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ORIGINAL PAPER

Association of oestrogen receptor gene polymorphism with the long-term results of rotational acetabular osteotomy

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Abstract Acetabular dysplasia (AD) contributes to the development of osteoarthritis of the hip. A rotational acetabular osteotomy (RAO) is one of the methods of pelvic osteotomy to prevent or treat secondary osteoarthritis of the hip. Although most of the patients that undergo RAO show satisfactory results, some have poor results. This study investigated whether gene polymorphisms of both the vitamin D receptor (VDR) and oestrogen receptor (ER) are involved in both AD and the postoperative results following RAOs. Sixty-four Japanese patients with AD who were treated by an RAO were enrolled in this study (59 women and 5 men, aged 13–59, with an average age of 40.3). Gene polymorphisms of the VDR [ApaI and TaqI restriction fragment length polymorphisms (RFLPs)] and ER (PvuII and XbaI RFLPs) were determined in these patients. The relationship between both the AD and radiographic postoperative changes of the hip joint after an RAO with these gene polymorphisms were examined. The frequencies of ER gene polymorphism coded as pp (RFLP/PvuII) in patients with AD were statistically significantly different (p=.011) from those coded as both PP and Pp. The joint space width narrowed even after RAO in 90% of the patients with the pp gene polymorphism, while it narrowed in only 35% of the patients with either PP or Pp seven years or longer after an RAO. The PvuII polymorphism in the ER gene was associated with the postoperative result of an RAO, while no association was observed between the AD with VDR and ER gene polymorphisms.

Résumé La dysplasie acétabulaire (AD) contribue à l'apparition d'une arthrose de hanche. L'ostéomie de rotation acétabulaire (RAO) est une des méthodes d'ostéotomie pelvienne pouvant prévenir ou traiter cette arthrose de hanche. Cependant, si la plupart des patients qui ont bénéficié d'une RAO montrent des résultats satisfaisants, certains ont de mauvais résultats. Cette étude a pour but d'analyser l'influence du polymorphisme génique sur le récepteur de la vitamine D (VDR) et sur le récepteur d'oestrogène (ER), afin d'analyser son influence sur la dysplasie acétabulaire et sur les résultats de l'ostéotomie de rotation acétabulaire. Méthode : 64 patients originaires du Japon présentant une dysplasie de hanche ont été traités par une RAO et inclus dans cette étude, 59 ,femmes et 5 hommes âgés de 13 à 59 ans (âge moyen 40,3 ans). Le polymorphisme génique de la VDR (Apa I et Taq I avec diminution de la longueur du bras Apa I et Taq I (RFLPs) sur le récepteur d'oestrogène ER (Pvu II et Xba I RFLPs) ont été analysés. La relation entre dysplasie acétabulaire et les modifications post-opératoires de la hanche après ostéotomie et le polymorphisme génique ont également été étudiées. Résultat : la fréquence du polymorphisme génique du récepteur de l'oestrogène (pp RFLP/Pvu II) chez ces patients présentant une dysplasie acétabulaire est statistiquement et significativement différent des patients codés PP et Pp. L'espace articulaire est souvent diminué

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après RAO pour 90% des patients présentant un polymorphisme génique avec pp alors qu'il est simplement réduit chez 35% des patients présentant un polymorphisme PP ou Pp 7 ans ou plus après l'ostéotomie. En conclusion, le polymorphisme génique des récepteurs de l'oestrogène PvuII peut être associé avec un bon résultat post-opératoire de RAO, alors qu'aucune relation n'a pu être observée entre la dysplasie acétabulaire et un polymorphisme génique portant sur VDR et ER.

Introduction

Acetabular dysplasia (AD) is a developmental disorder and an important cause of childhood disability. It is a gradually progressive disease that frequently occurs in women [40]. Ethnic variation in the prevalence of AD and hip osteoarthritis (hip OA) has been reported, with a notably higher rate in Japanese women [42]. The acetabular dimensions of the Japanese are shallower than those of the British. However, hip OA in the British occurs more frequently than in the Japanese [43].

It has been suggested that primary hip OA occurs as a consequence of AD in some patients. Approximately 7–25% of white people over the age of 55 have hip OA. The prevalence of hip OA appears to be lowest in Americans, followed by black African and native American populations and is highest in white Europeans [13, 34]. This disorder underlies approximately 10% of all primary hip replacements and approximately 30% of those in patients aged 60 years and younger [14].

AD patients show varying degrees of dysplasia from a mildly dysplastic hip that is unicentrically located and stable to a severely dysplastic and dislocated hip [3]. While a severely dysplastic and dislocated hip is a high risk factor for developing hip OA, the association between a mildly dysplastic but stable hip, which shows an intact Shenton's line, and hip OA in adult life remains controversial [11].

A genetic aetiology of AD has been suggested [40]. Genetic variation in hormone-related genes may represent a possible determinant of the risk or severity, especially when considering the possible effect of joint laxity on AD [2]. In Caucasians, oestrogen receptor (ER) and vitamin D receptor (VDR) gene polymorphism may be associated with AD, although no statistical significance has been observed [19]. An rotational acetabular osteotomy (RAO) is frequently performed to treat patients with symptomatic AD who show less than 20° of centre-edge (CE) angle to forestall the expected progress of degenerative change of the hip joint [25–27]. Although most of the patients that undergo RAOs show satisfactory results, some have poor results, as described below [27].

A large number of epidemiological studies have suggested that hereditary factors play important roles in osteoporosis and osteoarthritis [1, 9, 15, 20, 22–24, 36]. Among them, gene polymorphisms of both the VDR and ER have been reported to be involved in not only bone and cartilage development but also in their disorders [31]. This study investigated whether gene polymorphism of the VDR and ER are associated with AD and the radiographic postoperative changes following an RAO.

Patients and method

This study was approved by the Institutional Research Committee. Among 176 patients who underwent an RAO for symptomatic AD from 1989 to 2001, 64 patients who consented to this gene polymorphism analysis were enrolled in this study. The characteristics of the subjects of this study are shown in Table 1. All of the subjects in this study had symptomatic AD with a CE angle of less than 20°. The patients included 59 women and five men ranging in age from 13 to 59 years (mean: 40.3 years). The radiographic classification of the degenerative changes of the hip joint was defined by Tönnis [33]. In grade 0, there were no degenerative changes, although there was AD and incongruity of the hip. Grade 1 showed a slight loss of the joint space, widened zone of sclerosis and minimal formation of osteophytes. In grade 2, a moderate loss of joint space and cysts involving the femoral head and/or the acetabulum were observed. Grade 3 showed large cysts with either a gross narrowing or obliteration of the joint space.

The surgical technique for RAO has been previously reported [27]. An anterior curved skin incision was made from below the iliac crest towards the distal aspect of the greater trochanter and the hip was exposed in an anteroposterior direction. The gluteus medius and the tensor fascia lata were detached from the ilium minimally to approach the superior aspect of the acetabulum. The base of the pubic bone was exposed between the anterosuperior and anteroinferior iliac spines to avoid damage to the lateral femoral cutaneous nerve. The posterior border of the gluteus medius was separated from the anterior border of the gluteus maximus after dissection of the tensor fascia lata. The short external rotators were detached, except for the quadratus femoris, in order to maintain the blood supply to the femoral head, and the posterior portion of the acetabulum was exposed. The osteotomy was performed using an osteotome 1.5 cm away from the acetabular rim with great care to avoid penetrating the joint. The inner wall of the ilium was penetrated using a curved osteotome. The femoral head was covered by rotating the acetabulum inferolaterally. Two or three pieces of 5-mm thick cortical bone graft were inserted into the gap between the

Table 1 Basal characteristics of the study subject at the time for the operation

	Total (64)	Grade 0 (12)	Grade 1 (15)	Grade 2 (37)	*p* for trend
Sex (F:M)	59:5	12:0	13:2	37:2	
Age (years)	40.3 (11.2, 13-59)	29.1 (13.9, 13-49)	35.7 (8.2, 21-52)	45.7 (7.3, 31-59)	.000
		p=.000[a]	p=.000[a]		
CE angle (º)	3.3 (11.5, -34-20)	-0.5 (15.3, -31-11)	2.8 (12.0, -34-15)	4.7 (9.8, -17-20)	.740
AHI (%)	55.3 (11.7, 10-78)	52.4 (17.3, 10-69)	55.4 (11.6, 22-73)	56.3 (9.7, 34-78)	.995
JSW (mm)	3.1 (2.0, 0-7.0)	4.9 (1.2, 4.0-7.0)	4.8 (1.1, 2.0-6.0)	2.0 (1.5, 0-6.0)	.000
		p=.000[a]	p=.000[a]		

Data indicate means (SD, lower-upper). Radiographic classification of degenerative changes of hip joints with acetabular dysplasia was based on Tönnis [33]

CE angle centre-edge angle, *AHI* acetabular femoral head index, *JSW* joint space width

[a] Mann-Whitney test with Sidak adjustment

osteotomised surfaces together with the cancellous bone chips. The rotated acetabulum and the bone grafts were fixed to the ilium using two 2-mm diameter Kirschner wires. The abductor muscles were then re-sutured to the iliac crest. The patients were permitted to transfer to a wheelchair at two weeks after surgery. Walking on crutches with non-weight-bearing, partial weight-bearing and full-weight-bearing were allowed at three weeks, two months and four to six months postoperatively, respectively.

The patients were divided into three groups based on the postoperative radiographic changes of the joint (Fig. 1). The CE angle, the acetabular femoral head index (AHI) and the joint space width (JSW) on radiographic images were measured before and immediately after the operation and during follow-up [27]. The cases with preserved joint space width and sufficient remodelling of the articular surface were designated the "improvement group"; cases with no change in the joint space width after surgery were designated the "non-progression group"; and cases in which joint space width was narrowed after surgery were designated the "progression group" [27].

The gene analysis was conducted using 10 ml of peripheral blood collected after obtaining the written consent of the patients. Genomic DNA was extracted by the standard method and amplified by polymerase chain reaction (PCR), as reported previously [36]. DNA fragments including the ApaI and TaqI restriction sites in intron 8 and exon 9 in the VDR gene and the PvuII and XbaI restriction sites in intron 1 in the ER gene were amplified using the PCR [36]. The PCR product of the VDR gene (0.74 kb) was digested with restriction endonuclease (ApaI and TaqI) and separated by electrophoresis in 2% agarose gel. The PCR product of the ER gene (1.3 kb) was digested with restriction endonuclease (PvuII and XbaI) and separated by electrophoresis in 2% agarose gel. The restriction fragment length polymorphisms (RFLPs) were coded as Aa (ApaI), Tt (TaqI), Pp (PvuII), or Xx (XbaI), where the upper-case letter signifies absence of the site and lowercase signifies presence of the site.

Statistical analysis

The frequency of each gene polymorphism in the patients with AD was compared with that of normal controls using the chi-square independence test. The normal controls for VDR and ER gene polymorphisms were from the study by Tokita et al. [36] and that by Kobayashi et al. [20], respectively.

The relationship between the postoperative radiographic evaluation and gene polymorphisms was initially analysed by variance analysis (Kruskal-Wallis test) and subsequently by the multiple comparison test (Mann-Whitney U test) in the cases showing significant differences in the variance analysis.

A p value of less than 0.05 was considered to be statistically significant. These analyses were performed using SPSS v.16 (SPSS Inc., Chicago, IL, USA).

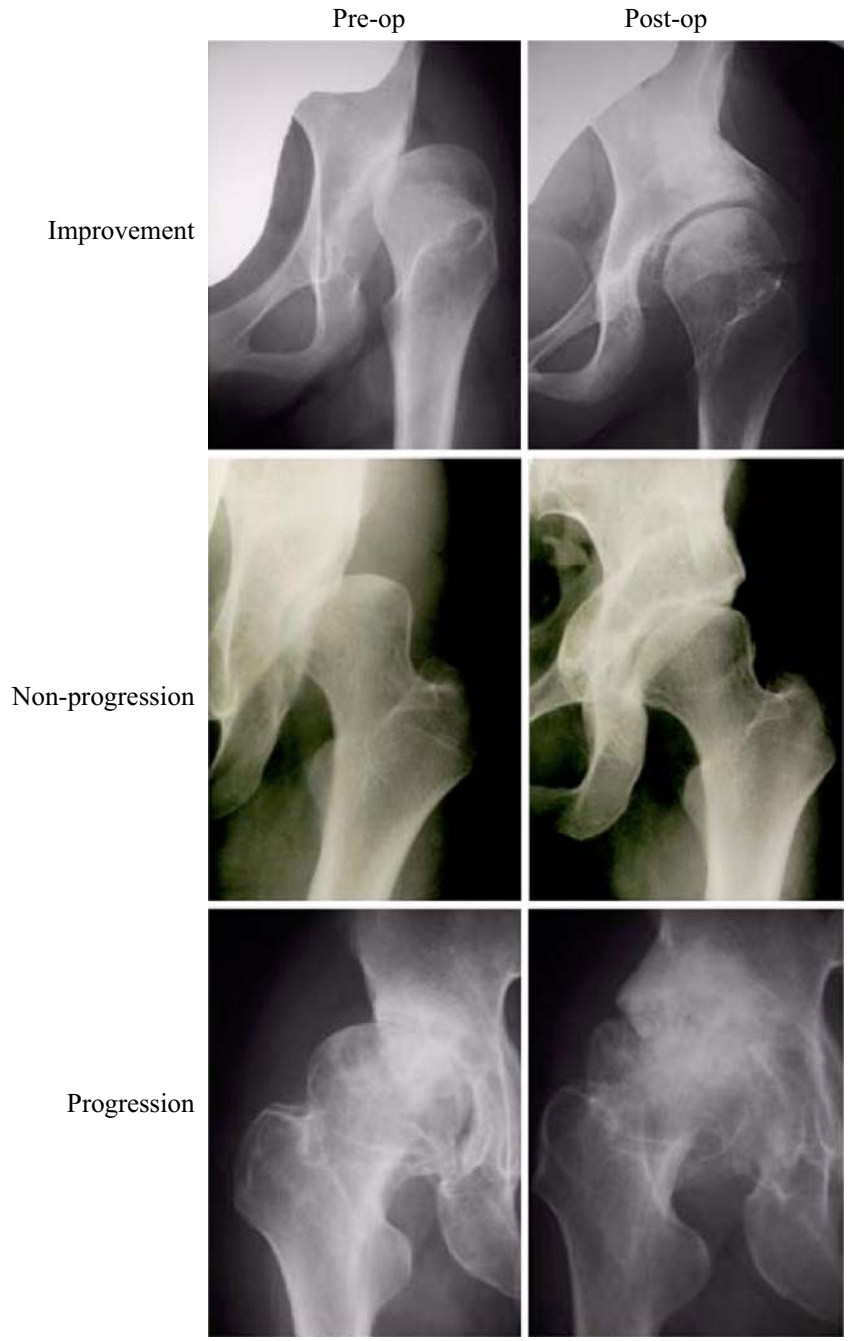

Fig. 1 The classification of the postoperative radiographic changes of the hip joint after rotational acetabular osteotomy (RAO)

Results

Radiographic classification of the degenerative changes of the hip joint of the patients with AD revealed that 12 patients were grade 0, 15 grade 1 and 37 grade 2 at the time of operation. The patients in group 2 were older than those in both grades 0 and 1 (Table 1, $p<.000$). The joint space widths in grade 2 were significantly reduced in comparison to those in both groups 0 and 1 (Table 1, $p<.000$).

The frequencies of the VDR RFLPs ApaI ($p=.082$) and Taq I ($p=.271$) and the ER RFLPs PvuII ($p=.065$) and Xba I ($p=.258$) did not show significant differences between the patients with AD and the standard Japanese population (Table 2). In addition, no differences of the frequencies of these gene polymorphisms were observed between the groups divided by the radiographic classifications of the degenerative changes of hip joint with AD (Table 3, $p=.438$ for Apa I, .319 for TaqI, .241 for PvuII, .260 for XbaI).

The subjects were divided into three groups by the radiographic postoperative changes of the hip joint, as shown in Table 4. No statistical differences were observed in the follow-up periods after the operation between these three

Table 2 Frequencies of gene polymorphisms of the subjects with acetabular dysplasia

		Acetabular dysplasia (64)	Control (488)	*p*
Vitamin D receptor gene polymorphism				
ApaI	AA	7 (10.9%)	42 (13.3%)	.082
	AB	27 (42.2%)	235 (40.0%)	
	BB	30 (46.9%)	211 (46.7%)	
		64 (100%)	488 (100%)	
TaqI	TT	47 (66.7%)	375 (76.8%)	.271
	Ta	15 (23.4%)	106 (21.7%)	
	aa	2 (3.1%)	7 (1.4%)	
		64 (100%)	488 (100%)	
Oestrogen receptor gene polymorphism				
PvuII	PP	17 (26.6%)	46 (19.3%)	.065
	Pp	31 (48.4%)	122 (51.3%)	
	pp	16 (25.0%)	70 (29.4%)	
		64 (100%)	238 (100%)	
XbaI	XX	6 (9.4%)	7 (2.9%)	.258
	Xx	14 (21.9%)	77 (32.4%)	
	xx	44 (68.8%)	154 (64.7%)	
		64 (100%)	238 (100%)	

Statistical analysis was conducted using the chi-square independence test. The normal controls for vitamin D receptor and oestrogen receptor were from the studies by Tokita et al. [36] and Kobayashi et al. [20], respectively

groups (Table 4, p=.840). The distributions of the radiographic stages of AD in the non-progression group were statistically different from those in both the improvement (p=.011) and progression groups (p=.021) (Table 4), while no significant differences were observed in the preoperative radiographic evaluations, such as CE angle (p=.999), AHI (p=.920) and JSW (p=.160), between these three groups (Table 4). The postoperative CE angles in the progression group were statistically reduced in comparison to those in the improvement group (Table 4, p=.013). The postoperative AHI and JSW in the progression groups were significantly reduced in comparison to those in both the improvement (p=.008) and non-progression groups (p=.025; Table 4). These results were consistent with a previous study in which an enlarged coverage of the acetabular roof was an important factor for the prevention of the progress of degenerative change of the hip joint [26].

Next, to examine the effects of the VDR and ER gene polymorphisms for the postoperative X-ray changes of the hip joint after RAO, in addition to the sufficient coverage of the acetabular roof by RAO, the frequencies of these gene polymorphisms were compared between the improvement and progression groups and excluded the non-progression group for this analysis, since the distribution of the radiographic grading of AD in the non-progression group showed statistically significant differences from that in both the improvement and progression groups, as described previously. No significant differences of the frequencies of VDR RFLPs ApaI and TaqI were observed between the improvement group (p=.769) and the progression group (p=.079, Table 5). In the ER gene polymorphism, no significant differences of the frequencies of the XbaI gene polymorphisms were observed in the improvement group in comparison to those in the progression group (Table 5, p=.072). However, the frequency of pp was found to be significantly different (p=.011) from that of both PP and Pp in the ER gene polymorphism PvuII (Table 5, Fig. 2). In 90% of the patients with the pp gene polymorphism, the joint space width was narrowed after RAO (Table 5). On the other hand, only approximately 35% of the patients with pp gene polymorphism showed a narrowing of joint space width and a progression of osteoarthritis of the hip after RAO (Table 5).

Table 3 Frequencies of gene polymorphisms of the subjects with acetabular dysplasia divided by radiographic classifications of degenerative changes of the hip joints

		Grade 0 (12)	Grade 1 (15)	Grade 2 (37)		*p* for trend
Vitamin D receptor polymorphism						
ApaI	AA	0 (0%)	2 (28.6%)	5 (71.4%)	7 (100%)	
	AB	7 (25.9%)	6 (22.2%)	14 (51.9%)	27 (100%)	.438
	BB	5 (16.7%)	7 (23.3%)	18 (60.0%)	30 (100%)	
					64	
TaqI	TT	8 (17.0%)	11 (23.4%)	28 (59.6%)	47 (100%)	
	Ta	4 (26.7%)	4 (26.7%)	7 (46.7%)	15 (100%)	.319
	aa	0 (0%)	0 (0%)	2 (100.0%)	2 (100%)	
					64	
Oestrogen receptor polymorphism						
PvuII	PP	2 (11.7%)	2 (11.8%)	13 (76.5%)	17 (100%)	
	Pp	7 (22.6%)	8 (25.8%)	16 (51.6%)	31 (100%)	.241
	pp	3 (18.8%)	5 (31.2%)	8 (50.0%)	16 (100%)	
					64	
XbaI	XX	0 (0%)	2 (33.3%)	4 (66.7%)	6 (100%)	
	Xx	1 (7.1%)	3 (21.4%)	10 (71.5%)	14 (100%)	.260
	xx	11 (25.0%)	10 (22.7%)	23 (52.3%)	44 (100%)	
					64	

Discussion

Congenital dislocation of the hip and AD are both diseases that frequently occur in women [5, 8]. Similar to these previous studies, 92.2% of the patients with AD in this study were women (Table 1). Ninety percent of those with coxarthrosis in Japan are considered to have a secondary form and 70–75% of those are thought to be caused by AD [26]. In Europe and the USA, secondary coxarthrosis is reported to account for 54% of all cases and AD is implicated as the cause of only 30% [10, 16]. It is reported that 95% of Western patients with secondary coxarthrosis are also women [17].

A genetic aetiology has been proposed in those with AD [15]. Hereditary factors, particularly sex hormones such as oestrogen, may be strongly associated with congenital dislocation of the hip and AD [19]. Kapoor et al. reported that ER gene polymorphism XbaI gene polymorphism was more common in AD than in controls. However, no statistical difference is observed in Caucasians [19]. This study also observed no significant difference for the frequency of XbaI polymorphism of ER between those with AD and the controls (Table 2). Combined with these results, the ER and VDR gene polymorphisms are not thought to influence the formation of the acetabular roof in Japanese individuals. However, this study had one limitation, namely these gene polymorphisms were examined in patients with AD who underwent an RAO, while they were not examined in the patients with AD who did not undergo an RAO.

An RAO for AD usually has a satisfactory outcome [25, 26]. However, since some cases show poor outcomes, studies have sought to identify the causes of these poor outcomes. An enlarged coverage of the acetabular roof is important to prevent the progress of degenerative change of the hip joint [26]. However, this is only one of the factors that determine the future result of RAO based on postoperative radiographic evaluation. Postoperative results are thought to be associated not only with the surgical techniques including the learning curve of the surgeon(s)

Table 4 Comparison of the pre- and post-operative data of the three groups divided by the post-operative radiographic changes of the hip joint after RAO

		Improvement (23)	Non-progression (20)	Progression (21)	*p* for trend
Radiographic stages of degenerative changes of the hip joint					
Grade 0		0	10	2	
Grade 1		8	3	4	.004
Grade 2		15	7	15	
			p=.011[a]	p=.021[a]	
Sex (F:M)		21:2	19:1	19:2	
Age (years)		41.3 (8.1, 25-59)	34.3 (11.3, 17-48)	44.8 (11.9, 13-59)	.001
			p=.002[a]		
Follow-up period after operation (months)		95.0 (30.2, 55-150)	95.9 (29.3, 57-142)	89.2 (27.1, 62-154)	.840
CE angle (°)	Pre-op	4.4 (8.4, -14.0-18.0)	1.6 (14.5,-34.0-16.0)	4.1 (11.0,-30.0-20.0)	.999
	Post-op	43.0 (9.8, 26.0-60.0)	39.4 (10.3, 21.0-58.0)	34.9 (10.2, 18.0-59.0)	.045
			p=.013[a]		
AHI (%)	Pre-op	56.4 (7.0, 40.0-70.0)	53.8 (13.5, 22.0-69.0)	56.3 (14.3, 10.0-7.0)	.920
	Post-op	90.8 (9.5, 76.0-115.0)	88.9 (9.1, 71.0-104.0)	82.8 (9.2, (67.0-104.0)	.017
			p=.025[a]		
			p=.008[a]		
JSW (mm)	Pre-op	3.0 (1.8, 0.5-6.0)	3.7 (2.0, 0-7.0)	2.5 (2.0, 0-7.0)	.160
	Post-op	3.4 (1.3, 0.5-5.0)	3.0 (1.5, 0-5.0)	1.2 (1.3, 0-4.0)	.000
			p=.000[a]		
			p=.001[a]		

Data indicate means (SD, lower-upper). Radiographic evaluations included stages of degenerative changes of the joint. Measurements of CE angles, AHI and JSW were conducted at the time of operation (pre-op). Post-operative radiographic evaluations were conducted using the X-ray taken immediately after the operation (post-op)

CE angle centre-edge angle, *AHI* acetabular femoral head index, *JSW* joint space width

[a] Mann-Whitney test with Sidak adjustment

Table 5 Frequencies of gene polymorphisms in the groups with different remodelling patterns after RAO

		Improvement (23)	Progression (21)		*p* for trend	Mann-Whitney[a]	
Vitamin D receptor polymorphism							
ApaI	AA	2 (40.0%)	3 (60.0%)	5 (100.0%)	*p*=.769		
	AB	9 (50.0%)	9 (50.0%)	18 (100.0%)			
	BB	12 (57.1%)	9 (42.9%)	21 (100.0%)			
TaqI	TT	20 (62.5%)	12 (37.5%)	32 (100.0%)	*p*=.079		
	Ta	3 (27.3%)	8 (72.7%)	11 (100.0%)			
	aa	0 (0%)	1 (100.0%)	1 (100.0%)			
Oestrogen receptor polymorphism							
PvuII	PP	9 (64.3%)	5 (35.7%)	14 (100.0%)	*p*=.011	*p*<.05	*p*<.05
	Pp	13 (65.0%)	7 (35.0%)	20 (100.0%)			
	pp	1 (10.0%)	9 (90.0%)	10 (100.0%)			
XbaI	XX	2 (33.3%)	4 (66.7%)	6 (100.0%)	*p*=.072		
	Xx	9 (81.8%)	2 (18.2%)	11 (100.0%)			
	xx	12 (44.4%)	15 (55.6%)	27 (100.0%)			

[a] Mann-Whitney test with Sidak adjustment

and indication for the operation but also various circumstantial factors such as body weight, activity levels, etc. The RAO in this study was performed by a single orthopaedic surgeon (M.N.) who had previously performed over 200 procedures with this technique at the start of this study.

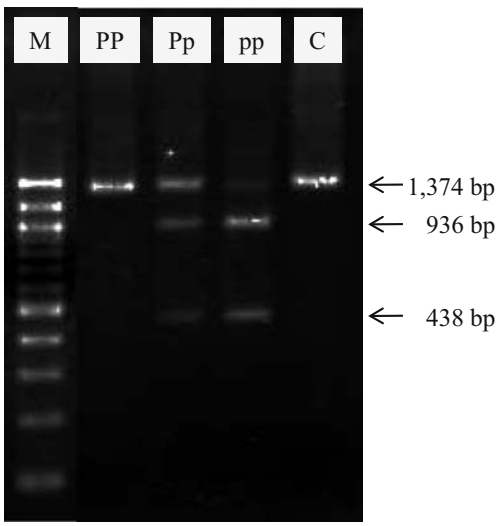

Fig. 2 PCR identification of the PvuII restriction fragment length polymorphisms (RFLPs) of the oestrogen receptor (ER) gene. The RFLPs were coded as P or p, where capital letters signify the absence of and small letters the presence of restriction sites. *C* control, *M* molecular marker

Therefore, the learning curve of the surgeon(s) can be ruled out. The influence of gene polymorphisms, on the other hand, has remained largely obscure. To determine whether the VDR and ER gene polymorphisms are involved in the likely result of RAOs, the frequencies of those gene polymorphisms in the improvement group were compared with those in the progression group, because these two groups show no other differences, such as the stages of AD, ages, preoperative radiographic variables, except for the surgical coverage of the acetabular roof, which is already known to be a factor that influences the long-term result of RAO [26] (Table 4). In addition, the non-progerssion group was excluded, because the stages of the AD of this group were significantly different from those of the other two groups (Table 4).

A number of studies have reported the effect of vitamin D-VDR signalling on bone and cartilage metabolism [6, 28, 35]. The ApaI and TaqI polymorphisms in the VDR gene are associated with the length of the 3′ untranslated region (UTR) of the VDR and this length affects its transcription activity [37]. The results of this study suggest that the ApaI and TaqI polymorphisms in VDR gene signalling may not play an important role in either the acetabular roof formation or the remodelling of arthritic changes following RAO.

ER is expressed in osteoblasts [12], osteoclasts [30] and osteoarthritic cartilage [7, 32, 38]. PP homozygotes, which carry two copies of the gene variant without a PvuII

restriction site, have higher bone mineral density than other subjects in women before menopause in the USA [41]. On the other hand, in Thailand, the bone mineral density in women before menopause with PP homozygotes has been reported to be lower than that of those without PP homozygotes [29]. This suggests that the effect of this gene polymorphism may differ depending upon the race of the subjects. The PvuII gene polymorphism has a linkage disequilibrium with the TA repeats in the promoter region of the ER gene [4], which is one of the determinants that regulates bone mineral density [21]. The polymorphic sites investigated are in the 5′ end of the ER gene. These were the PvuII and XbaI RFLPs in intron 1, about 400 bp upstream of exon 2. The polymorphisms are assigned as anonymous polymorphisms, since no functional effect on expression or function of the ER protein has been established. It is possible that genetic variation in the ER gene could lead to differences in mRNA expression, which might result in different responsiveness to the circulating levels of its ligand, oestrogen. This can result in genotype-dependent differences in bone mass, bone metabolism and postoperative results [18, 39]. Considering these findings, oestrogen-ER signalling may play an important role in the remodelling of the joint after an RAO, while it does not have a critical role and/or another compensational system may exist for the acetabular roof formation in the Japanese. In addition, this oestrogen-ER signalling for joint remodelling after an RAO may be enhanced especially in women, because all eight women (100%) among the ten subjects with pp homozygotes in the ER gene polymorphisms PvuII showed narrowing of the joint space width with the RAO, while four women of the 12 subjects with PP (33.3%) and seven women of the 20 subjects (35.0%) with Pp showed narrowing of the joint space width following the RAO. These frequencies of PvuII/RFLPs for the long-term results of the RAO were emphasised, when the patients were limited to women, thus suggesting the involvement of gender regarding the effect of this PvuII gene polymorphism.

The VDR and ER gene polymorphisms are not involved in the formation of AD. Furthermore, in addition to the enlarged coverage of the acetabular roof by RAOs, ER gene polymorphisms were involved in the seven year or longer follow-up results of RAO. This study revealed that the cases with the polymorphic variant pp of the ER gene after RFLP/PvuII restriction showed poorer postoperative results after RAO. Based on the result of this study, the patients who are scheduled to undergo RAO should therefore be screened for this gene polymorphism and informed of the results of this study, if they have this polymorphic variant pp of the ER gene. Furthermore, a RAO might not be indicated in patients with this gene polymorphism if further studies reveal an alternative method which is not influenced by this gene polymorphism. Therefore, this observation needs to be explored in future studies both on molecular and clinical levels, in order to resolve all these questions.

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Conflict of interest The authors declare that they have no conflict of interest.

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