtain haplotype and allele counts to perform a meta-analysis with a minimum amount of bias. We were not able to retrieve allele counts for the controls of one Japanese Study⁷ and for the London samples published by Smith *et al.* excluding participants from the CS¹⁵. Therefore, these samples were not included in the meta-analysis. In addition, in the study of Meulenbelt *et al.* a subset of the RSI was used¹⁰. For this study we have now included the complete RSI and therefore results of Meulenbelt *et al.* are not shown separately.

Meta-analysis

For the meta-analysis we were able to include 14 studies on knee OA for one or more variants and eight studies on hip OA with a total number of up to 3595 hip OA cases and 6559 controls and 5013 knee OA cases and 9132 controls. In addition, one study ($n = 130$ knee radiographic osteoarthritis (ROA) cases from two cohorts) published data on radiographic severity of knee OA and common genetic variation in the IL-1 region⁵. We included this study in the meta-analysis of severity of knee OA. One study with already published data on the relationship between knee and hip OA and common genetic variation in the IL-1 region, provided also unpublished data on severity of knee and hip OA (GOAL Study)⁸ and was therefore also included in the meta-analysis on severity of knee OA.

Laboratory methods

GARP study

The genotypes of rs1143634, rs16944 and rs419598 were determined by mass spectrometry (homogeneous Mass ARRAY

Table 1a
Baseline characteristics of unpublished studies assessing the relationship between common genetic variation in the II-1 region and risk of hip and knee OA

Study		Chingford study	Estonia cohort	GARP study	Hertfordshire cohort study	Nottingham case-control study	Rotterdam study I	Rotterdam study III	TwinsUK	Total
Study characteristics	<i>Type of study</i>	Cohort	Cohort	Cohort	Cohort	Case-control	Cohort	Cohort	Cohort	
	<i>Origin</i>	UK	Estonia	Netherlands	UK	UK	Netherlands	Netherlands	UK	
Controls	<i>Definition</i>	No ROA	No ROA	–	No ROA	No ROA & no symptoms	No ROA	No ROA	No ROA	6836/4920
	<i>Number*</i>	547/671	430	–†	772	750	2115/2777	1514	708/722	
	<i>Age mean (range)</i>	63.6 (54–76)‡	46.5 (32–59)	–	64.9 (59–71)	66.4 (43–93)	66.1 (55–89)	55.8 (46–89)	52.0 (32–70)	
	<i>BMI mean (range)</i>	24.8 (17–42)‡	27.7 (15–45)	–	26.6 (17–45)	26.6 (17–42)	25.7 (16–60)	27.5 (14–57)	24.3 (16–37)	
	<i>% women</i>	100%	70%	–	51%	56%	54%	56%	100%	
Hip OA cases	<i>Definition</i>	ROA	–	COA/ROA	–	THR	ROA	–	ROA	1884
	<i>Number</i>	95	–	81	–	1126	512	–	70	
	<i>Age mean (range)</i>	66.1 (55–76)	–	63 (62–65)	–	68.5 (40–90)	68.2 (55–93)	–	56.6 (41–79)	
	<i>BMI mean (range)</i>	24.9 (19–37)	–	26.5 (26–27)	–	27.7 (15–50)	26.5 (18–43)	–	25.3 (16–40)	
	<i>% women</i>	100%	–	75%	–	63%	59%	–	100%	
Knee OA cases	<i>Definition</i>	ROA	ROA	COA/ROA	ROA	ROA + 80% TKR	ROA	ROA	ROA	2882
	<i>Number</i>	264	65	115	143	1174	866	151	104	
	<i>Age mean (range)</i>	65.9 (55–76)	51.0 (36–60)	61.6 (60–63)	65.2 (59–71)	69.3 (40–96)	70.3 (55–94)	58.0 (47–81)	58.9 (41–79)	
	<i>BMI mean (range)</i>	27.3 (19–45)	30.6 (21–47)	28.0 (27–29)	29.4 (21–48)	29.9 (16–51)	27.7 (18–50)	29.9 (19–48)	27.5 (21–52)	
	<i>% women</i>	100%	66%	82%	42%	56%	73%	57%	100%	

ROA = radiographic osteoarthritis; COA = clinical osteoarthritis; THR = total hip replacement; TKR = total knee replacement.

* Knee OA controls and hip OA controls respectively if both phenotypes are present in one study.

† Controls of the RSI are used as controls for the GARP Study.

‡ Average for hip and knee controls.

Table 1b
Baseline characteristics of published studies assessing the relationship between common genetic variation in the II-1 region and risk of hip and knee OA

Study		Bristol Study	Chinese Study	Czech Study	GOAL	Oxford Study	Turkish Study	Total
Study characteristics	<i>Reference</i>	Smith <i>et al.</i> ^{13,14}	Ni <i>et al.</i> ¹⁰	Ruzickova <i>et al.</i> ¹¹	Limer <i>et al.</i> ⁷	Loughlin <i>et al.</i> ^{5,8}	Sezgin <i>et al.</i> ¹²	
	<i>Type of study</i>	Case-control	Case-control	Case-control	Case-control	Case-control	Case-control	
	<i>Origin</i>	UK	China	Czech Republic	UK	UK	Turkey	
	<i>Age mean (range)</i>	62*	58	54.1†	66.5 (45–86)	73 (56–90)	61.3 (41–83)	
	<i>BMI mean (range)</i>	–	–	–	29.3 (17–58)	–	29.9 (21–44)	
	<i>% women</i>	52%	68%	68%‡	49%	61%	75%	
Controls	<i>Definition</i>	Unrelated healthy blood donors	Healthy controls§	Healthy individuals	No ROA & no symptoms	Unaffected spouses	No OA according to ACR criteria	2296/1639
	<i>Number </i>	195	487	170	820	557	67	
Hip OA cases	<i>Definition</i>	THR	–	–	Croft score ≥3	THR	–	1711
	<i>Number</i>	29	–	–	1299	383	–	
Knee OA cases	<i>Definition</i>	COA/ROA	COA/ROA	COA/ROA	COA/ROA	TKR	ACR criteria	2131
	<i>Number</i>	141	453	50	1247	133	107	

* Mean age in cases.

† Median age in cases.

‡ Percentage women in cases.

§ Healthy controls from the Center at Physical Examination.

|| Knee OA controls and hip OA controls respectively if both phenotypes are present in one study; ROA = radiographic osteoarthritis; COA = clinical osteoarthritis; THR = total hip replacement; TKR = total knee replacement.

system; Sequenom Inc., San Diego, CA), using standard conditions. Genotypes were analysed by using Genotyper 3.0 software (Sequenom Inc.). Control subjects of the RSI were used as controls for the GARP study.

RSI and III

Genotypes were subtracted from the genome-wide association (GWAS) dataset of the RSI and III. Genotyping of the samples with the Illumina HumanHap550v3 Genotyping BeadChip was carried out at the Genetic Laboratory of the Department of Internal Medicine of Erasmus Medical Center, Rotterdam, the Netherlands. The BeadStudio GenCall algorithm was used for genotype calling and quality control procedures were as described previously^{25,26}. Missing genotypes for RSI and III were imputed as described previously²⁷. Subsequently, genotypes of rs1143634, rs16944, rs419598, rs315952 and rs9005 were subtracted using PLINK software V1.07²⁸. All five polymorphisms were in HWE in controls in both studies ($P > 0.05$, data not shown).

TwinsUK Study

Genotypes were subtracted from the GWAS dataset of the TwinsUK study²⁷ using the same methods as for RSI and RSIII. All polymorphisms were in HWE in controls ($P > 0.05$, data not shown).

Other studies

For the NCCS, HCS, CS and ECS study participants, genomic DNA was extracted from peripheral blood leukocytes of affected individuals and controls using standard protocols. Genotyping was carried out by Kbioscience Ltd, Hertfordshire UK. The IL-1 SNPs were genotyped using the KASPar chemistry, which is a competitive allele-specific PCR SNP genotyping system using FRET quencher cassette oligos. Genotyping accuracy, as determined from the genotype concordance between 52 duplicate samples was 99.35% for all three SNPs. All three polymorphisms were in Hardy–Weinberg equilibrium in controls ($P > 0.05$).

Haplotype estimation

In Supplementary Fig. 1 we show the LD plot for *IL-1*. LD is low between the rs16944, rs1143634 and rs419598 (lowest D' = 0.38 and r^2 = 0.02). In addition, in Supplementary Table I we show D' and r^2 values between rs16944, rs1143634 and rs419598 for all studies contributing novel data to this meta-analysis. For all new studies as well as for GOAL we estimated haplotypes on a population level using the program Haploview v 4.1²⁹. In all studies, seven common haplotypes were present for hip OA (rs1143634, rs16944 and rs419598). For the remainder of published studies the haplotype frequencies reported by authors were used and the

reader is referred to the original studies (see Table Ia and Ib and Supplementary Table II).

Statistical analysis

Allele and genotype ORs were calculated by comparing the allele and genotype frequencies between cases and controls. Three SNPs, previously implicated in risk of hip and knee OA, rs16944, rs1143634 and rs419598, were tested for association with knee and hip OA. In addition, the haplotype C–G–C or 1–1–2 which was reported as significantly associated with hip OA in two previous studies (rs1143634, rs16944 and rs419598), was tested for association with hip OA^{10,14}.

To be consistent with the previously published study by Attur *et al.* we classified patients as severe knee OA case if the K/L score of the knee was 3 or 4 and as mild to moderate knee OA with a K/L score of 1 or 2⁵. The studies with data for this type of analysis are CS, GARP, GOAL, HCS, NCCS, RSI, RSIII and TwinsUK, totalling 3297 individuals with K/L 1 or 2, and 2243 with K/L 3 or 4 (Table III). These were combined to 130 individuals with K/L 1 or 2 from the original US study and individuals with K/L 3 or 4. In addition, for TwinsUK, RSI and RSIII were able to estimate the C–T–A haplotype consisting of respectively rs419598, rs315952 and rs9005. A meta-analysis was performed for both the C allele of rs419598 and for the C–T–A haplotype with severity of knee OA. We carried out both fixed-effects and random-effects meta-analyses as follows:

Meta-analyses

We synthesized the effect estimates in each study using fixed- and random-effects models. In fixed-effects calculations it is assumed that the true effect of risk allele is the same value in each study, whereas in random-effects calculations the risk allele effects for the individual studies are assumed to vary around some overall average effect. We assessed the presence of heterogeneity using the Cochran's Q-statistic³⁰. The heterogeneity was quantified by using the I^2 ³¹. In the absence of at least moderate inter-study heterogeneity within samples ($I^2 < 25\%$) we conducted a Mantel–Haenszel meta-analysis of data from the samples to assess the overall evidence of association³². For the random-effects models we used the DerSimonian–Laird method which incorporates the heterogeneity between studies. The overall treatment effect is estimated by a weighted average of the individual effects with weights inversely proportional to the variance of the observed effects. The statistical significance of the DerSimonian–Laird OR was estimated using the Z-statistic (the point estimate to its standard error). If evidence of heterogeneity existed, defined as either $P < 0.10$ for the Q-statistic and/or $I^2 > 25\%$, a random-effects model was applied for the meta-analysis.

Table II

Meta-analyses association results for common genetic variation in the IL-1 region and risk of hip and knee OA

SNP/Haplotype	Phenotype	N cases	N controls	Association results			Heterogeneity statistics				Statistical power Minimal OR for 80% power alpha = 0.05
				OR	95%CI	P-value	I^2	Q	df	P-value (Q)	
rs1143634	Knee OA	4429	8549	1.03*	0.95–1.12	0.43	21%	12.7	10	0.24	1.088
rs16944		4761	8770	1.02	0.96–1.08	0.57	0%	6.4	10	0.78	1.078
rs419598		4900	9195	1.05*	0.97–1.14	0.24	32%	17.5	12	0.13	1.082
rs1143634	Hip OA	3634	7918	0.97	0.90–1.04	0.40	0%	3.7	6	0.72	1.096
rs16944		3605	7725	1.04*	0.95–1.14	0.35	36%	9.4	6	0.16	1.088
rs419598		3619	7897	1.00	0.93–1.08	0.97	0%	5.7	6	0.46	1.093
C–G–C haplotype		3654	8131	1.04*	0.93–1.17	0.52	44%	12.4	7	0.09	1.148

All association results are fixed-effects ORs unless indicated otherwise; OA = osteoarthritis; df = degrees of freedom.

C–G–C haplotype = rs1143634–rs16944–rs419598.

* Random-effects model.

Table III
Genotype and haplotype frequencies for knee severity replication studies

study	Nottingham Case-Control study	HCS	CS	GOAL	GARP Study	RSI	RSIII	TwinsUK
<i>K/L score 1–2</i>								
N	399	310	180	329	161	1283	490	145
rs419598 CC/CT	45.4%	44.8%	57.6%	50.5%	45.3%	46.1%	46.1%	53.1%
C-T-A haplotype	N/A	N/A	N/A	N/A	N/A	24.9%	24.6%	27.9%
<i>K/L score 3–4</i>								
N	981	45	164	796	58	103	40	56
rs419598 CC/CT	48.8%	66.7%	54.5%	50.1%	43.1%	45.6%	37.5%	48.2%
C-T-A haplotype	N/A	N/A	N/A	N/A	N/A	21.3%	19.9%	25.6%

Results for the C-T-A haplotype refer to: rs419598-rs315952-rs9005 C-T-A haplotype; n = number of subjects.
N/A = not applicable.

Statistical power

Statistical power was computed using Quanto 1.2.4 (University of Southern California, USA, <http://hydra.usc.edu/gxe>).

Results

For the statistical power for each meta-analysis, given the frequency of the minor allele and the sample sizes available, it was estimated that we had 80% power to find associations with an OR = 1.09–1.15 (depending on the allele frequency and on the number of studies with data for each SNP) for hip OA and OR = 1.08–1.09 for knee OA with $P < 0.05$ (Table II).

The allele and haplotype frequencies for cases and controls in each study are presented in Supplementary Table IIa and b respectively for unpublished and published studies. The summary results of the hip and knee OA meta-analyses for rs1143634, rs16944 and rs419598 and haplotype C-G-C for hip OA are presented in Table II. No significant associations were observed between rs16944, rs1143634 or rs419598 and hip or knee OA ($P > 0.05$). No association was seen between the C-G-C haplotype and hip OA OR = 1.06 (95%CI 0.90–1.24 $P = 0.52$) (Fig. 1).

The genotype and haplotype frequencies for severe knee OA cases (K/L 3 and 4) and controls (K/L 1 or 2) in each study are presented in Table III. No evidence of association between risk of severe knee and the *ILRN* SNP rs419598 region was observed [Fig. 2(A)]. Specifically, rs419598 had an OR of 1.06 (95%CI 0.93–1.22, $P = 0.78$) for severe knee OA. Very strong heterogeneity ($I^2 = 70%$, Q -statistic $P = 0.002$) was observed for this analysis. Excluding the initial significant report and data from the HCS (which shows a significant association in the opposite direction) no between study heterogeneity remained

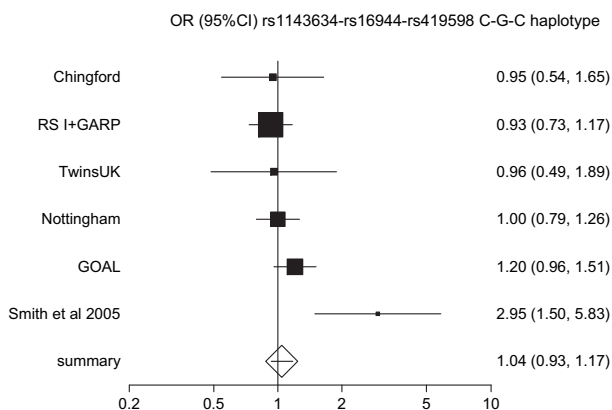


Fig. 1. Study specific estimates and summary association (random-effects) between risk of hip OA and rs1143634-rs16944-rs419598 “C-G-C” haplotype on risk of hip OA.

($I^2 = 0%$) and the effect of this genotype became OR = 1.00 (95%CI 0.87–1.15; $P = 0.97$) indicating no role for this genotype in severity of knee OA. When a fixed-effects meta-analysis were performed for the haplotype reported to be associated with OA radiographic severity [Fig. 2(B)] a trend was observed in the same direction in all three replication studies and combined with the initial report from Attur and co-workers¹⁶ a summary effect of OR = 0.71 (95%CI 0.56–0.91; $P = 0.006$) was observed. Nevertheless, the extremely strong effect reported by the first study introduces significant heterogeneity ($I^2 = 74%$ Q $P = 0.008$) and a random-effects meta-analysis resulted in OR = 0.61 (95%CI 0.35–1.06 $P = 0.08$) [Fig. 2(B)].

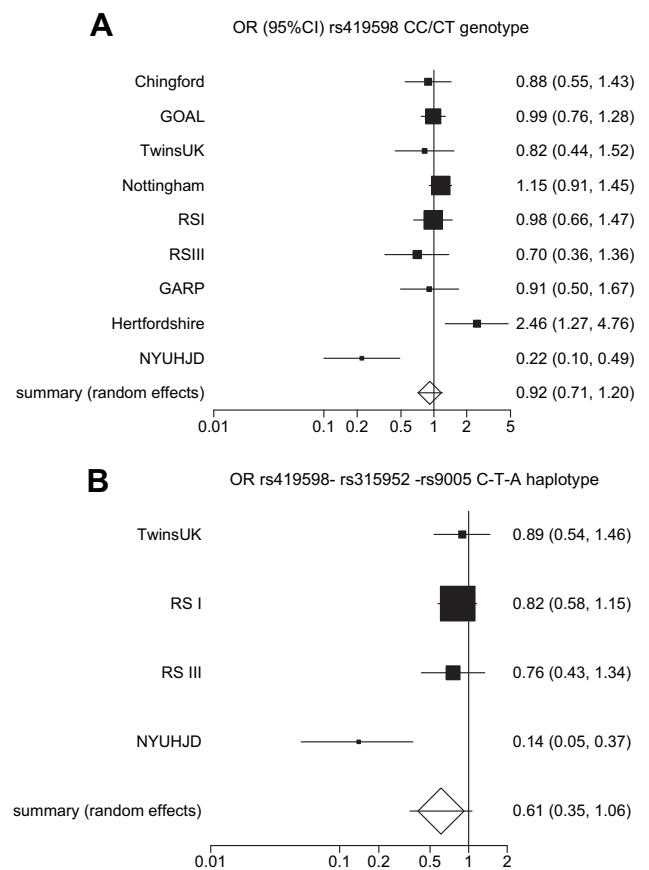


Fig. 2. Study specific estimates and summary association (random-effects) between severity of knee OA defined as K/L 1 or 2 vs K/L 3 or 4 and (A) rs419598 CC/CT genotype, (B) haplotype rs419598, rs315952 and rs9005 “C-T-A”.

Discussion

This meta-analysis on common genetic variation in the *IL-1* region and risk of hip and knee OA is the largest to date, including all available published studies ($n = 6$) and unpublished novel data ($n = 8$), and shows no evidence for a consistent association with knee or hip OA. In this study we had 80% power to detect $OR = 1.09$ – 1.15 for hip OA and $OR = 1.08$ – 1.09 for knee OA with $\alpha = 0.05$. Therefore it is not likely that we have observed false-negative associations with regards to risk. Nevertheless, we find that the *IL1RN* C-T-A haplotype may indeed have a role in severe knee OA which is consistent with the well known *IL1*'s established role as a regulator of cartilage degradation^{3,5}. Since there is a limited sample size of subjects of a non-Caucasian origin, we cannot exclude that there might be evidence of association between the SNPs studied and OA in subjects from a different ethnic origin.

So far, the literature has been inconclusive on the role of *IL-1* polymorphisms and/or haplotypes in risk of knee and hip OA, probably due to low sample sizes of individual studies. An attempt was made by Moxley and colleagues to perform a meta-analysis, but the results remained inconclusive¹⁶. One of the reasons for this could be that they did not include all published studies on genetic variation in the *IL-1* region. More importantly the authors did not add unpublished novel data. This approach resulted in not only low power to detect statistically significant associations, but could potentially also lead to publication bias. There were not enough published studies examining the same genetic variant in relation to OA to study presence of publication bias.

In two previous publications the C-G-C haplotype was associated with an increased risk of hip OA, although this could not be replicated by another larger study⁶. In this meta-analysis, which had 25 times more cases compared to the first two publications, we could not find evidence of an association between this haplotype and hip OA. Therefore we conclude that the previous two observations were false positive^{10,14}. We also have to note that there is low LD between the three SNPs (two SNPs in the *IL1B* gene and one SNP in the *IL1RN* gene) in all Caucasian populations studied and therefore an analysis of haplotypes in Caucasian populations is not appropriate, which is true for this study and all previous publications.

Recently, a small study ($n = 130$ cases) showed that genetic variation in the *IL-1* region was associated with severity of knee OA⁵. We find very strong heterogeneity in the association between the *ILRN* variant rs419598 and knee OA severity and overall there is no significant effect. Yet, when we tested the C-T-A haplotype associated with severe knee OA we found that in all studies it had a lower frequency among severe OA cases than non-severe cases suggesting that it might be truly involved in this phenotype. We observed a borderline significant effect in the random-effects model for the C-T-A haplotype and severe knee OA, but power was limited for this analysis and therefore a larger sample size or functional studies are needed to confirm the role of *ILRN* in severe knee OA.

In conclusion, common genetic variation in the *IL-1* region is not associated with prevalence of hip or knee OA but our data suggest that *IL1RN* might have a role in severity of knee OA.

Author's contributions

Responsible for the integrity of the work as a whole: AM Valdes and HJM Kerkhof.

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Conflict of interest

Dr RA Maciewicz is employed by, owns stock and has patent applications for AstraZeneca.

Dr Abramson and Dr Attur have a patent application in the field of *IL-1* family gene polymorphisms for determining the risk of OA incidence, severity and progression.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2010.12.003.

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