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Vitamin D receptor gene polymorphisms and osteoarthritis of the hand, hip, and knee: a case–control study in Japan

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Abstract

Objective. To investigate the association between vitamin D receptor (VDR) gene polymorphisms and Japanese female patients with osteoarthritis (OA) of the hand, hip, and knee.

Methods. *Bsm*I, *Apa*I, and *Taq*I restriction fragment length polymorphisms (RFLPs) of the VDR gene were analysed in 270 Japanese female patients with radiographic OA of the hand, hip, tibiofemoral (TF) joint, and patellofemoral (PF) joint, as well as in female controls.

Results. There was no significant association between the VDR gene RFLPs and OA of the hand, hip, TF joint, PF joint, or polyarticular involvement. The previously detected preventive genotype of the VDR gene was uncommon in our test population.

Conclusion. The relative importance of VDR gene polymorphism in the development of OA may vary between ethnic groups.

KEY WORDS: Osteoarthritis, Hand, Hip, Knee, Vitamin D receptor gene, Polymorphism.

Osteoarthritis (OA) is a common disease that is most prevalent in aged people [1]. It is considered to be a group of clinically heterogeneous disorders sharing common pathological features of articular cartilage loss and subchondral bone reaction. Although the aetiology of OA is unknown, abundant epidemiological evidence suggests the importance of genetic factors in some subgroups of OA, especially in hand and knee OA [2–6]. Until now, some candidate genes have been proposed in OA of the hand, hip, knee, spine, and polyarticular involvement [7–11].

Vitamin D receptor (VDR) gene polymorphism is known for its association with osteoporosis [12], and the inverse relationship between osteoporosis and OA suggests that VDR gene polymorphism might be associated with both diseases [13, 14]. Recent studies have revealed the association of VDR gene polymorphism with some OA sites. Uitterlinden *et al.* [15] demonstrated that VDR gene polymorphism is related to radiographic OA of the knee, especially in osteophyte formation, in subjects in The Netherlands. A study by Keen *et al.* [16] also showed that this gene influenced the risk of early knee OA within the British population and that it had no relationship with nodal arthritis. Jones *et al.* [17] reported that allelic variations of the VDR gene and lifestyle factors were both associated with the presence and severity of spinal degenerative disease. Aerssens *et al.* [18] and Tamai *et al.* [19] reported the lack of association between OA of the hip and VDR gene polymorphisms in Belgian women and Japanese women, respectively.

Since there are inter-racial differences in the frequency of distribution of VDR gene polymorphisms [12, 20, 21] and because previous reports suggest that its association with OA depends on the joints, the association between the VDR gene and OA of various joint sites should be examined in different races. In this study, we investigated the frequency distributions of the VDR gene *Bsm*I, *Apa*I, and *Taq*I restriction fragment length polymorphisms (RFLPs) in Japanese female patients with OA of the hand, hip, tibiofemoral (TF) joint, and patellofemoral (PF) joint, and compared them with those of Japanese female controls.

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Subjects and methods

Definition of radiographic OA

OA was defined radiographically using the Kellgren–Lawrence scale [22] as follows. Regarding hand OA, subjects with symmetrical polyarticular involvement of the interphalangeal joints of the hands, a characteristic feature of generalized OA, were chosen as having hand OA. Thus, hand OA was radiographically defined as having grade 2 or more changes according to the Kellgren–Lawrence scale in at least three interphalangeal joints of each hand in a radiograph of the hands (posteroanterior view), as previously described by others [23]. Hip OA, TF joint OA, and PF joint OA were

defined as having grade 2 or more changes according to the Kellgren–Lawrence scale in at least one side of the respective joint in radiographs of the pelvis (non-weight-bearing anteroposterior view) and knees (weight-bearing anteroposterior view and non-weight-bearing lateral view), respectively. Polyarticular OA was defined as having hand, hip, and TF OA.

Subjects with OA of each joint were further divided into two groups, mild and severe. Among patients with hand OA, those who showed grade 3 or more changes according to the Kellgren–Lawrence scale in one or more IP joints of each hand were defined as having severe hand OA. For the hip, TF, and PF joints, severe OA of the respective joint was defined as having grade 3 or more changes according to the Kellgren–Lawrence scale in at least one side of the respective joint. The remainder with OA were defined as having mild OA of the respective joint.

OA patients

Among consecutive female patients visiting our out-patient clinic between April 1996 and February 1999, 270 women (mean age 63.8 yr, range 29–87 yr) who were diagnosed as having radiographic OA in either the hand, hip, or TF joint were included in this study as cases. Four radiographs were taken for each case: the hands, the pelvis, and the knees as described above. One hundred and nine of them returned for a post-operative follow-up of orthopaedic surgery, of which 71 underwent hip surgery, 34 knee surgery, two spine surgery, and two both hip and knee surgery. The remaining non-operated patients visited our clinic for consultation regarding an operation, or with hip, knee, and hand complaints. The majority of women who had radiographic hand OA voiced minor complaints of hand symptoms. All radiographs were assessed by a single blind observer. If the patient had undergone surgery for the hip or knee, pre-operative radiographs of these joints were reviewed.

According to the definition of radiographic OA, 270 cases were classified into one or more of the following categories (Table 1): hand OA, 134 cases (mean age 66.6 yr, range 45–87 yr) with 38 mild cases and 96 severe cases; hip OA, 146 cases (mean age 62.8 yr, range 29–84 yr) with 21 mild cases and 125 severe cases; TF joint OA, 180 cases (mean age 67.6 yr, range 42–87 yr) with 58 mild cases and 122 severe cases; PF joint OA, 167 cases (mean age 67.6 yr, range 42–87 yr) with 108 mild cases and 59 severe cases; and polyarticular OA, 46 cases (mean age 68.8 yr, range 55–84 yr).

The height and body weight were measured for all OA subjects, but clinical evidence of nodes was not systematically recorded.

Control subjects

Women aged 60 yr or more, who were routine visitors to three municipal daycare centres for the elderly, located in our catchment population, and who responded to our invitation for a health check examination, were chosen as control subjects. They were not hospitalized,

TABLE 1. Case characteristics

Category	No. of cases	Age (yr) mean (range)	BMI (kg/m^2) mean (S.D.)	No. of subjects with hand OA		No. of subjects with hip OA		No. of subjects with TF OA		No. of subjects with PF OA		No. of subjects with polyarticular OA
				Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe	
Hand OA	134	66.6 (45–87)	24.3 (3.4)	38	96	15	43	31	70	63	34	46
Hip OA	146	62.8 (29–84)	23.7 (3.8)	22	36	21	125	38	46	48	25	46
TF OA	180	67.6 (42–87)	24.7 (3.7)	31	70	21	63	58	122	96	59	46
PF OA	167	67.6 (42–87)	24.7 (3.6)	30	67	19	54	39	116	108	59	41
Polyarticular OA	46	68.8 (55–84)	24.1 (3.6)	17	29	15	31	18	28	27	14	46

BMI, body mass index; TF, tibiofemoral; PF, patellofemoral; S.D., standard deviation; OA, osteoarthritis.

had independent daily lives, and were able to walk without support. Medical history-taking, measurements of body weight and height, and a physical examination were performed. Rheumatic complaints were systematically recorded by joint site on a chart. The presence and severity of bony swelling in the interphalangeal joints were clinically assessed by a single observer, according to the previous report by Hart *et al.* [24]. The grades of clinical nodes were defined as follows: grade 0, no bony swelling; grade 1, possible bony swelling; grade 2, definite bony swelling, not severe; grade 3, severe bony swelling but no deformity; grade 4, severe bony swelling with deformity [24]. Having clinical nodes was defined as having at least one joint of grade 2 or more. Radiographs were not taken of the control subjects.

Women with a history of rheumatoid arthritis or other inflammatory joint disease were excluded from this study. A total of 161 women (mean age 72.2 yr, range 60–90 yr) were included in the study and placed into at least one of the following control groups. Of these, 127 women without clinical nodes of the hands were chosen as the controls for hand OA, 158 without present hip pain were chosen as the controls for hip OA, and 105 without present knee pain were chosen as the controls for both TF and PF OA. Eighty-eight women in whom clinical nodes of the hands were absent, and who had no present pain in either the hip or knee, were chosen as the controls for polyarticular OA. The characteristics of the control subjects are shown in Table 2.

Analysis of VDR gene polymorphisms

Peripheral blood was collected from the 270 cases and 161 control subjects. Analysis of VDR gene RFLPs was performed according to the method of the previous report, with a slight modification [21]. Briefly, 100 ng of genomic DNA, extracted from peripheral blood, was amplified by polymerase chain reaction (PCR) using specific primers in the same PCR conditions [21]. The amplified PCR product was digested with restriction endonucleases *Bsm*I, *Apa*I, and *Taq*I (Nippongene, Tokyo, Japan) and electrophoresed on a 1.0% agarose gel. The RFLPs were represented by Bb (*Bsm*I), Aa (*Apa*I), and Tt (*Taq*I) with upper- and lower-case letters signifying the absence or presence of restriction sites, respectively.

Statistical analysis

An odds ratio (OR) and 95% confidence interval (CI) were calculated with respect to the presence of the reference VDR genotype as compared with other genotypes. A multivariate analysis using logistic regression was performed to control for body mass index. The software used for this analysis was SPSS (SPSS Inc., Chicago, IL, USA).

Results

The frequencies of *Bsm*I, *Apa*I, and *Taq*I RFLPs of the VDR gene in the control subjects were similar to those previously described for Japanese women [20] and essentially obeyed the Hardy–Weinberg law.

There was no significant difference in VDR genotype frequency in each *Bsm*I, *Apa*I, and *Taq*I site between the control and each OA group: OA of the hand, the hip, the TF joint, and the PF joint (Table 3). Furthermore, no significant difference could be found when the patients with polyarticular OA were compared with the controls (Table 4). The distribution of the VDR genotypes by a combination of *Bsm*I, *Apa*I, and *Taq*I sites also revealed no significant differences between the controls and OA of various sites (Tables 5 and 6). Mild and severe OA cases were compared with the controls separately, again yielding no significant differences (data not shown).

VDR genotypes 'bb' and 'bbaaTT', which were reported as the preventive genotypes for osteoporosis in Japanese pre-menopausal women [20], did not reveal any association for any site of OA.

In a separate analysis, both VDR genotypes and body mass index were included as dependent variables in a logistic regression model to control for body mass index. However, the results were essentially similar to those without adjusting for obesity (data not shown).

Discussion

In this study, we failed to find any significant relationship between VDR gene polymorphism and OA in Japanese women. In the study in The Netherlands, which included both men and women, the 'baT' haplotype was over-represented and the 'bAT' haplotype under-represented

TABLE 2. Control characteristics

Category	No. of subjects	Age (yr) mean (range)	BMI (kg/m^2) mean (S.D.)	No. of subjects with clinical nodes	No. of subjects with hip pain	No. of subjects with knee pain
Controls for hand OA	127	71.7 (60–90)	23.6 (3.5)	0	0	39
Controls for hip OA	158	72.2 (60–90)	23.7 (3.3)	31	0	56
Controls for TF/PF OA	105	72.2 (60–90)	23.2 (3.2)	17	3	0
Controls for polyarticular OA	88	71.8 (60–90)	23.1 (3.2)	0	0	0

BMI, body mass index; TF, tibiofemoral; PF, patellofemoral; OA, osteoarthritis; S.D., standard deviation.

TABLE 3. Frequency of vitamin D receptor (VDR) genotype distribution in female patients with hand osteoarthritis (OA), hip OA, tibiofemoral (TF) OA and patellofemoral (PF) OA

VDR genotypes		Hand OA (generalized OA)			Hip OA			TF OA			PF OA		
		Controls *n* (%)	Cases *n* (%)	OR (95% CI)	Controls *n* (%)	Cases *n* (%)	OR (95% CI)	Controls *n* (%)	Cases *n* (%)	OR (95% CI)	Controls *n* (%)	Cases *n* (%)	OR (95% CI)
*Bsm*I	BB	0 (0.0)	0 (0.0)	NC	0 (0.0)	1 (0.7)	NC	0 (0.0)	0 (0.0)	NC	0 (0.0)	0 (0.0)	NC
	Bb	26 (20.5)	27 (20.1)	0.98 (0.54, 1.79)	31 (19.6)	30 (20.5)	1.06 (0.60, 1.86)	18 (17.1)	32 (17.8)	1.05 (0.55, 1.97)	18 (17.1)	25 (15.0)	0.85 (0.44, 1.65)
	bb	101 (79.5)	107 (79.9)	1.02 (0.56, 1.87)	127 (80.4)	115 (78.8)	0.91 (0.52, 1.58)	87 (82.9)	148 (82.2)	0.96 (0.51, 1.81)	87 (82.9)	142 (85.0)	1.18 (0.61, 2.28)
*Apa*I	AA	11 (8.7)	12 (9.0)	1.04 (0.44, 2.44)	11 (7.0)	16 (11.0)	1.64 (0.74, 3.67)	7 (6.7)	14 (7.8)	1.18 (0.46, 3.03)	7 (6.7)	11 (6.6)	0.99 (0.37, 2.63)
	Aa	55 (43.3)	66 (49.2)	1.27 (0.78, 2.07)	71 (44.9)	63 (43.2)	0.93 (0.59, 1.46)	44 (41.9)	75 (41.6)	0.99 (0.61, 1.61)	44 (41.9)	69 (41.3)	0.98 (0.59, 1.60)
	aa	61 (48.0)	56 (41.8)	0.78 (0.48, 1.27)	76 (48.1)	67 (45.8)	0.92 (0.58, 1.44)	54 (51.4)	91 (50.6)	0.97 (0.60, 1.56)	54 (51.4)	87 (52.1)	1.03 (0.63, 1.67)
*Taq*I	TT	102 (80.3)	109 (81.4)	1.07 (0.58, 1.98)	128 (81.0)	118 (80.8)	0.99 (0.56, 1.75)	88 (83.8)	149 (82.8)	0.93 (0.49, 1.77)	88 (83.8)	140 (83.8)	1.00 (0.52, 1.94)
	Tt	25 (19.7)	24 (17.9)	0.89 (0.48, 1.66)	30 (19.0)	27 (18.5)	0.97 (0.54, 1.72)	17 (16.2)	30 (16.7)	1.04 (0.54, 1.98)	17 (16.2)	26 (15.6)	0.95 (0.49, 1.86)
	tt	0 (0.0)	1 (0.7)	NC	0 (0.0)	1 (0.7)	NC	0 (0.0)	1 (0.6)	NC	0 (0.0)	1 (0.6)	NC

OR, odds ratio; 95% CI, 95% confidence interval; NC, not calculated. OR value for not having each reference genotype is 1.

TABLE 4. Frequency of vitamin D receptor (VDR) genotype distribution in patients with polyarticular osteoarthritis (OA)

VDR genotypes		Controls *n* (%)	Cases *n* (%)	OR (95% CI)
*Bsm*I	BB	0 (0.0)	0 (0.0)	NC
	Bb	15 (17.0)	7 (15.2)	0.87 (0.33, 2.32)
	bb	73 (83.0)	39 (84.8)	1.14 (0.43, 3.04)
*Apa*I	AA	7 (8.0)	5 (10.9)	1.41 (0.42, 4.72)
	Aa	36 (40.9)	24 (52.1)	1.58 (0.77, 3.23)
	aa	45 (51.1)	17 (37.0)	0.56 (0.27, 1.16)
*Taq*I	TT	74 (84.1)	40 (87.0)	1.26 (0.45, 3.54)
	Tt	14 (15.9)	6 (13.0)	0.79 (0.28, 2.22)
	tt	0 (0.0)	0 (0.0)	NC

OR, odds ratio; 95% CI, 95% confidence interval; NC, not calculated. OR value for not having each reference genotype is 1.

in OA of the TF joint [15], while in the British study, the risk of TF joint OA was associated with the presence of the 'T' allele in women [16]. Neither VDR genotype was related to TF OA in this study. Furthermore, we also could not find any significant relationship between VDR gene polymorphism and OA of the hand, hip, PF joint, or polyarticular involvement. Our results for hip OA were in accordance with previous studies in Belgium and Japan [18, 19].

In previous TF OA studies, cases were sampled from the general population, whereas our study was of hospital attenders, which resulted in a greater percentage of symptomatic and severe cases being included, causing the inevitable selection bias to occur. Spector *et al.* noted that the prevalence of symptomatic knee OA was only 2.3 per 100 compared with that of radiographically defined knee OA which was 17 per 100 [25]. From those results, the majority of radiographically detected cases from general population samples may be asymptomatic. Interestingly, increasing osteophytosis was not associated with a worsening of symptoms or function in the study by Ledingham *et al.* [26]. In previous studies, the association between the VDR gene and TF OA appeared to be related to osteophyte presence rather than cartilage loss [15, 16]. Taken together, it is possible to speculate that VDR gene polymorphism may not be related to progression or severe cases of TF OA.

In the present study, radiographs were not taken for the control subjects, possibly weakening its statistical power, and we did not control for possible confounders, such as occupation and sports activity. We believe, nevertheless, that these limitations did not influence the nature of our study results. To detect a three-fold increased risk of OA, with the chance of not detecting the relative risk as significant being 0.2 (type II error rate), the required sample sizes [27] in the Japanese population are estimated to be from 54 (for genotype 'Aa') to 124 (for genotype 'TT'), except for genotypes 'BB' and 'tt' which were extremely rare in our population. In consideration of the required sample sizes, it would appear that the study was adequately powered to detect an effect attributable to the *Apa*I locus but not the *Bsm*I nor *Taq*I loci. Given that the 'T' allele is responsible for developing OA with a prevalence of knee

TABLE 5. Combination of *Bsm*I, *Apa*I, and *Taq*I restriction fragment length polymorphisms (RFLPs) of the vitamin D receptor (VDR) gene in female patients with hand osteoarthritis (OA) hip OA, tibiofemoral (TF) OA and patellofemoral (PF) OA

VDR genotypes	Hand OA (generalized OA)			Hip OA			TF OA			PF OA		
	Controls *n* (%)	Cases *n* (%)	OR (95% CI)	Controls *n* (%)	Cases *n* (%)	OR (95% CI)	Controls *n* (%)	Cases *n* (%)	OR (95% CI)	Controls *n* (%)	Cases *n* (%)	OR (95% CI)
bbaaTT	60 (47.2)	56 (41.9)	0.80 (0.49, 1.31)	75 (47.5)	65 (44.5)	0.89 (0.57, 1.40)	53 (50.4)	90 (50.0)	0.98 (0.61, 1.59)	53 (50.4)	87 (52.1)	1.07 (0.65, 1.74)
BBAAtt	0 (0.0)	0 (0.0)	NC	0 (0.0)	1 (0.7)	NC	0 (0.0)	0 (0.0)	NC	0 (0.0)	0 (0.0)	NC
bbAATT	3 (2.4)	7 (5.2)	2.28 (0.58, 9.01)	3 (1.9)	6 (4.1)	2.21 (0.54, 9.02)	2 (1.9)	10 (5.6)	3.03 (0.65, 14.1)	2 (1.9)	9 (5.4)	2.93 (0.62, 13.9)
BbAaTt	17 (13.4)	18 (13.4)	1.00 (0.49, 2.05)	22 (13.9)	18 (12.3)	0.87 (0.45, 1.70)	12 (11.4)	24 (13.3)	1.19 (0.57, 2.50)	12 (11.4)	21 (12.6)	1.11 (0.52, 2.37)
bbAaTT	38 (29.9)	42 (31.3)	1.07 (0.63, 1.81)	49 (31.0)	42 (28.8)	0.90 (0.55, 1.47)	32 (30.5)	46 (25.6)	0.78 (0.46, 1.34)	32 (30.5)	43 (25.7)	0.79 (0.46, 1.36)
BbAATt	8 (6.3)	3 (2.2)	0.34 (0.09, 1.31)	8 (5.1)	7 (4.8)	0.94 (0.33, 2.67)	5 (4.8)	4 (2.2)	0.45 (0.12, 1.73)	5 (4.8)	2 (1.2)	0.24 (0.05, 1.27)
Others	1 (0.8)	8 (6.0)	—	1 (0.6)	7 (4.8)	—	1 (1.0)	6 (3.3)	—	1 (1.0)	5 (3.0)	—

OR, odds ratio; 95% CI, 95% confidence interval; NC, not calculated. OR value for not having each reference genotype is 1.

TABLE 6. Combination of *Bsm*I, *Apa*I, and *Taq*I restriction fragment length polymorphisms (RFLPs) of the vitamin D receptor (VDR) gene in female patients with polyarticular osteoarthritis (OA)

VDR genotypes	Controls *n* (%)	Cases *n* (%)	OR (95% CI)
bbaaTT	44 (50.0)	16 (34.8)	0.53 (0.26, 1.11)
BBAAtt	0 (0.0)	0 (0.0)	NC
bbAATT	2 (2.3)	3 (6.5)	3.00 (0.48, 18.6)
BbAaTt	9 (10.2)	3 (6.5)	0.61 (0.16, 2.38)
bbAaTT	27 (30.7)	19 (41.4)	1.59 (0.76, 3.34)
BbAATt	5 (5.7)	2 (4.3)	0.76 (0.14, 4.05)
others	1 (1.1)	3 (6.5)	—

OR, odds ratio; 95% CI, 95% confidence interval; NC, not calculated. OR value for not having each reference genotype is 1.

OA, at least TF joint OA should have been much higher in our population than in Europe, because the previously detected preventive genotype 'tt' was hardly detectable in our population. However, the population-based radiographic study of knee OA in Japan did not show a significant difference from those in Europe and North America. For example, the prevalence of knee OA, defined as having grade 2 or more changes by the Kellgren–Lawrence scale, among women aged between 55 and 64 yr was 7.3% in US National Health Surveys [28], 18.6% in the Zoetermer Community Survey in The Netherlands [29], and 9.8% in the Japanese study [30]. It is therefore probable that VDR gene polymorphism is in linkage disequilibrium with a nearby susceptibility locus, and the strength of the relationship between the VDR gene and OA may vary between ethnic groups.

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