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INVESTIGATION OF THE ASSOCIATION OF THE CRTM AND CRTL1 GENES WITH RADIOGRAPHICALLY EVIDENT OSTEOARTHRITIS IN SUBJECTS FROM THE ROTTERDAM STUDY

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Objective. **To investigate whether radiographically evident osteoarthritis (ROA) in 55–65-year-old men and women is associated with specific alleles or genotypes of the cartilage matrix protein (CRTM) and cartilage link protein (CRTL1) genes.**

Methods. **Cases were selected from a population-based study on the presence of ROA of the knee or hip. Further radiographic analysis included scoring for spine and hand ROA. Controls, selected from the same population, were free of ROA in all joints.**

Results. **The CRTM locus was significantly associated with hip ROA in men (odds ratio 0.50, 95% confidence interval 0.26–0.95). A significant association between ROA and the CRTL1 gene was not observed.**

Conclusion. **These results suggest that the CRTM locus may play a role in the sex- and joint site–specific pattern of ROA development.**

Osteoarthritis (OA) is a degenerative disease of the joints, which is clinically characterized by local joint pain, stiffness, limitation in movement, and deformity. Pathologic changes, visible on radiographs, include osteophyte formation, joint space narrowing, bony sclerosis, and subchondral cysts. Although the relation between clinical signs and radiographic findings of OA is relatively poor (1,2), determination of the presence of the radiographic characteristics of OA is a widely used indication of OA pathogenesis in population-based studies.

The occurrence of radiographically evident OA (ROA) and the pattern of joint involvement is sex dependent. In general, ROA in multiple joints occurs more frequently in females than in males. Between the ages of 55 and 64 years, 47% of women and only 29% of men show ROA in 4 or more joints (3). Men more often have ROA in the hip joints, whereas in women, the joints of the hands and knees are most frequently affected (4,5).

A genetic influence in the onset of OA was first demonstrated by the finding of a significantly increased risk of OA in first-degree relatives of women with generalized OA (GOA; determined based on the presence of radiological signs of OA with a Kellgren-Lawrence grade [6] of ≥ 2 in 3 or more joint groups) in combination with Heberden's nodes (7). In a study of mono- and dizygotic female twins, Spector et al (8) reported a heritability estimate of 0.39–0.65 for different combinations of scores for osteophytes and joint space narrowing at hand and knee sites in women, indicating a genetic effect in the development of OA at these sites. These findings indicate that genetic predisposition may contribute importantly to ROA, but to a varying extent in men and women depending on the joint site(s) considered. The relevance of the genetic component

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varies among subgroups of patients, and it is as yet not clear which genes are involved.

Several association and sibling pair studies have investigated the possibility of predisposing type II procollagen gene (COL2A1) alleles in middle-aged patients with GOA (9–13). Results obtained in these studies, however, remain controversial and can explain only a fraction of the genetic component in OA. The contribution of other, noncollagenous, proteins of the extracellular matrix (ECM) to the etiology of ROA is an area of increasing interest. Genes encoding such proteins are the cartilage link protein (CRTL1) gene and the cartilage matrix protein (CRTM) gene. The cartilage link protein stabilizes proteoglycan aggregates by binding both to the proteoglycan core protein and to hyaluronic acid (14). The cartilage matrix protein is a component of cartilage collagen fibrils with an as-yet-unknown function (15). A study of these genes in a small number of sibling pairs (n = 38 pairs) expressing GOA and Heberden's nodes before the age of 60 years did not support any association between GOA and the CRTL1 or CRTM gene (12).

In the present study, we investigated whether alleles and/or genotypes of the dinucleotide repeat polymorphism in the 3′-untranslated region of CRTM (16) and in the promoter region of CRTL1 (17) are associated with ROA in 55–65-year-old male and female subjects, irrespective of possible manifestations of clinical OA. Cases (73 men and 107 women) had ROA in knee or hip joints and were stratified on the basis of ROA in hand joints. To maximize the difference between this case group and the control group, cases were compared with a control group (63 men and 72 women) consisting of subjects without any ROA at the joints assessed, i.e., knee, hip, hand, and spine.

PATIENTS AND METHODS

Subjects. We studied the association of the CRTM and CRTL1 genes with ROA in unrelated cases with ROA of the knee or hip joints and unrelated controls free of ROA in the knees, hips, hands, wrists, and thoracolumbar spine. Cases and controls were derived from a prospective population-based cohort study of determinants and prognosis of chronic diseases in the elderly (the Rotterdam study) (18). All residents of a suburb of Rotterdam who were age ≥55 years were invited to participate in the Rotterdam study. In total, 7,983 participants were examined. The response rate was 78%. Informed consent was obtained from all subjects, and the study was approved by the Medical Ethics Committee of the Erasmus University Medical School.

To distinguish genetic predisposition to ROA from other determinants, the current study was restricted to noninstitutionalized participants ages 55–65 years. Radiographs of the knees and hips had previously been scored in a random subset of 1,040 individuals in this age category (425 men and 615 women) (19). From this subset, the radiographs of the hands and thoracolumbar spine were scored for the presence of ROA. The present study utilized a case–control design in which the contrast between cases and controls was maximized with regard to ROA status. Cases included subjects with ROA in at least 1 or both knee joints (n = 36 men and 90 women) or 1 or both hip joints (n = 37 men and 17 women). Controls (n = 63 men and 72 women) from the subset of 1,040 individuals were included in the study on the basis of absence of ROA in all radiographed joints. Given the sex differences in prevalence and site-specific expression of ROA, the CRTM and CRTL1 gene associations with ROA were investigated in men and women separately. Furthermore, information on age (in years) and body mass index (BMI; measured as kg/m^2) was recorded.

Measurements. At the research center, weightbearing anteroposterior radiographs of the pelvis and knees, anteroposterior radiographs of the hands and wrists, and lateral radiographs of the spine (T4–S1) were obtained. ROA was assessed by the grading system proposed by Kellgren and Lawrence (6). All radiographs were scored by 2 independent readers who were blinded to all clinical data on the participant. When the scores differed by >2 points or one reader assigned a score of 1 and the other assigned a score of ≥2, a consensus score was agreed upon. For each individual joint, definite ROA was defined as a Kellgren-Lawrence score of ≥2. ROA of the hand was assessed individually in each inter- and metacarpophalangeal joint. For the carpometacarpal and intercarpal joints, only the first carpometacarpal and the trapezioscaphoidal joints were assessed. ROA of the wrist was assessed at the radiocarpal and distal radioulnar joints. Hand ROA was defined as a Kellgren-Lawrence score of ≥2 in at least 1 of the 36 joints that were scored (for this purpose, the joints of the wrist were included in the hand ROA category). For the spine, each individual level from T4 to S1 was scored with regard to osteophytes and disc space narrowing.

Genotyping. Genotypes of the dinucleotide repeat polymorphism in the 3′-untranslated region of the CRTM gene were determined as described by Wang et al (16). Genotypes of the CA-repeat polymorphism in the promoter region of the CRTL1 gene were determined as described by Hecht et al (17), using the nomenclature and allelic ladder also described by Hecht et al (17). Polymerase chain reaction (PCR) was performed in a reaction volume of 25 μl containing 25–50 ng genomic DNA; 2.5 pmoles of each primer; 1× Super *Taq* buffer (Sphaero Q; Leiden, The Netherlands); 2 μCi α^{32}P-dCTP; 200 μmoles each of dCTP, dGTP, dTTP, and dATP; and 0.05 units of Super *Taq* DNA polymerase (Sphaero Q). Amplification was initiated with 3 minutes denaturation at 94°C, followed by 35 cycles of 15 seconds at 94°C, 30 seconds at appropriate annealing temperature, and 30 seconds at 72°C. The amplification was completed by a final incubation at 72°C for 3 minutes. Alleles were separated by electrophoresis through a denaturing polyacrylamide gel (6%) and analyzed by autoradiography.

One of the extra alleles detected in our population (CRTL1 A9.3; see below) showed a small length variation to A10. This was confirmed by heteroduplex analysis of genotypes

containing CRTL1 A9.3 by denaturation of PCR products at 100°C for 5 minutes and re-annealing at room temperature for 1 hour. Heteroduplex patterns were analyzed by electrophoresis through 4–6% polyacrylamide gels and visualized by staining with ethidium bromide (20).

Statistical analysis. Demographic variables (age and BMI) were compared between cases and controls by using *t*-tests for independent samples. Allele frequencies for cases and controls were assessed by counting alleles and calculating sample proportions. Tests for goodness of fit into Hardy-Weinberg equilibrium were calculated using the HWE program (LINKUTIL package) (21). For the multiallelic CRTL1 marker, the alleles with an observed allele frequency of <0.05 were pooled and designated as allele AX. The likelihood ratio test was used to investigate association of CRTM and CRTL1 alleles with the occurrence of ROA (22). As an extension to this likelihood ratio test, a logistic regression model was used to adjust for covariables in the association between CRTM and CRTL1 alleles and ROA. The strength of association between an allele and the occurrence of ROA was estimated using the odds ratio (OR). Adjusted OR were calculated by logistic regression models with adjustment for age (in years) and BMI as continuous variables, after determining that age and BMI as categorized dummy variables in the model led only to trivial differences for the estimators of interest. OR are presented with 95% confidence intervals (95% CI). The SPSS statistical package was used, and *P* values less than 0.05 were considered significant.

RESULTS

Population description. Allele frequencies of dinucleotide repeat polymorphisms identified in the 3′-untranslated region of the CRTM gene (16) and in the 5′ promoter region of the CRTL1 gene (17) were determined in 73 men and 107 women with knee or hip ROA (cases) and 63 men and 72 women without ROA in the knee, hip, hand, or spine (controls). Table 1 shows the mean age and BMI of the men and women studied, and the number of individuals in each subgroup. The mean age and BMI of men and women with ROA differed significantly from the age and BMI of controls, except for the mean age of men with hip ROA and the mean BMI of women with hip ROA (Table 1). A difference in the frequency of ROA in specific joint sites among male and female cases is reflected in Table 1 as an excess of men in the hip ROA group (69%), with an OR (adjusted for age and BMI) of 2.6 (95% CI 1.3–5.3). In contrast, an excess of women in the knee ROA group (71%) and in the group with knee ROA in combination with hand ROA (76%) was observed (adjusted OR 1.9, 95% CI 1.1–3.4 and adjusted OR 4.0, 95% CI 1.9–8.3, respectively). The number of controls in the study population was small because only 135 individuals (of 1,040 55–65-year-old subjects) were free of ROA in all joints investigated.

Table 1. Baseline population characteristics of a random subset of 55–65-year-old subjects from the Rotterdam study*

Group	ROA cases		ROA controls (n = 135)
	Knee (n = 126)†	Hip (n = 54)‡	
Men			
Age, years	61.0 ± 0.3§	60.7 ± 0.4	59.6 ± 0.3
BMI, kg/m^2	26.8 ± 0.3¶	26.5 ± 0.4¶	25.3 ± 0.3
No. (% of total)	36 (29)	37 (69)	63 (47)
No. with hand ROA (% of knee or hip ROA)#	15 (42)	24 (65)	–
Women			
Age, years	60.7 ± 0.3§	60.9 ± 0.5¶	59.3 ± 0.3
BMI, kg/m^2	28.7 ± 0.4§	25.1 ± 0.5	24.9 ± 0.4
No. (% of total)	90 (71)	17 (31)	72 (53)
No. with hand ROA (% of knee or hip ROA)#	68 (76)	13 (76)	–

* Cases had radiographically evident osteoarthritis (ROA) of the knee or hip. Controls were included on the basis of absence of ROA at the knee, hip, hand, and spine. Unless otherwise indicated, values are the mean ± SEM. BMI = body mass index.
† Individuals with ROA exclusively in 1 or both knees.
‡ Individuals with ROA exclusively in 1 or both hips.
§ $P < 0.01$ versus controls.
¶ $P < 0.05$ versus controls.
# Men or women with hand ROA in addition to ROA of the knee or hip.

CRTM gene association. Allele frequencies of the dinucleotide repeat polymorphism in the 3′-untranslated region of the CRTM gene were determined as described by Wang et al (16). Table 2 shows overall allele frequencies, allele frequencies among men and women with ROA in the knee or hip (cases), and allele frequencies among those without ROA in any of the joint groups investigated (controls). In total, 3 alleles (A1–A3), similar to those described by Fujimori et al (23), were identified in 315 subjects. CRTM allele A4, previously described by Wang et al (16), was not observed in this population. Overall allele frequencies corresponded to those reported by Fujimori et al (23) and differed, especially for alleles A1 and A3, from those reported by Wang et al (16). The overall arrangement of alleles in genotypes in men and women was not significantly different from that expected for a population in Hardy-Weinberg equilibrium ($P = 0.30$ and $P = 0.38$, respectively). In addition, the subsequent Hardy-Weinberg equilibria tested for male and female cases and controls were not significant (male cases and controls $P = 0.60$ and $P = 0.61$, respectively; female cases and controls $P = 0.29$ and $P = 0.76$, respectively).

As seen in Table 2, there was an association of

Table 2. Allele frequencies of dinucleotide repeat polymorphism in the 3′-untranslated region of the cartilage matrix protein (CRTM) gene in ROA cases and in controls*

Group	Allele (length in bp)			No. of alleles	P†
	1 (110)	2 (108)	3 (106)		
Overall	0.59	0.34	0.07	630	
Men					
Controls	0.51	0.40	0.09	126	
Knee ROA	0.56	0.40	0.04	72	≥0.50
Hip ROA	0.66	0.26	0.08	74	0.04
Women					
Controls	0.61	0.35	0.04	144	
Knee ROA	0.62	0.31	0.07	180	≥0.50
Hip ROA	0.59	0.35	0.06	34	≥0.50

* See Table 1 for explanations and definitions.
† By likelihood ratio association test ($\Lambda = -2\text{Ln}[L(H_0)/L(H_1)]$), cases versus controls.

the CRTM polymorphism in men with hip ROA, as compared with controls ($P = 0.04$). This association was not observed in women. The contrast in men was caused by a decreased frequency of A2 in male cases with hip ROA and an increase of A2 in male controls, as compared with the overall frequency (which resembled the overall frequency reported by Fujimori et al [23]). The opposite was found for allele A1.

To estimate the strength of the association of the CRTM locus in men with hip ROA, the OR was calculated by entering the CRTM alleles into a logistic regression model. The corresponding crude OR for CRTM allele A2, with the most frequent allele (A1) as reference, for men with hip ROA was 0.50 (95% CI 0.26–0.95). Subsequent adjustment for age (OR 0.50, 95% CI 0.26–0.97) and BMI (OR 0.51, 95% CI 0.26–0.99) did not alter this effect, and there was no observed interaction of the variables tested. Since the ROA status of the control group was relatively rare in this age category of the general population (of whom only 13% had no ROA), the association was also tested by comparing men with hip ROA with a less stringently defined control group, men without hip ROA (i.e., controls plus cases with knee ROA). The corresponding OR (adjusted for age and BMI) was 0.53 (95% CI 0.29–0.97). The effect of the CRTM genotype A2/A2, as compared with A1/A1, among men with hip ROA was not significant (adjusted OR 0.32, 95% CI 0.07–1.41).

CRTL1 gene association. Allele frequencies of the CA-repeat polymorphism in the promoter region of the CRTL1 gene were determined, using nomenclature similar to that described by Hecht et al (17). Table 3 shows the frequencies of the most common alleles (>5%) for men and women in partitioned case and control groups. Overall allele frequencies were similar to those reported by Hecht et al (17). Five extra low-

Table 3. Allele frequencies of the dinucleotide repeat polymorphism in the promoter region of the cartilage link protein (CRTL1) gene in ROA cases and in controls*

Group	Allele (length in bp)							No. of alleles	P‡
	3 (236)	4 (234)	5 (230)	7 (226)	8 (225)	10 (222)	X†		
Overall	0.13	0.09	0.07	0.15	0.27	0.22	0.08	630	
Men									
Controls	0.13	0.12	0.06	0.10	0.33	0.18	0.07	126	
Knee ROA	0.15	0.14	0.10	0.06	0.26	0.22	0.07	72	≥0.50
Hip ROA	0.08	0.11	0.07	0.15	0.28	0.22	0.10	74	≥0.50
Women									
Controls	0.12	0.06	0.07	0.15	0.25	0.27	0.08	144	
Knee ROA	0.15	0.07	0.07	0.18	0.26	0.20	0.07	180	≥0.50
Hip ROA	0.12	0.09	0.00	0.21	0.29	0.27	0.03	34	≥0.50

* See Table 1 for explanations and definitions.
† Pooled low-frequency alleles.
‡ By likelihood ratio association test ($\Lambda = -2\text{Ln}[L(H_0)/L(H_1)]$), cases versus controls.

frequency alleles (CRTL1 alleles A0, A9.2, A9.3, A11, and A12; not shown in Table 3) were identified in our study population, whereas CRTL1 allele A9 was not detected. Overall Hardy-Weinberg equilibrium was calculated for CRTL1 genotypes with an expected value of ≥5 and was not statistically significant ($P = 0.87$). The findings of subsequent tests for Hardy-Weinberg equilibrium in male and female case and control groups were also not significant (male cases and controls $P = 0.22$ and $P = 0.80$, respectively; female cases and controls $P = 0.22$ and $P = 0.47$, respectively). The likelihood ratio disequilibrium test investigating nonrandom association of CRTL1 alleles with the occurrence of ROA did not show evidence for association of CRTL1 alleles with ROA in either men or women ($P \geq 0.50$; Table 3).

DISCUSSION

We investigated the role of the CRTM and CRTL1 gene loci in a population-based study of cases (age 55–65 years) with knee or hip ROA as compared with controls from the same population, without ROA in the knee, hip, hands, or spine. The allele frequencies of the dinucleotide repeat polymorphisms in the 3′-untranslated region of the CRTM gene in our study corresponded to those reported by Fujimori et al (23) and differed, especially with regard to alleles A1 and A3, from those reported by Wang et al (16). This may suggest that the Caucasian population described by Wang et al and colleagues was of a different origin (for example, with recent admixture) than the Caucasian populations in the present study and that of Fujimori and coworkers.

A significant association was found for the CRTM locus in the comparison of male controls and cases with hip ROA (OR 0.50, 95% CI 0.26–0.95). The fact that alleles A2 and A1 inversely contribute to the association may indicate that CRTM A2 is associated with a decreased risk for the development of hip ROA in men and A1 is associated with an increased risk, or that only one of the associations is true and the other is the consequence of compensating allele frequencies. The independent effect of these alleles could not be tested by exclusion of individuals with either CRTM A1 or A2 since the remaining number of individuals (carrying CRTM allele A3) was not sufficient. The likelihood ratio disequilibrium test did not show evidence for an association of CRTL1 alleles with ROA in either men or women ($P \geq 0.50$; Table 3).

A sibpair analysis of British siblings expressing GOA and Heberden's nodes before the age of 60 years (12) did not reveal associations between ROA and the CRTL1 or CRTM genes. That study, however, included a small number of sibpairs (n = 38 pairs) with a relatively severe disease subset, and the subjects were not stratified by sex. Furthermore, the control group was not selected based on absence of ROA, but consisted of randomly selected individuals without clinical joint disability. This is in contrast to the reference group in our study, which comprised 55–65-year-old subjects without ROA. The relatively strict selection criteria for our controls may have attenuated the association. In this age group the absence of ROA in all joint sites investigated is uncommon (only 13% of the cohort of 1,040 individuals).

In view of the presence of the CRTM protein in cartilage ECM and the close proximity of the dinucleotide repeat polymorphism to the gene, the reported association may be due to a role of this gene, and not another locus in linkage disequilibrium with the markers, in the etiology of ROA. However, since disease association studies are sometimes subject to false-positive results, the observed association requires confirmation in a second population-based sample. The association we have found follows the sex- and joint site–specific pattern of ROA development in the population. Typically, hip ROA is most frequently present in men in the 55–65-year age group (4,5). The observed association for this specific subgroup may be due to the larger number of individuals in this case group, or it may reflect a sex- and/or joint-specific effect of the allele on the development of ROA.

An effect of genetic variation at the CRTM locus on, especially, the development of hip ROA may be explained by the fact that the CRTM protein is expressed within the epiphyseal growth plate (postmitotic stages), during the process of endochondral bone formation (24,25). During this process, the length and shape of the bone are determined. Although the function of CRTM in epiphyseal cartilage remains unclear, it may affect the overall shape of the joint. Since ROA particularly of the hip is often considered to arise due to anatomic abnormalities (26), the possible effect of CRTM alleles on hip ROA might be exhibited in this way.

The results of this population-based study suggest that genotypic variation in the gene encoding CRTM may play a role in the etiology of ROA. This gene may contribute to a sex- and joint-site–specific pattern of ROA, but the nature of the effect of CRTM remains to be elucidated.

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