

**Supplementary Table 1.** Linkage disequilibrium parameters  $D'$  and  $r^2$  for *IL1RN* single nucleotide polymorphisms (SNPs) rs419598, rs315952 and rs9005 for all three cohorts: New York University School of Medicine (NYU), Genetics of Generalized Osteoarthritis (GOGO) and Osteoarthritis Initiative (OAI).

SNP pair	$D' / r^2$		
	NYU	GOGO	OAI
rs419598 / rs315952	0.62 / 0.21	0.72 / 0.22	0.57 / 0.22
rs419598 / rs9005	0.81 / 0.61	0.86 / 0.75	0.72 / 0.67
rs35952 / rs9005	0.68 / 0.31	0.99 / 0.35	0.82 / 0.35

**Supplementary Table 2: *IL1RN* haplotype TTG association with mJSW and radiographic severity in combined (NYU, GOGO, and OAI) cohorts.**

<b>Panel A: <i>IL1RN</i> SNP All Combined (n=1066)</b>	<b>mJSW: beta (<math>\pm</math> SE), p value, FDR</b>
<b>TTG-0</b> vs. TTG-1 haplotype	-0.35 (0.11), p=0.001, FDR=0.004
<b>TTG-0</b> vs. TTG-2 haplotype	-0.45 (0.14), p=0.001, FDR=0.007
<b>Panel B: <i>IL1RN</i> SNP All Combined (n=1066)</b>	<b>KL severity: OR (95% CI), p value, FDR</b>
<b>TTG-0</b> vs. TTG-1 haplotype	1.53 (1.12-2.08), p=0.008, FDR=0.017
<b>TTG-0</b> vs. TTG-2 haplotype	1.69 (1.27-2.24), p=0.000, FDR=0.001

In panel A, an association of medial joint space width (mJSW) in millimeters (mm) with *IL1RN* haplotypes were studied by comparing the indicated haplotype (TTG-0) with TTG-1 or TTG-2 using linear regression analysis. In panel B, Patients were classified by radiographic severity of knee OA by stratifying the KL scores to compare KL 1 or 2 versus KL 3 or 4. Odds ratios (OR) of KL vs. *IL1RN* haplotype also shows the association of Kellgren-Lawrence (KL) score with *IL1RN* haplotype.

**Supplementary Table 3: Regression analysis of *IL1RN* haplotype (TTG) with radiographic medial joint space width (mJSW) in three cohorts of symptomatic knee OA patients.**

	<b>ALL (n=1022) Beta (SE); P=value</b>
<b>mJSW (mm) (Baseline), TTG Haplotype (0 vs. 1/2)</b>	
crude	-0.35 (0.11); 0.001
adjusted for age, sex	-0.35 (0.10); 0.001
adjusted for age, sex, BMI	-0.36 (0.10); 0.001
<b>mJSW (mm) (Baseline), TTG Haplotype (0 vs 2)</b>	
crude	-0.45 (0.14); 0.001
adjusted for age, sex	-0.40 (0.14); 0.004
adjusted for age, sex, BMI	-0.40 (0.14); 0.003
<p>Medial joint space width (mJSW) in millimeters comparing the indicated haplotype (TTG-0) with TTG-1 or TTG-2. Haplotypes TTG-0 or TTG-1 or TTG-2, respectively, represent carriers of 0 or 1 or 2 copies of <i>IL1RN</i> haplotype produced using 3 <i>IL1RN</i> SNPs (rs419598, rs315952 and rs9005). Linear regression was performed unadjusted, adjusted for age and sex, as well as adjusted for age, sex, and body mass index (BMI) together.</p>	

**Supplementary Table 4: Association of *IL1RN* haplotype (TTG) in male and female with radiographic signal knee medial joint space width (mJSW) in combined (NYU, GOGO, and OAI) cohorts of symptomatic knee OA patients.**

	Beta (SE), p-value
<b>mJSW (mm) (Baseline), TTG Haplotype (0 vs 1/2) – Male</b>	<b>ALL (n=355)</b>
Crude	-0.48 (0.20), 0.018
adjusted for age, sex	-0.54 (0.19), 0.006
adjusted for age, sex, BMI	-0.50 (0.19), 0.009
<b>mJSW (mm) (Baseline), TTG Haplotype (0 vs 2) – Male</b>	<b>ALL (n=164)</b>
Crude	-0.58 (0.26), 0.027
adjusted for age, sex	-0.51 (0.25), 0.042
adjusted for age, sex, BMI	-0.49 (0.24), 0.047
<b>mJSW (mm) (Baseline), TTG Haplotype (0 vs 1/2) – Female</b>	<b>ALL (n=667)</b>
Crude	-0.28 (0.12), 0.021
adjusted for age, sex	-0.27 (0.12), 0.025
adjusted for age, sex, BMI	-0.28 (0.12), 0.023
<b>mJSW (mm) (Baseline), TTG Haplotype (0 vs 2) – Female</b>	<b>ALL (n=317)</b>
Crude	-0.38 (0.16), 0.018
adjusted for age, sex	-0.34 (0.16), 0.033
adjusted for age, sex, BMI	-0.34 (0.16), 0.034
Medial joint space width (mJSW) in millimeters comparing the indicated haplotype (TTG-0) with TTG-1 or TTG-2. Haplotypes TTG-0 or TTG-1 or TTG-2, respectively, represent carriers of 0 or 1 or 2 copies of <i>IL1RN</i> haplotype produced using 3 <i>IL1RN</i> SNPs (rs419598, rs315952 and rs9005). A linear regression model was performed and adjusted for age and sex, as well as for age, sex, and body mass index (BMI) in the combined cohort.	

**Supplementary Table 5: Association of *IL1RN* haplotype (TTG) in Blacks with radiographic signal knee medial joint space width (mJSW) in combined (NYU and OAI) cohorts of symptomatic knee OA patients.**

	Beta (SE), p-value
<b>mJSW (mm) (Baseline), TTG Haplotype (0 vs 1/2)</b>	<b>ALL (n=82)</b>
Crude	-0.48 (0.34), 0.165
adjusted for age, sex	-0.46 (0.34), 0.183
adjusted for age, sex, BMI	-0.44 (0.34), 0.201
<b>mJSW (mm) (Baseline), TTG Haplotype (0 vs 2)</b>	<b>ALL (n=45)</b>
Crude	-0.77 (0.44), 0.091
adjusted for age, sex	-0.79 (0.44), 0.080
adjusted for age, sex, BMI	-0.82 (0.45), 0.072
<p>Medial joint space width (mJSW) in millimeters comparing the indicated haplotype (TTG-0) with TTG-1 or TTG-2. Haplotypes TTG-0 or TTG-1 or TTG-2, respectively, represent carriers of 0 or 1 or 2 copies of <i>IL1RN</i> haplotype produced using 3 <i>IL1RN</i> SNPs (rs419598, rs315952 and rs9005). A linear regression model was performed and adjusted for age and sex, as well as for age, sex, and body mass index (BMI), in the combined cohort.</p>	

**Supplementary Table 6: Association of *IL1RN* haplotype (TTG) in Hispanic and non-Hispanic with baseline radiographic signal knee medial joint space width (mJSW) in combined (NYU and OAI) cohorts of symptomatic knee OA patients.**

<b>Hispanic</b>	<b>Beta (SE); P value</b>
mJSW (mm), TTG Haplotype (0 vs 1/2)	ALL (n=347)
crude	-0.39 (0.24); 0.106
adjusted for age, sex	-0.33 (0.24); 0.160
adjusted for age, sex, BMI	-0.38 (0.24); 0.108
mJSW (mm), TTG Haplotype (0 vs 2)	ALL (n=122)
crude	-0.56 (0.29); 0.052
adjusted for age, sex	-0.37 (0.27); 0.176
adjusted for age, sex, BMI	-0.42 (0.27); 0.126
<b>Non-Hispanic</b>	<b>Beta (SE); P value</b>
mJSW (mm), TTG Haplotype (0 vs 1/2)	ALL (n=587)
crude	-0.33 (0.17); 0.057
adjusted for age, sex	-0.29 (0.17); 0.088
adjusted for age, sex, BMI	-0.31 (0.17); 0.066
mJSW (mm), TTG Haplotype (0 vs 2)	ALL (n=211)
crude	-0.63 (0.22); 0.005
adjusted for age, sex	-0.49 (0.21); 0.022
adjusted for age, sex, BMI	-0.49 (0.21); 0.021

Medial joint space width (mJSW) in millimeters comparing the indicated haplotype (TTG-0) with TTG-1 or TTG-2. Haplotypes TTG-0 or TTG-1 or TTG-2, respectively, represent carriers of 0 or 1 or 2 copies of *IL1RN* haplotype produced using 3 *IL1RN* SNPs (rs419598, rs315952 and rs9005). A linear regression model was performed and adjusted for age and sex, as well as for age, sex, and body mass index (BMI), in the combined cohort.

**Supplementary Table 7: The *IL1RN* risk haplotype TTG (1 or 2) associated with decreased soluble IL-1Ra levels in chondrocytes**

	Unstimulated, mean ( $\pm$ SD)			IL-1 induced, mean ( $\pm$ SD)		
	Extra-cellular (s)	Intra-cellular (ic)	Ratio (s vs. ic)	Extra-cellular (s)	Intra-cellular (ic)	Ratio (s vs. ic)
<b><i>IL1RN</i> haplotype</b>						
TTG-1,2 (n=15)	5.05 ( $\pm$ 8.1)	7.93 ( $\pm$ 14.9)	1 : 1.2	6.19 ( $\pm$ 7.1)	33.71 ( $\pm$ 22.0)	1 : 5.4
TTG-0 (n=14)	1.46 ( $\pm$ 2.2)	1.41 ( $\pm$ 2.5)	1 : 1	10.36 ( $\pm$ 11.9)	12.28 ( $\pm$ 8.4)	1 : 1.2
<b>P-value</b>						
TTG-1, 2 vs. TTG-0	<b>0.05</b>	0.06	—	0.22	0.07	—
TTG-1,2 – Con vs. IL-1	—	—	—	0.62	<b>0.04</b>	—
TTG-0 – Con vs. IL-1	—	—	—	<b>0.01</b>	<b>0.0005</b>	—

We analyzed total cell lysate for extracellular and cell-associated IL-1Ra protein expression in primary chondrocytes by ELISA. Haplotypes TTG-0 or TTG-1 or TTG-2, respectively, represent carriers of 0 or 1 or 2 copies of *IL1RN* haplotype produced using 3 *IL1RN* SNPs (rs419598, rs315952 and rs9005). Chondrocytes with *IL1RN* TTG-1/2 haplotype produced significantly lower levels of soluble IL1Ra than TTG-0 carriers in both spontaneous conditions and following 24h IL-1 $\beta$  induction. The data represent mean ( $\pm$ SD), for n=15 individuals with TTG-1/2 and n=14 individuals with TTG-0. Mann Whitney U test was used to analyze difference between groups.