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ORIGINAL ARTICLE

Modic changes and interleukin 1 gene locus polymorphisms in occupational cohort of middle-aged men

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Abstract According to recent systematic reviews, Modic changes are associated with low-back pain. However, their pathophysiology remains largely unknown. A previous study of Northern Finnish males implicated that *IL1A* and *MMP3* polymorphisms play a role in type II Modic changes. The purpose of the current study was to examine the association of *IL1* cluster polymorphisms with Modic changes amongst middle-aged men in Southern Finland. The final study sample consisted of 108 men from three different occupations, who underwent magnetic resonance imaging (MRI) with a 0.1 T-scanner. Six single nucleotide polymorphisms (SNP) in the IL1 gene cluster (*IL1A* c.1-889C>T; *IL1B* c.3954C>T; *IL1RN* c.1812G>A; *IL1RN* c.1887G>C; *IL1RN* c.11100T>C; *IL1RN* c.1506G>A) were genotyped with the SNP-TRAP method or by allele-specific primer extension on modified microarray. In all, 45 subjects had Modic changes at one or more disc levels. The presence of the minor allele of *IL1A* (c.1-889C>T) was associated with these changes (any Modic change $p = 0.031$, type II changes $p = 0.036$). The carriers of the T-allele had a 2.5-fold risk of Modic change and the association was independent of the other *IL1* gene cluster loci studied. In addition, a minor haplotype, with a frequency of 7.5% in the study population, including the minor alleles of *IL1A* c.1-889C>T, *IL1RN* c.1812G>A, and *IL1RN* c.1506G>A, was significantly associated with Modic changes. This observation is in accordance with the previous finding from a different geographical area, and thus confirms the importance of the *IL1A* gene in the pathophysiology of Modic changes.

Keywords Modic changes · MRI · Genetic factors · Interleukin

Introduction

Modic changes (MC) are vertebral endplate and adjacent bone marrow changes visible in magnetic resonance imaging (MRI). Michael Modic classified MRI changes into three categories [27]: type I changes show a low signal intensity (SI) in T1-weighted images (T1WI) and a high SI in T2-weighted images (T2WI), type II changes show a high SI both in T1WI and in T2WI, and type III changes show a low SI both in T1WI and in T2WI. Type I changes indicate an ongoing active inflammatory degenerative process, whereas type II changes are thought to reflect fatty degeneration of the bone marrow. Type III changes on the other hand, demonstrate a late regenerative process, which is rare in middle-aged populations [14, 17].

The current evidence, including two systematic reviews, indicates that MC are associated with low-back pain (LBP)

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[10, 15, 17, 49]. The pathomechanism of LBP due to MC, however, remains poorly understood. It has been hypothesized that MC is a result of a biomechanically induced inflammation around the intervertebral disc [38]. This inflammatory aetiology is also supported by the finding of an increased number of tumour necrosis factor (TNF) immunoreactive nerve cells and fibres in endplates with MC, especially in type I changes [30].

Genetic factors are regarded as important risk factors of intervertebral disc degeneration [37, 47]. The predisposing genetic risk factors identified in association studies include mutations in collagen IX [3, 11, 31], vitamin D receptor [7, 12, 46], matrix metalloproteinase (MMP)-1 and -3 [41, 44], interleukin-6, *IL6* [29], and *IL1* genes [39, 48]. IL-1 is an interesting molecule, as an association was found between LBP and polymorphisms in the genes coding for both interleukins 1-α and -β, more precisely C-889T in *IL1A* and C3954T in *IL1B* [39]. IL-1 is known to be involved in the pathogenesis of disc degeneration by decreasing the synthesis and increasing the catabolism of proteoglycans [19]. Recently, we have observed that a combination of polymorphisms in the *IL1A* and *MMP-3* considerably increase the risk of type II MC [13].

The purpose of the current study was to more closely examine the associations of *IL1* cluster polymorphisms with MC in a population of middle-aged Finnish male workers.

Subjects and methods

Subjects

The subjects of this study were a subgroup of a cohort of 1,832 men from three occupations, machine drivers, construction carpenters, and office workers, who had participated in two repeated questionnaire studies (in years 1984 and 1987) concerning occupational effects on LBP [35, 36]. In 1991, 70 men aged 40–45 years were selected from each occupational group, using the place of residence (Helsinki or its neighbouring cities) as an inclusion criterion for a new study [21]. Of these, 164 (78%) men underwent an MRI of the lumbar spine and completed a self-administered questionnaire about low-back symptoms, individual characteristics, and life-style factors; of them 131 (80%) donated a blood sample for genetic analysis in 1999 [39, 40].

Fourteen subjects were excluded from the final analysis due to the poor technical quality of MR images, and nine persons due to missing data. The final study group comprised 108 men (mean age 44 years): 28 machine drivers, 36 construction carpenters, and 44 municipal office workers.

Magnetic resonance imaging (MRI) of the lumbar spine

Sagittal slices (Dual Echo 2000/25-86) with two acquisitions were obtained with a 0.1 T-device. The first echo was a gradient echo and the second a spin echo. Slice thickness was 7 mm, field of view (FOV) 410 mm × 410 mm, and pixel size 1.6 mm × 1.6 mm. There were no gaps between the slices. Coronal slices, perpendicular to the L4/L5-disc space, were obtained through a gradient echo technique (partial saturation 175/25), one acquisition, 5 mm slice thickness, FOV 358 mm × 358 mm and pixel size 1.4 mm × 1.4 mm.

Assessment of Modic changes

A joint reading was performed by two experienced neuroradiologists for assessing the presence and size of MC in disc spaces L1/2 to L5/S1. The observation was classified as missing if the endplates could not be reliably evaluated. MC in T2WI were assessed by separately evaluating the size of the hyperintense change at both end plates of the disc space.

The lesion type was assessed using the coronal T1WI as: M0 = no MC; MI = hypointense lesion; MII = hyperintense lesion; MI/II = mixed hypo- and hyperintense lesion. A lesion at the end plates was considered a positive finding if it was found in one of the slices with a height and width of at least 5% of that of the vertebral body. Modic type III lesions, hypointense on both T1WI and T2WI were rare, difficult to detect on T2WI, and always associated with a Modic type I lesion. Thus, they were not analysed separately.

IL1 gene cluster genotyping

Six single nucleotide polymorphisms (SNP) in the IL1 gene cluster (*IL1A* c.1-889C>T, *IL1B* c.3954C>T, *IL1RN* c.1812G>A, *IL1RN* c.1887G>C, *IL1RN* c.11100T>C, and *IL1RN* c.1506G>A) were genotyped using the SNP-TRAP method or by allele-specific primer extension on modified microarray [32, 39].

For SNP-TRAP, genomic DNA was amplified by polymerase chain reaction (PCR), using 40 ng of template, 0.3 units of Taq polymerase (DyNAzyme; Finnzymes Oy, Finland), 3 pmol of each PCR primer, 3 nmol of dNTPs in the DyNAzyme buffer in a 15 µl reaction. The PCR programme used, the purification procedure, and primer extension reactions have been previously described in detail [39].

The biotin-dNTP labelled primer was then trapped onto a Reacti-Bind™ Neutravidin™ coated plate (Pierce, USA), followed by washing with TENT-buffer (40 mM Tris–HCl, 1 mM EDTA, 50 mM NaCl, 0.1% Tween 20) 6 times. The bound oligonucleotide was quantified using

single stranded DNA-specific fluorescent dye, OliGreen® (1:250 dilution) (Molecular Probes, USA), and the fluorescence was measured using a Victor2^{TM} 1420 Multilabel counter fluorometer (Wallac, Finland).

The genotypes were determined on the basis of the above-mentioned fluorescent signal intensities. A chart was formed using $A_1/(A_1 + A_2)$ on the *X*-axis and $\log(A_1 + A_2)$ on the *Y*-axis, where A_1 represents the signal given by allele 1, and A_2 a signal by allele 2. Each one of the SNPs formed three distinct clusters from which the genotype limits for each SNP were set.

For the allele-specific primer extension DNA was amplified in a multiplex PCR reaction as described previously [39]. The multiplex PCR products were then transcribed to RNA by Ampliscribe T7 High Yield Transcription Kits (Epicentre Technologies) [39]. After transcription reaction the DNA was degraded using the DNAseI provided with the kit.

Two allele-specific oligonucleotides for each SNP, differing at their 3′ nucleotide and thereby defining the alleles, were synthesized from the reverse direction with 5′ aminolinker and a poly-T (9) stretch. The oligonucleotides were spotted as duplicates on silane–isothiocyanate treated microscope slides as described earlier [32]. The produced RNAs were hybridized on the arrays in 1.67 M NaCl buffer in 42°C for 20 min. The slides were washed twice in washing buffer containing 0.3 M NaCl, 0.5× TE, 0.1% Triton X-100, followed by a rinse in ice cold water. The allele-specific extension was performed as described before [39]. We scanned the slides using ScanArray 4000 (Packard Bioscience, USA) and analysed the images using the QuantArray software. Final genotyping was carried out using SNPSnapper, a genotype-calling programme developed in-house. Genotypes were checked for the Hardy–Weinberg equilibrium.

For technical reasons, not all candidate genes were successfully genotyped from all blood samples. Thus, in the final material we had 108 subjects for *IL1A* c.1-889C>T, 107 for the *IL1B* c.3954C>T, the *IL1RN* c.1812G>A, and the *IL1RN* c.1887G>C polymorphisms, and 102 subjects for the *IL1RN* c.11100T>C.

Questionnaire

Data regarding individual characteristics were collected by self-administered questionnaires in 1984, 1987, and 1991. The questionnaires included items on anthropometric measures, smoking habits, and the history of back injuries, physical exercise and car-driving. Body mass index (BMI) [weight (kg) per height (m) squared] was calculated based on self-reported height and weight at the time of the MRI examination (in 1991). Job title was used as the measure of occupational load.

Statistical analysis

Potential deviation in the Hardy–Weinberg equilibrium was tested using the chi-square test. Fisher's exact probability test or chi-square test was used to compare different allele and genotype frequencies between individuals with and without MC. Haplotypes were statistically reconstructed from the described population genotype data of the studied single nucleotide polymorphisms (SNPs) with the PHASE programme [42].

We examined the associations between the SNPs and MC by logistic regression analysis, in which occupation and body mass index were adjusted for. Crude and adjusted odds ratios (OR) and their 95% confidence intervals (CI) were calculated using the SPSS statistical package (Statistical Package for the social Sciences, version 14.0, SPSS Inc, USA).

Results

In total, 45 subjects had one or more Modic changes (MC). Of these, 64% had MC at only one level. Of the subjects with MC, 39 (87%) had a type II lesion (15% of them had a type I lesion in addition to type II MC), whilst six (13%) had only a type I lesion. MC were typically located at L4/5 (38%) or L5/S1 (33%).

Risk factors of Modic changes

Table 1 shows the association of occupation, BMI, history of back injuries, smoking, history of physical exercise, and history of car-driving with MC. Only high current overweight (BMI $\geq$ 25 kg/m^2 vs. BMI $<$ 25 kg/m^2) was associated with an increased risk of any MC (type I and type II combined; $p = 0.02$; Table 1).

IL1 cluster genotypes, allele carriage rates and allele frequencies versus Modic changes

We observed an association between the *IL1A* c.1-889C>T polymorphism and MC. The minor allele was more frequent among the subjects with type II changes and any MC ($p = 0.036$ and 0.031, respectively; Table 2). Furthermore, the carriers of the T-allele had an increased risk of any MC (OR = 2.50, 95% CI = 1.09–5.71, $p = 0.03$), compared to non-carriers of the allele. No association with MC was found for the *IL1B* c.3954C>T, *IL1RN* c.1812G>A, *IL1RN* c.1887G>C, *IL1RN* c.11100T>C, and *IL1RN* c.1506G>A polymorphisms (Table 2).

As the high degree of linkage disequilibrium (LD) for the studied polymorphisms, the observed association between the *IL1A* c.1-889C>T minor allele and MC could

Table 1 Occurrence of Modic changes by potential risk factors ($N = 108$)

Variable	No Modic changes		Modic changes			
			Any		Type II	
	N	%	*N*	%	*N*	%
Occupation						
Machine driver	15	53.6	13	46.4	11	38.3
Construction carpenter	20	55.6	16	44.4	14	38.9
Office worker	28	63.6	16	36.4	14	31.8
Body mass index (BMI)						
BMI < 25 kg/m^2	39	69.6	17	30.4	14	25.0
BMI ≥ 25 kg/m^2	24	46.2*	28	53.8*	25	48.1
History of accidental back injuries						
No injuries	47	63.5	27	36.5	23	31.1
One or more injuries	16	47.1	18	52.9	16	47.1
Smoking status						
Non-smoker	18	50.0	18	50.0	14	38.9
Ex- or current smoker	43	61.4	27	38.6	25	35.7
History of physical exercise[a]						
Less than twice/week	18	52.9	16	47.1	15	44.1
Intermediate	31	63.3	18	36.7	15	30.6
2 or more times/week	14	56.0	11	44.0	9	36.0
History of car driving						
≤15,000 km/year	42	57.5	31	42.5	27	37.0
>15,000 km/year	19	59.4	13	40.8	11	34.4

* $p = 0.02$

[a] History of physical exercise was classified as less than twice per week at all time points (7 and 4 years earlier and currently), intermediate, and two or more times per week at all time points

be due to some other SNP in LD with the one in question. To study the independent effects of the six loci, the alleles were added simultaneously as covariates in the logistic regression analysis. The minor allele of the *IL1A* c.1-889C>T polymorphisms was associated with an approximately 2.5-fold increased risk of MC (Table 3). The ORs were slightly reduced but remained statistically significant after the inclusion of other covariates (occupation and current BMI) into the model.

IL1 cluster haplotype associations with Modic changes

Finally, we evaluated the association of six-marker *IL1A–IL1B–IL1RN* haplotypes with MC. Based on the genotypes a total of 21 haplotypes were constructed by the PHASE programme. Four of the haplotypes (2-2-2-1-1-2, 1-1-1-2-2-1, 1-1-2-1-2-2, and 1-1-2-1-1-2; see explanations in Table 4) were relatively common, exhibiting frequencies of 0.206, 0.188, 0.183, and 0.165, respectively, whereas the frequencies of other haplotypes were <0.05.

The common haplotypes were not associated with MC, whereas one rare haplotype (2-1-2-1-1-2) including the minor alleles of *IL1A* c.1-889C>T, *IL1RN* c.1812G>A, and *IL1RN* c.1506G>A was statistically significant and associated with any MC ($p = 0.043$, OR = 8.72) and type II changes ($p = 0.015$, OR = 10.13; Table 4).

Discussion

In this study, six SNPs in the *IL1* gene cluster (*IL1A* c.1-889C>T, *IL1B* c.3954C>T, *IL1RN* c.1812G>A, *IL1RN* c.1887G>C, *IL1RN* c.11100T>C, and *IL1RN* c.1506G>A) were genotyped and their association with MC was analysed in an occupational cohort of middle-aged males from Southern Finland. Polymorphisms in the *IL1B* and *IL1RN* were not associated with MC, whereas the presence of the minor allele of *IL1A* (c.1-889C>T) was significantly so. The carriers of the T-allele were at a 2.5-fold increased risk of any Modic change, and the association was independent of the other studied *IL1* gene cluster loci. None of the major haplotypes of the *IL1* gene cluster was associated with MC, whereas a minor haplotype with a frequency of 7.5% in the study population, including the minor alleles of *IL1A* c.1-889C>T, *IL1RN* c.1812G>A, and *IL1RN* c.1506G>A, was significantly associated with these changes.

Only one previous study has so far evaluated the genetic factors of MC [13]. In an occupational cohort of Northern Finnish males, the presence of a combination of the minor alleles of *IL1A* (c.1-889C>T) and *MMP3* (5A) showed a 3-fold higher likelihood for type II MC. In the current study the minor allele of *IL1A* was independently associated with MC, whereas polymorphisms in the *MMP3* were not evaluated. We are therefore not able to confirm the earlier results of a gene–gene interaction between *IL1A* and *MMP3*. The minor allele of *IL1B* (c.3954C>T) was not associated with MC in this study, or in the previous one [13]. Unfortunately, the number of type I MC was too low in this study for a reliable statistical analysis.

The signal intensity changes in the discs and subchondral bone marrow were assessed using MR images obtained at low field strength (0.1 T). Signal-to-noise ratio is known to depend on the field strength being better at higher field strengths. The detectability of focal lesions with abnormal signal intensity may be better on high rather than on low field strength, in the case of Modic type I lesions on T2WI in particular. On the other hand, the contrast between high and low field images is different. Relaxation times are field dependent, most T1 relaxation times being shorter at lower field strengths [28]. This enhances T1 contrast on low field images, which may affect the number of MC found.

Table 2 Distribution of the *IL1* gene cluster genotypes, alleles, and carriage rates in persons with and without Modic changes ($N = 108$)

	No Modic changes ($N = 63$)		Modic type II ($N = 39$)		Any Modic ($N = 45$)	
	N	%	*N*	%	*N*	%
IL1A c.1-889C>T						
CC	30	47.6	11	28.2	12	26.7
CT	28	44.4	21	53.8	26	57.8
TT	5	7.9	7	17.9	7	15.6
T-allele carriage	33	52.4	28	71.8	33	73.3*
T-allele frequency	38	30.2	35	44.9**	40	44.4***
IL1B c.3954C>T						
CC	32	51.6	19	48.7	20	44.4
CT	24	36.7	16	41.0	20	44.4
TT	6	9.7	4	10.3	5	11.1
T-allele carriage	30	48.4	20	51.3	25	55.6
T-allele frequency	36	29.0	24	30.8	30	33.3
IL1RN c.1812G>A						
GG	34	54.8	21	53.8	24	53.3
GA	25	40.3	15	38.5	17	37.8
AA	3	4.8	3	7.7	4	8.9
A-allele carriage	28	45.2	18	46.2	21	46.7
A-allele frequency	31	25.0	21	26.9	25	27.8
IL1RN c.1887G>C						
GG	34	54.0	21	53.8	23	51.1
CG	26	41.3	15	38.5	18	40.0
CC	3	4.8	3	7.7	4	8.9
C-allele carriage	29	46.0	18	46.2	22	48.9
C-allele frequency	32	25.4	21	26.9	26	28.9
IL1RN c.11100T>C						
TT	17	28.8	9	24.3	13	30.2
CT	30	50.8	25	67.6	27	62.8
CC	12	20.3	3	8.1	3	7.0
C-allele carriage	42	71.2	28	75.7	30	69.8
C-allele frequency	54	45.8	31	41.9	33	38.4
IL1RN c.1506G>A						
GG	35	58.3	16	45.7	18	43.9
GA	24	40.0	16	45.7	19	46.3
AA	1	1.7	3	8.8	4	9.8
A-allele carriage	25	41.7	19	54.3	23	56.1
A-allele frequency	26	21.7	22	31.4	27	32.9

$N = 107$ for IL1B c.3954C>T, IL1RN c.1812G>A, and IL1RN c.1887G>C polymorphisms, and $N = 102$ for IL1RN c.11100T>C

* $p = 0.030$, OR = 2.50, 95% CI = 1.09–5.71; ** $p = 0.036$, OR = 1.85, 95% CI = 1.05–3.39; *** $p = 0.031$, OR = 1.85, 95% CI = 1.05–3.25

The prevalence of MC in our study was relatively high compared to earlier cohort studies with 0.2 T [14] and 1.5 T [17], and even when compared to studies with LBP patients [ref. 10]. Our results may be more easily comparable with those obtained using low field strength. However, the inclusion criteria of the MC may be more important in the evaluation of different studies. We excluded small type II lesions in association with large osteophytes, whereas we included lesions associated with endplate defects or indentations. An association between endplate defects and type I MC has been found previously [22]. The evaluation of coronal slices in addition to sagittal ones, as in our study, may also have improved the detectability of the lesions. Theoretically, the different image

Table 3 Association of minor IL-1 cluster alleles with Modic changes ($N = 216$)

	Any Modic change			Type II change		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Mutually adjusted						
IL1A-889T	2.45	1.26–4.79	0.01	2.54	1.26–5.12	0.01
IL1B 3954T	1.47	0.71–3.03	0.30	1.16	0.53–2.51	0.71
IL1RN 1812A	0.82	0.18–3.75	0.80	1.03	0.21–5.11	0.97
IL1RN 1887C	1.67	0.78–3.56	0.19	1.62	0.73–3.63	0.24
IL1RN 11100C	0.95	0.46–1.99	0.90	1.20	0.55–2.59	0.64
IL1RN 1506A	2.94	0.64–15.48	0.16	2.30	0.46–11.57	0.31
ORs are adjusted for occupation, current BMI and other alleles						
IL1A-889T	2.24	1.11–4.50	0.02	2.32	1.12–4.82	0.02
IL1B 3954T	1.47	0.69–3.13	0.31	1.10	0.49–2.46	0.82
IL1RN 1812A	0.88	0.17–4.41	0.87	1.06	0.18–6.28	0.95
IL1RN 1887C	1.71	0.78–3.74	0.18	1.66	0.72–3.80	0.23
IL1RN 11100C	0.80	0.37–1.72	0.56	1.02	0.45–2.27	0.97
IL1RN 1506A	3.15	0.63–15.91	0.16	2.68	0.44–16.12	0.28

$N = 214$ for IL1B c.3954C>T, IL1RN c.1812G>A, and IL1RN c.1887G>C polymorphisms, and $N = 204$ for IL1RN c.11100T>C

Logistic regression analysis was carried out for all SNPs

contrast in this study with low field as compared to that in studies with high field, should underestimate the prevalence of MC, as type I lesions in particular may remain undetected on low field.

It is thought that MC can convert from one type to another and that they all represent different stages of the same pathological process [5]. Type I changes commonly progress to type II, or convert to bone marrow with normal signal intensity [16, 22, 27]. We believe that the association of the minor allele of *IL1A* (c.1-889C>T) was stronger with type II changes than with combined type I and II changes, because type II changes represent a more chronic entity, whilst some type I changes may represent a more reversible, "benign" phenotype, converting to normal bone marrow instead of progressing to type II [49].

Histologically, type I MC demonstrates disruption and fissures in the endplates, which are assumed to indicate an ongoing active inflammatory degenerative process, whereas type II changes are associated with the fatty degeneration of bone marrow [27]. The endplate is the weak spot of the spine in compression, and always fails before the intervertebral disc [1, 6]. This can result in morphologic changes in the bone marrow including microfractures and structural disorganization [4]. However, endplate damage may not always be needed to induce MC. In experimental models, injury to the intervertebral disc was found to lead to histological bone marrow changes similar to MC [25, 45]. Second, MC most often occur after lumbar disc herniations [2].

In an MRI follow-up study, type I MC were found to be associated with bony endplate defects or irregularities at baseline and the decrease or enlargement in the type I lesions or conversion of type I into type II lesions was associated with an increase or change of the endplate

Table 4 Estimated haplotype frequencies for the *IL1A* c.1-889C>T, *IL1B* c.3954C>T, *IL1RN* c.812G>A, *IL1RN* c.1887G>C, *IL1RN* c.11100C>T, *IL1RN c.1506G>A* polymorphisms ($N = 216$)

Haplotype	Total		Modic changes					
			No		Any		Type II	
	N	Freq.	*N*	Freq.	*N*	Freq.	*N*	Freq.
2-2-2-1-1-2	45	0.206	27	0.214	18	0.196	16	0.200
1-1-1-2-2-1	41	0.188	22	0.175	19	0.207	17	0.213
1-1-2-1-2-2	40	0.183	26	0.206	14	0.152	12	0.150
1-1-2-1-1-2	36	0.165	25	0.198	11	0.120	11	0.138
2-1-2-1-2-2	9	0.041	5	0.040	4	0.043	3	0.038
2-2-2-1-2-2	9	0.041	3	0.024	6	0.065	6	0.075
2-1-2-1-1-2	7	0.032	1	0.008	6	0.065*	6	0.075**
Other	29	0.134	17	0.135	14	0.152	9	0.112

The common alleles of the SNPs are designated as 1; the rare alleles are designated as 2

* $p = 0.043$, OR = 8.72, 95% CI = 1.03–73.73, ** $p = 0.015$, OR = 10.13, 95% CI = 1.20–85.64

lesions [22], as well as with an accelerated progression of degeneration in the adjacent intervertebral disc [23]. The presence of Modic type I lesion and its change was found to be associated with the presence or change into an exceptionally bright signal intensity in the nucleus pulposus of the degenerated disc [23]. This is believed to be a radiological sign of an infectious process in its early phase. These findings could be explained not only by non-specific inflammatory changes but also by the common pathomechanism behind MC, disc degeneration, and irregularities and defects in the endplates and subchondral bone.

Ulrich et al. [45] observed that repeated stab injuries to rat discs induced chronic inflammation in the disc, with

elevated levels of TNF-α and IL-1β before Modic-type changes in the bone marrow appeared. Moreover, an increased number of TNF-α immunoreactive nerve cells and fibres have been found particularly in endplates with type I changes [30] suggesting an inflammatory component in the pathomechanism of MC. An inflammatory aetiology is supported by the finding that the level of high-sensitive CRP was higher among chronic LBP patients with type I MC than among LBP patients with type II changes or no changes [34]. C-reactive protein (CRP) is an acute-phase protein synthesized mainly in the liver and is largely regulated by circulating levels of IL-6, and also by TNFa and IL-1 [18].

IL-1 plays a central role in cartilage degradation through the inhibition of matrix synthesis and catabolism. In contrast, TNF-α seems to be a less potent inducer of matrix–enzyme expression than IL-1 [26]. Findings that the *IL1* gene cluster polymorphisms contribute to the pathogenesis of low-back pain and lumbar intervertebral disc degeneration [39, 40, 48] correlate with the observation that the TT genotype (-889) in the *IL1A* gene increases its transcriptional activity [8] and upregulates IL1-β expression [9]. Blocking of IL-1 has been observed to reduce bone erosions and cartilage degradation in experimental arthritis models [43], whilst both the IL-1α and IL-1β isoforms of IL-1 have been shown to increase proteoglycan release and degradative enzyme production in the intervertebral disc [24, 33]. It has been shown that human disc cells produce IL-1 in increasing amounts with the severity of degeneration, and that IL-1 treatment of disc cells results in increased gene expression of matrix-degrading enzymes [19, 20]. Therefore, it is plausible that IL-1 is involved in the pathomechanisms of MC, as appears on the basis of these genetic studies.

In summary, our observation of an association between *IL1A* gene variation and type II MC replicates a previous finding from a different Finnish geographic area, thus confirming the importance of the *ILA* gene in the pathophysiology of MC.

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