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Radiographic Severity of Knee Osteoarthritis is Conditional on Interleukin-1 Receptor Antagonist Gene Variations

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Abstract

Objective. The lack of biomarkers that identify patients at risk for severe osteoarthritis (OA) complicates development of disease-modifying OA drugs (DMOADs) This study determined whether inflammatory genetic markers could stratify knee OA patients into high and low risk for destructive disease.

Methods. Genotype associations with knee OA severity were assessed in two Caucasian populations. Fifteen SNPs in six inflammatory genes were evaluated for association with radiographic severity and with synovial fluid mediators in a subset of the patients.

Results. Interleukin-1-receptor antagonist (IL1RN) single-nucleotide polymorphisms (rs419598; rs315952; and rs9005) predicted Kellgren-Lawrence scores independently in each population. One IL1RN haplotype was associated with lower odds of radiographic severity (OR 0.16; 95% CI 0.06-0.40), greater joint space width (JSW; p=0.0038), and lower synovial fluid cytokine levels. Carriage of the IL1RN haplotype influenced the age relationship with severity.

Conclusion. IL1RN Polymorphisms reproducibly contribute to disease severity in knee OA and may be useful biomarkers for patient selection in DMOAD trials.

Keywords: osteoarthritis, genetics, inflammation, severity

Introduction

Osteoarthritis (OA) is characterized by progressive loss of joint articular cartilage and subchondral bone remodeling. Although OA is the greatest cause of disability and much of the population is susceptible, some patients remain relatively stable with minimal change in their symptoms over time. Other patients, however, experience progression to severe structural deterioration that often leads to disability and joint replacement. One challenge in both clinical management of OA and development of disease modifying drugs is the lack of imaging or biomarker tools that predict which OA patients are more likely to progress to severe disease. Genetics explain substantial osteoarthritis variance,[1] but genetic associations with knee OA severity or progression have not been replicated.

Inflammatory mediators regulate breakdown of collagen, proteoglycans, and bone that constitute the articular joint tissues and appear to be part of the destructive process in OA. We and others have previously shown that an imbalance in interleukin-1 (IL-1) and IL-1 antagonists contribute to cartilage loss and increased inflammatory mediators in OA.[2]

Variations in several genes for proteins that regulate inflammation, including interleukin-1α (IL-1α), IL-1β, IL-1 receptor antagonist (IL-1Ra), IL-10, TNFα, and estrogen receptor-α (ESR1), have been associated with differential expression of inflammatory mediators,[3-5] and most of these gene variations have been associated with susceptibility to OA in various joints.[6-10] In this study, we therefore evaluated whether polymorphisms in selected inflammatory genes and genes that regulate Inflammation could stratify knee OA patients into high and low risk for radiographic severity in two independent populations.

Patients and Methods

Patient populations. Two independent populations were recruited at New York University Hospital for Joint Diseases (NYUHJD) and from the Prediction of Osteoarthritis Progression (POP) study (Duke University Medical Center). Institutional Review Board approval of protocols and informed consent of patients for this study were obtained. All Caucasian patients in the NYUHJD and POP populations that met clinical symptomatic criteria (American College of Rheumatology) and radiographic criteria for OA (Kellgren-Lawrence (KL) grade>1) of at least one knee and were age $\geq$ 38 years were included. Patients with histories of corticosteroids, bilateral knee replacements, other forms of arthritis, cancer, or other chronic diseases beyond hypertension or hypercholesterolemia were excluded. POP included subjects with knee OA of Kellgren-Lawrence (KL) grade 1-3 in at least one knee and excluded subjects

with bilateral knee KL=4 scores, since the primary goal of the POP study was to evaluate the risk factors for progression and to develop a predictive model. Patient demographics are shown in **Table 1**. Patients underwent standardized fixed-flexion posteroanterior knee radiographs with a positioning frame (SynaFlexer™; Synarc, San Francisco, CA USA). Radiographs were scored for KL grade (0-4), medial and lateral joint space width (JSW) at the midportion of the joint space via electronic calipers in NYUHJD cohort, or minimal joint space width with digital calipers (TESA ISO 9001) in POP cohort.

Table 1

	NYUHJD[1]	POP Study[2]
Number of patients	80	50
Age (Mean ± sd)	65.6 + 9.9	61.2 + 11.9
Gender: % Female	61.3	82
BMI (Mean ± sd)	26.4 + 3.7	31.1 + 6.3
Trauma history	20%	18%
Hand involvement[3]	53%	58%

[1] New York University Hospital for Joint Diseases
[2] Prediction of Osteoarthritis Progression (POP); Duke University Medical Center
[3] By clinical examination

Genotyping. Blood samples (5cc) were collected (pyrogen-free heparinized tubes) for DNA extraction. Fifteen SNPs in six inflammatory response genes, including those for IL-1α, IL-1β, IL-1Ra, TNFα, IL-10, estrogen receptor 1, were genotyped. SNPs genotyped (gene, rs number, frequent nucleotide> less frequent nucleotide, minor allele frequency) were: IL1A(+4845), rs17561, G>T, 30.5%; IL1B(-511), rs16944, C>T, 33.4%; IL1B(-1464), rs1143623, G>C, 32.8%; IL1B(-3737), rs4848306, C>T, 44.7%; IL1B(+3954), rs1143634, C>T, 24.2%; IL1B(+3877), rs1143633, A>G, 39.7%; IL1RN(+2018), rs419598, T>C, 27.3%; IL1RN, rs315952, C>T, 25.8%; IL1 RN, rs9005, G>A, 30.5%; IL10(-1082), rs1800896, A>G, 46.7%; IL10(819), rs1800871, T>C, 17.3%; IL10(-592), rs1800872, A>C, 20.2%; TNFA(-308), rs1800629, A>G, 21.7%; ESR1_PvuII, rs2234693, T>C, 44.9%; ESR1_Xbal, rs9340799, A>G, 33.8%. Genotyping was accomplished (Interleukin Genetics Clinical Laboratory; Waltham, MA, USA; CLIA certified) by polymerase chain reactions (PCR) targeting the sequence surrounding SNPs studied. Multiplexed single base extension (SBE) reactions were performed. Genotypes were analyzed (Beckman Coulter CEQ8800) and final genotypes were scored by laboratory personnel blinded to all patient data.

Synovial Fluid (SF) Analysis: Synovial fluid samples were a required component of participation in the POP study, so synovial fluid samples were available from all subjects in the POP cohort. Fifty POP subjects met the entrance criteria for this study as described above; therefore, the synovial fluid samples represented no selection bias. Fluid samples were aspirated directly (n= 36) or by lavage (n= 14), corrected for dilution by the urea method [11] and analyzed blinded to the clinical information. Cytokines (pg/ml) were quantified by multiplex bead assays (Bio-Plex, Biorad). High sensitivity C-Reactive Protein (CRP) concentrations (mg/L) were measured using the UBI Magiwel Enzyme

Immunoassay (United Biotech Inc., Mountain View, CA, minimum detectable concentration of 0.00035 mg/L, inter-assay variation was ≤7.4%). Cartilage Oligomeric Matrix Protein (COMP) was measured by sandwich ELISA with monoclonal antibodies 17C10 and 16F12 to human COMP (minimum detection 120 ng/ml, intra-assay and inter-assay variation ≤5.8% and 8.7%). IL-1ra was measured using the Quantikine Human IL-1ra Immunoassay from R&D Systems (Minneapolis, MN), with a minimum detectable dose of 6.26 pg/ml.

Statistical Methods: Primary analyses evaluated associations between genotypes and radiographic severity, as measured by KL scores. Patients with KL scores of 1,2 were compared to those with scores of 3,4. To determine if results were potentially due to aberrant KL score distributions, a second analysis was performed comparing KL1 to KL2-4 (results were unchanged). Genotype deviation from Hardy-Weinberg equilibrium was tested (Pearson's chi-square test) in the control sample. Genotype associations with radiographic severity were determined using chi-square statistics or Fisher's Exact test, adjusted for non-genetic risk factors, age, BMI and gender, where appropriate, using multivariate logistic regression analysis. The effect of multiple comparisons was considered in the discovery population (NYUHJD) involving 15 SNPs. The comparisons of joint space width between genotypes were determined using non-parametric Wilcoxon test and a mixed model analysis of variance for correlated data to adjust for two knees in the same subject.

Results

The NYUHJD population was analyzed first. Patients with more severe knee OA (KL 3,4 versus 1,2) were older (p=0.013) but did not differ by gender (p= 0.96) or BMI (p= 0.46). Subsequent analyses were age adjusted.

All SNPs were in Hardy-Weinberg equilibrium and were evaluated for association with radiographic severity. After adjustment for multiple-comparisons, one SNP in the IL-1Ra gene (IL1RN) was significantly associated with decreased risk for severe OA, and two other IL1RN SNPs showed the same protective trend (**Table 2**). IL-10 SNPs, also associated with radiographic severity, were not significant after adjustment for multiple comparisons. We then tested the Duke POP cohort for IL1RN gene variations, based on association with severity in the NYUHJD population. In the POP study, age, gender, or BMI were not significant influences, but two of three IL1RN SNPs were significantly associated with knee OA severity (**Table 2**). All other SNPs tested in the NYUHJD population were subsequently evaluated in the POP patients, and none were significant (data not shown).

Since all significant SNPs were in one gene, we evaluated haplotype effects on severity. Of nine possible haplotypes from three IL1RN SNPs, four had a frequency >1%, and one (rs419598/rs315952/rs9005= CTA) was associated with reduced risk for severity in both populations (**Table 2**).

Table 2: Genotype Association with Radiographic Severity of Knee OA in Two Populations

Gene	rs Number	Genotypes compared	NYUHJD Population n=80[1] Kellgren-Lawrence Score >2 Odds Ratio (CI)	Duke POP Study n=50 Kellgren-Lawrence Score >2 Odds Ratio (CI)
IL1 A (+4845)	rs17561	GG vs. GT/TT	1.26 (0.48-3.28); p=0.63	
IL1 B (-511)	rs16944	CC vs. CT/TT	0.89 (0.32-2.47); p=0.82	
IL1 B (-1464)	rs1143623	GG vs. GC/CC	1.96 (0.75-5.11); p=0.17	
IL1 B (-3737)	rs4848306	CC vs. CT/TT	1.25 (0.45-3.48); p=0.68	
IL1 B (+3954)	rs1143634	CC vs. CT/TT	1.36 (0.53-3.47); p=0.52	
IL1 B (+3877)	rs1143633	GG vs. GA/AA	1.12 (0.43-2.91); p=0.81	
IL1 RN (+2018)	rs419598	TT vs. CT/CC	0.49 (0.175-1.37); p=0.174	**0.031 (0.004-0.27) p=0.0016[3]**
IL1 RN	rs315952	CC/CT vs. TT	0.46 (0.15-1.20); p=0.113	0.32 (0.090- 1.00) p=0.071
IL1 RN	rs9005	GG vs. GA/AA	**0.25 (0.091- 0.680); p=0.0067[2]**	**0.084 (0.02- 0.343) p=0.0006[3]**
IL1RN Haplotype	rs419598/ rs315952/ rs9005	Haplotype C,T,A (1 or 2 copies) vs. no copies	**0.29 (0.09-0.93); p=0.037[3]**	**0.031 (0.004-0.270) p=0.0016[3]**
TNFA (-308)	rs1800629	GG vs. GA/AA	1.37 (0.040-4.70); p=0.62	
IL10 (-1082)	rs1800896	CC vs. CT/TT	3.00 (0.87-10.34); p=0.081	
IL10 (-819)	rs1800871	CC vs. CT/TT	3.32 (1.08-10.28); p=0.037	
IL10 (-592)	rs1800872	CC vs. CA/AA	3.32 (1.08-10.28)[4]; p=0.037	
SR1_PvuII	rs2234693	TT vs. CT/CC	0.57 (0.22-1.49); p=0.25	
ESR1_Xbal	rs9340799	AA vs. AG/GG	0.48 (0.18-1.25); p=0.13	

[1] Number of Caucasian patients with knee osteoarthritis who met inclusion criteria and had complete genotype data

[2] For each single SNP, p-values < 0.027 were considered statistically significant to account for multiple comparisons in the discovery population (NYUHJD) involving 15 SNPs.

[3] IL1RN SNPs of interest from the NYUHJD population were then tested in the Duke POP population, and common haplotypes in the IL1RN gene were tested in both populations. p-values <0.05 were considered statistically significant. All other SNPs tested in the NYUHJD population were subsequently evaluated in the POP patients, and none were significant (data not shown).

[4] IL10(-819) and IL10(-592) alleles were completely concordant in this population

We then combined the two populations for further analyses focused on the IL1RN loci. In the combined data set, age was associated with severity (p=0.0065) but gender and BMI were not. IL1RN SNPs and haplotypes were associated with decreased risk for severe disease by KL grade and JSW (**Table 3**). The first JSW analysis was knee-based and included the smaller JSW for all knees (n=251 knees with complete data; 126 patients from NYUHJD and Duke POP). JSW analyses were adjusted for age, gender and BMI, and the knee-based analysis used a mixed model analysis of variance for inter-correlated data to adjust for two knees in the same subject. Two IL1RN SNPs were significantly associated with greater mean JSW, as was the IL1RN CTA haplotype (mean JSW in patients carrying CTA haplotype =3.99mm±1.77, versus reference haplotypes =3.14mm+1.93; p=0.0008). In addition to the IL1RN genotype and haplotype effects observed for the signal knees, a similar IL1RN CTA haplotype effect was seen in the contralateral knees when analyzed for KL scores of 3-4 (OR= 0.065; 95% CI: 0.0076-0.55; p=0.0024) and JSW (p=0.008).

Table 3: IL1RN Genotype Association with Two Radiographic Parameters of Severity in the Combined Populations

Genotype or haplotype	Frequency of Indicated Genotype or Haplotype[1]	Kellgren-Lawrence Score >2 Odds Ratio (CI)[2] N= 130	*Joint space width (JSW in mm)[3] Mean ± standard deviation*		
			Test genotype	*Reference genotype*	*p-value[4]*
IL1RN rs419598 CC/TC	**.35**	**0.22 (0.091- 0.508) p=0.0005**	***3.83±1.91 n=89***	***3.19±1.88 n=162***	***0.036***
IL1RN rs315952 TT	**.53**	**0.44 (0.21- 0.92) p=0.0297**	***3.69±1.80 n=132***	***3.11±2.01 n=117***	***0.069***
IL1RN rs9005 AA/GA	**.45**	**0.15 (0.065- 0.349) p<0.0001**	***3.86±1.71 n=114***	***3.04±2.01 n=135***	***0.0063***
IL1RN rs419598/ rs315952/rs9005 Carriage of Haplotype C,T,A	**.32**	**0.14 (0.053 - 0.368) p< 0.0001**	***3.99±1.77 n=80***	***3.14±1.93 n=169***	***0.0008***

[1] Frequency within the total patients (n=130 with complete genetic data) with knee osteoarthritis from two separate populations (NYUHJD; Duke POP Study)

[2] Odds ratio for severe OA, as measured by Kellgren-Lawrence score, comparing the indicated genotype or haplotype to all other genotypes for that SNP. Patients were classified by radiographic severity of knee OA by stratifying the Kellgren-Lawrence (KL) scores to compare KL=1 or 2 versus KL= 3 or 4. Similar significant associations were found when patients were stratified so that KL=1 was compared to KL=2-4 (data not shown).

[3] The smaller JSW in millimeters for each knee was included in the knee-based analysis (n=251 knees with complete data in 126 patients from the NYUHJD and Duke POP populations). Statistical analysis was adjusted for age, gender and BMI in a mixed model analysis of variance for inter-correlated data to adjust for the subject effect on two knees.

[4] Wilcoxon test

In a person-based analysis of signal knees only, all signal knees (n=126 with complete data) from NYUHJD and Duke, were classified as to medial (n=95) or lateral-dominant (n=31) disease. The protective effect was apparent for medial knee OA (mean JSW in patients carrying the CTA haplotype =3.37mm$\pm$1.66, versus reference haplotypes =2.29mm+1.73; p=0.0054). There were no significant IL1RN genotype associations for the lateral compartment (mean JSW in patients carrying the CTA haplotype =2.74mm$\pm$2.21, versus reference haplotypes =2.23mm+1.67; p=0.53).

Since age has strong epidemiological associations with prevalence and severity of knee OA and was associated with severity in the combined studies, we evaluated the interaction between age and IL1RN genotype relative to severity. In regression models, there was a significant interaction between genotype and age ($p<0.0001$) relative to KL scores, with the effect of genotype being stronger at greater ages. The addition of the IL1RN haplotype to regression models that included age provided a better fit than with age alone ($p<0.0001$). To examine the effect of genotype at different ages, we divided the population into age tertiles. Carriers of the CTA IL1RN haplotype were at significantly lower risk for severe KL scores in each age group (**Figure 1a**). In regression models, age was associated with KL>2 in patients without the CTA haplotype (p=0.032) but not in those carrying the haplotype. Similarly, age was associated with JSW narrowing only in knee OA patients who do not carry the CTA haplotype (**Figure 1b** vs. **Figure 1c**).

Given that IL1RN alleles have been associated with different expression levels of inflammatory mediators, we evaluated the influence of the IL1RN CTA haplotype on inflammatory mediators in synovial fluid from the POP study (N=50). Patients carrying the IL1RN CTA haplotype had significantly lower synovial fluid mean levels of IL-10 (p=0.034), and trending lower levels of IL-1β and IL-6 (**Table 4)**. No differences by IL1RN haplotype were seen for IL-1Ra protein, monocyte chemotactic protein-1, macrophage inflammatory protein-1β, C-reactive protein, or cartilage oligomeric matrix protein (**Table 4**). IL-1Ra protein levels were positively correlated with IL-6 levels in both patients without the CTA haplotype (p=0.002 with exclusion of 1 outlier; mixed model considering two knees from an individual: p=0.04) and in patients with the CTA haplotype (p=0.029; mixed model: p=0.078). There was a positive correlation between levels of IL-10 and IL-1ra levels only in samples from patients without the IL1RN CTA haplotype (p=0.0048; mixed model: p=0.056). No association was seen between levels of IL-10 and IL-1ra levels in patients who carry the IL1RN CTA haplotype (p=0.37; mixed model: p=0.55) This effect appears to be due in part to the fact that in the lower levels of IL-10 (tertiles 1 & 2) IL-1Ra appears to be elevated in CTA carriers, as evidenced by the CTA haplotype carriers compared to non-carriers being enriched in the highest quartile of IL-1ra (54.5% versus 16.7; p=0.07).

Table 4: Synovial Fluid Inflammatory Mediators Relative to Carriage of IL1RN Haplotypes

Synovial Fluid Analyte	IL1RN haplotype Rs419598/315952/9005 =CTA	N[5]	Mean[6]	Standard deviation	p value[7]
CRP (ng/ml)	0 1 or 2 copies	28 21	5195.3 5160.4	4991.4 4045.8	0.74
IL-6 (pg/ml)	0 *1 or 2 copies*	28 19	687.1 430.2	633.5 437.4	0.38
IL-10[1] (pg/ml)	0 *1 or 2 copies*	28 19	109.4 13.4	222.7 42.7	0.034
IL-1β[1] (pg/ml)	0 *1 or 2 copies*	28 19	3.46 0.63	8.38 2.04	0.40
IL-1Ra (pg/ml)	0 *1 or 2 copies*	16[8] 7	483 468.5	334.6 184.2	0.72
MCP[2] (pg/ml)	0 *1 or 2 copies*	29 21	763.7 789.7	389 303.3	0.49
MIP[3] (pg/ml)	0 *1 or 2 copies*	29 21	380.9 360.6	233.4 169.1	0.91
COMP[4] (ng/ml)	0 *1 or 2 copies*	29 21	35020 30441	23280 20677	0.52

[1] Values of these parameters that were below the lower limit of detection of the assay were assigned the value of 0.5 times the lower limit to facilitate data analysis. 52% of the IL-10 values and 82% of the IL-1β values were below the detection threshold limit.

[2] Monocyte chemotactic protein-1; [3] Macrophage inflammatory protein-1β ; [4] Cartilage oligomeric matrix protein; [5] Number of patients; [6]The mean of the mediator values of the two knees were used to represent the mediator value for the patient; [7] Non-parametric Wilcoxon test; [8] IL-1Ra analysis was performed at a later time than the other analytes and fewer samples remained available with sufficient volume for analysis.

Discussion

Inflammatory mediators are produced by articular joint tissues in osteoarthritis and have been implicated in disease pathogenesis.[2, 12] Of 15 SNPs in six inflammatory genes, variations in the gene for IL-1Ra were significantly associated with severe radiographic knee OA in two independent populations. One IL1RN haplotype was associated with decreased risk for radiographic severity, greater joint space width, lower levels of synovial fluid inflammatory mediators, and reduction of the age influence on severity. Although both populations were modest in size, these findings are unlikely to be false positives because: a) statistically significant associations were observed for multiple SNPs in the same gene, IL1RN, whereas no associations were found for SNPs in other genes; b) a specific IL1RN haplotype was protective in two independent populations and with two different severity parameters; and c) in the combined dataset, associations with severity were highly significant ($p<0.0001$).

It is of interest that the IL1RN protective effect was only evident in the medial compartment. Although power to show a protective effect for lateral knee OA dominant disease was less, these findings are consistent with previous reports of a stronger genetic effect on medial disease. In a female twins study[1] changes over time in the medial compartment were clearly heritable but not changes in the lateral compartment, and a magnetic resonance imaging-based study[13] also found a stronger genetic influence for medial cartilage loss. The differential compartment effects observed for genetic influence can presumably be attributed to the combination of genetic susceptibility and weight-bearing load (70% concentrated in the medial compartment) that together are necessary and sufficient to cause OA preferentially in the medial compartment.

IL-1 is well-established as a regulator of cartilage degradation[14] and resorption of bone.[12] We and others have previously shown that imbalances in IL-1 and IL-1 antagonists, such as the IL-1 receptor antagonist and the type II decoy receptor, contribute to cartilage loss and increased inflammatory mediators in OA.[2] Although blocking IL-1 activity by means of intra-articular injections or by gene transfer of IL-1Ra reduced cartilage and bone changes in animal models of OA,[15, 16] intra-articular IL-1Ra injections in humans have produced mixed results for symptomatic knee OA.[17]

The IL1 gene cluster region has been repeatedly associated with susceptibility to OA in various joints, but the results have been inconsistent.[7-9, 18-20] An extended haplotype including SNPs in the IL1A, IL1B and IL1RN genes has been associated with increased susceptibility to OA in various joints [9, 19], but that haplotype is not consistent with the IL1RN haplotypes that contributed to knee OA severity in the present study.

Of the three IL1RN SNPs associated with severity in this study, two (rs419598, exon3 Ala/Ala; rs315952, exon 5, Ser/Ser) are in the coding regions of the IL1RN gene but do not change the amino acid sequence. The third, rs9005, is in the 3' UTR of exon 4. Blood levels of IL-1Ra have been associated with various polymorphic loci within the IL1RN gene, but the findings have been inconsistent. In two recent studies of more than 1,000 subjects,[5, 21] significantly higher blood levels of IL-1Ra protein were associated with allele T at one polymorphism (rs4251961) that is part of the broader haplotype marked by the CTA alleles included in this report. In addition, allele C at rs419598 of the CTA haplotype has been associated with increased peripheral blood mononuclear cell expression of IL-1Ra and decreased risk for osteolysis after total hip arthroplasty.[22]

IL-1β is among the first genes activated with any tissue challenge, including biomechanical stress, and activates downstream cytokines including IL-6 and IL-10. The lower synovial fluid levels of IL-10, IL-1β, and IL-6 in the presence of the IL1RN CTA haplotype are consistent with lower IL-1 biologic activity, as would be expected in individuals with increased IL-1Ra expression and a lower level of activation of local cytokine producing cells.

Although there was not a simple relationship observed between the synovial fluid levels of IL-1Ra and carriage of the IL1RN CTA haplotype in all patients, this relationship was evident in patients who were not in the highest tertile of IL-10 levels. IL-1Ra expression is directly activated by IL-10 in both monocytes and neutrophils.[23, 24] The finding of a higher level of IL-Ra in synovial fluid samples from patients carrying the CTA haplotype only in the lower two tertiles of IL-10 protein is consistent with a genetic effect that may be evident only under sub-maximal activation conditions. For example, if one assumes near maximal activation of IL-1Ra when IL-10 is strongly elevated, as would be expected in tertile 3 of IL-10 levels, a genotype effect on IL-1ra expression may be less evident than at sub-maximal levels of IL-10.

This study has potential limitations including the moderate sample size, yet consistent and significant severity associations with the IL1RN loci were observed in two independently ascertained populations. In addition, although the genotype association is with severity, longitudinal data are not available to assess actual disease progression rates. In this study age was associated with radiographic severity, and although adjusted for in the statistical models, age may have had other confounding effects on the results. It should be emphasized that the IL1RN haplotype that was associated with protection in late stages of a chronic disease that involve both bone and cartilage, may have different or no effect on early disease initiation.

A substantial part of the variance in clinical expression of OA is attributed to genetics,[1] and multiple SNPs have been associated with OA susceptibility.[25] Few studies have evaluated the role of genetic factors in severity or progression of knee OA,[26, 27] and, other than the current report, we are not aware of genetic markers for knee OA severity validated in a second population.

The IL1RN CTA haplotype appears to identify a substantial segment of knee OA patients who are at low risk for severe destruction, and the data suggest that IL-1 biologic activity is a determinant of knee OA severity. Biomarkers that identify patients more likely to develop severe disease should expedite successful development of DMOADs and improvements in medical and surgical management of knee OA.

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Figure Legends:

Figure 1:
Influence of IL1RN haplotypes on the age relationship to severity of knee OA. 1a: The figure stratifies knee OA patients into thirds by age (<59 n=42; 59-68 n=40; >68 n=47). The numbers in each group are not exactly equal due to the distribution of patients at the intersection of the groups. Patients within each age group were then stratified by carriage (▨) or no carriage (■) of the IL1RN haplotype CTA of the SNPs rs419598/315952/9005. For each age strata and haplotype status, the frequency of severe radiographic knee OA (Kellgren-Lawrence score >2) is plotted. 1b, 1c: The joint space width (JSW) of each knee in knee OA patients who do not (fig. 1b) or do carry (Fig 1c) the IL1RN CTA haplotype (rs419598/ rs315952/rs9005) is plotted relative to age, and the regression line is shown for JSW relative to age. The JSW is significantly associated with age (p=0.0059) in knee OA patients who do not carry the IL1RN CTA haplotype, but JSW narrowing was not associated with age (p=0.56) in patients who carried one or two copies of the CTA haplotype.

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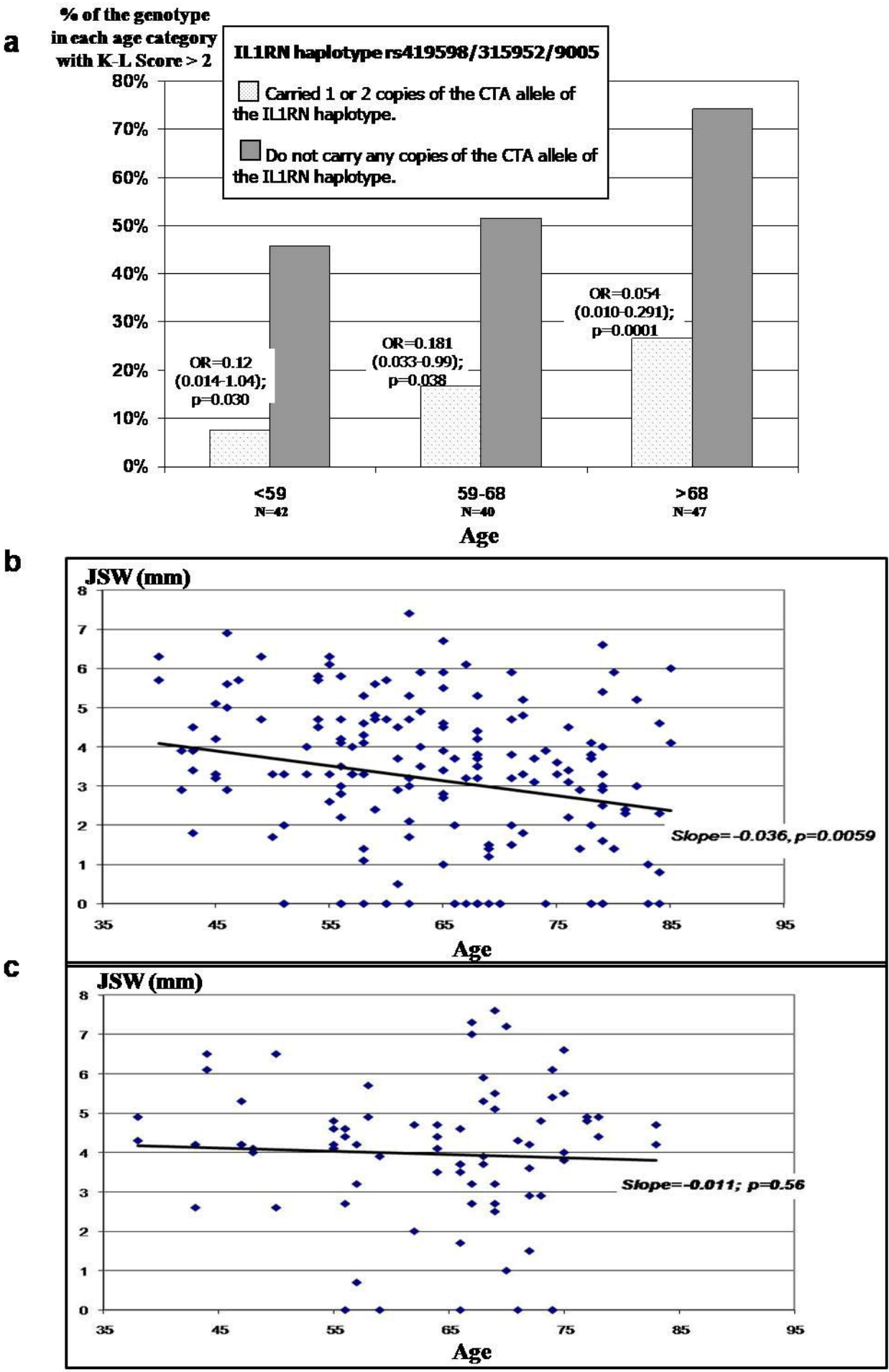
a
% of the genotype in each age category with K-L Score > 2
IL1RN haplotype rs419598/315952/9005
Carried 1 or 2 copies of the CTA allele of the IL1RN haplotype.
Do not carry any copies of the CTA allele of the IL1RN haplotype.
80%
70%
60%
50%
40%
30%
20%
10%
0%
OR=0.12 (0.014-1.04); p=0.030
OR=0.181 (0.033-0.99); p=0.038
OR=0.054 (0.010-0.291); p=0.0001
<59 N=42
59-68 N=40
>68 N=47
Age
b
JSW (mm)
Slope= -0.036, p=0.0059
Age
c
JSW (mm)
Slope=-0.011; p=0.56
Age

Radiographic severity of knee osteoarthritis is conditional on interleukin-1 receptor antagonist gene variations

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