Estrogen receptor-α gene haplotype is associated with primary knee osteoarthritis in Korean population

Sheng-Yu Jin¹, Seung-Jae Hong², Hyung In Yang³, Sang-do Park³, Myung-Chul Yoo⁴, Hee Jae Lee¹, Mee-Suk Hong¹, Jae-Geong Park¹, Seo Hyun Yoon¹, Bum-Shik Kim¹, Sung-Vin Yim¹, Hun-Kuk Park¹ and Joo-Ho Chung¹

¹Kohwang Medical Research Institute, Department of Pharmacology, College of Medicine, Kyung Hee University, Seoul, Korea
²Department of Internal Medicine, College of Medicine, Pochon CHA University, Sungnam, Korea
³Division of Rheumatology, Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul, Korea
⁴Department of Orthopedic Surgery, College of Medicine, Kyung Hee University, Seoul, Korea

* Contributed equally

Corresponding author: Joo-Ho Chung, jhchung@khu.ac.kr

Received: 19 Feb 2004  Revisions requested: 5 Apr 2004  Revisions received: 26 May 2004  Accepted: 8 Jun 2004  Published: 19 Jul 2004

Arthritis Res Ther 2004, 6:R415-R421 (DOI 10.1186/ar1207)

© 2004 Jin et al.; licensee BioMed Central Ltd. This is an Open Access article: verbatim copying and redistribution of this article are permitted in all media for any purpose, provided this notice is preserved along with the article’s original URL.

Abstract

Estrogen and estrogen receptors (ERs) are known to play important roles in the pathophysiology of osteoarthritis (OA). To investigate ER-α gene polymorphisms for its associations with primary knee OA, we conducted a case–control association study in patients with primary knee OA (n = 151) and healthy individuals (n = 397) in the Korean population. Haplotyping analysis was used to determine the relationship between three polymorphisms in the ER-α gene (intron 1 T/C, intron 1 A/G and exon 8 G/A) and primary knee OA. Genotypes of the ER-α gene polymorphism were determined by PCR followed by restriction enzyme digestion (PvuII for intron 1 T/C, XbaI for intron 1 A/G, and BtgI for exon 8 G/A polymorphism). There was no significant difference between primary knee OA patients and healthy control individuals in the distribution of any of the genotypes evaluated. However, we found that the allele frequency for the exon 8 G/A BtgI polymorphism (codon 594) was significantly different between primary knee OA patients and control individuals (odds ratio = 1.38, 95% confidence interval = 1.01–1.88; P = 0.044). In haplotype frequency estimation analysis, there was a significant difference between primary knee OA patients and control individuals (degrees of freedom = 7, χ² = 21.48; P = 0.003). Although the number OA patients studied is small, the present study shows that ER-α gene haplotype may be associated with primary knee OA, and genetic variations in the ER-α gene may be involved in OA.

Keywords: estrogen receptor, haplotype, knee osteoarthritis, polymorphism

Introduction

Osteoarthritis (OA) is a common disorder among the elderly. It is multifactorial disorder, with predisposing factors included advanced age, and genetic, hormonal and mechanical factors [1,2]. Furthermore, recent studies have revealed a role for the inflammatory process in the pathogenesis of OA [3-5]. It has been reported that the development of OA may be influenced by multiple genes [6]. A number of candidate genes have been suggested to mediate susceptibility to OA, including collagen genes (COL1A1, COL2A1, COL9A1, COL11A2), and the genes encoding cartilage matrix protein 1 (CMP1), vitamin D receptor (VDR), insulin-like growth factor-1 (IGF1), transforming growth factor-β1 (TGFβ1), aggrecan-1 (AGC1), tissue inhibitor of metalloproteinase 3 (TIMP3), interleukin-1 receptor (IL1R), and the estrogen receptor [6].

The human estrogen receptor (ER) has two isoforms: ER-α and ER-β. The former isoform is a ligand-activated transcription factor composed of several important domains for hormone binding, DNA binding, and activation of transcription [7]. ER-α is an important mediator in the signal transduction pathway [7]. The ER is a member of the steroid/thyroid hormone superfamily of nuclear receptors [8]. The ER-α gene is greater than 140 kilobases, contains eight exons, and is located on chromosome 6q25 [9]. The coding region has a length of 1785 nucleotides, and it is translated into a protein of 595 amino acids and 66 kDa [10].
Several variations in the DNA sequence of the ER-α gene have been reported [11,12]. A few reports have examined the association between ER-α gene polymorphisms and OA; the findings are controversial. Ushiyama and co-workers [13] reported associations between a genotype of PvuII and XbaI polymorphisms in intron 1 of the ER-α gene and generalized OA. Bergink and co-workers [14] found that an ER-α haplotype of PvuII and XbaI polymorphisms was associated with radiographic OA of the knee. However, Loughlin and co-workers [15] found no association between ER-α gene polymorphisms and idiopathic OA. Some studies of BtgI polymorphisms have been conducted in other diseases. Cancel-Tassin and co-workers [16] reported that a BtgI (594 A/G) polymorphism was not associated with risk for prostate cancer. Tanaka and colleagues [17] reported similar findings in prostate cancer patients. In another study, the BtgI (594 A/G) polymorphism was not associated with renal cell carcinoma [18]. Curran and co-workers [19] reported an association of A/G polymorphism in exon 8 of the ER gene with sporadic breast cancer. However, no findings regarding the relationship between exon 8 A/G polymorphism and OA have been reported.

In the present study, we first analyzed the association between the exon 8 G/A BtgI polymorphism (database-single nucleotide polymorphism number rs2228480; codon 594) of the ER-α gene and primary knee OA in patients from the Korean population. In another study, the BtgI (594 A/G) polymorphism was not associated with renal cell carcinoma [18]. Curran and co-workers [19] reported an association of A/G polymorphism in exon 8 of the ER gene with sporadic breast cancer. However, no findings regarding the relationship between exon 8 A/G polymorphism and OA have been reported.

Materials and methods

Study subjects

A total of 151 patients with primary knee OA (98 women and 53 men) from the Korean population were included in the study. Patients were examined at the Rheumatology Clinic in Kyung Hee University Medical Center, Seoul, Korea. In total, 397 control individuals (207 women and 190 men) underwent the 2003 health examination. OA was diagnosed according to American College of Rheumatology criteria, which include primary OA with any symptom and/or sign of OA, positive finding on radiographs according to the Kellgren-Lawrence grading [20], and no evidence of arthritis due to other disease. The study was approved by the ethics review committee of the Medical Research Institute, Kyung Hee University Medical Center, Seoul, Korea.

Clinical information and classification of primary knee osteoarthritis

The age at onset of OA is important clinically because it is associated with long-term prognosis. During the study, we were able to identify the current age and age at onset of disease in the 151 knee OA patients by individual interview conducted at our outpatient clinic. The current age of OA patients (mean ± standard deviation) was 58.8 ± 9.6 years, and the age at onset of OA was 52.0 ± 9.5 years. We therefore stratified clinical data according to mean onset age of disease: older or younger than 52.0 years. The group with disease onset at age ≤52.0 years was defined as the ‘early’ onset, and the group of disease onset at age >52.0 years was defined as the ‘late’ onset group.

The Kellgren-Lawrence grade represents disease severity, as reflected on radiographs, and Lequesne’s functional index represents functional or symptomatic status of patients [21]. Radiographic findings of OA were classified into mild (Kellgren-Lawrence grade 1 or 2) or severe (Kellgren-Lawrence grade 3 or 4). The functional or symptomatic status of OA patients was classified as functionally or symptomatically good (Lequesne’s functional index = 10) or poor (Lequesne’s functional index > 10; Table 1).

| Characteristic                        | Findings          |
|--------------------------------------|-------------------|
| Age (years)                          | 58.8 ± 9.6        |
| Number women/men (n)                 | 98/53             |
| Age at onset (years)                 | 52.0 ± 9.5        |
| Body mass index (kg/m²)              | 25.2 ± 2.9        |
| Duration of osteoarthritis (years)   | 6.8 ± 5.9         |
| Kellgren-Lawrence grade (n): 1/2/3/4 | 6/84/56/5         |
| Lequesne's index                     | 10.2 ± 2.5        |

A total of 151 patients with primary knee osteoarthritis were included. Values are expressed as mean ± standard deviation or as numbers.
pmol antisense primer, 0.5 µl 10 pmol sense primer, 0.5 µl 2.5 mmol/l dNTP (Takra, Shiga, Japan), 1 U Taq DNA polymerase (Neurotics Inc., Seoul, Korea), and in buffer containing 25 mmol/l MgCl₂, 750 mmol/l Tris-HCl (pH 9.0), 150 mmol/l ammonium sulphate, and 1 mg/ml bovine serum albumin. Samples were subjected to 35 cycles of amplification in GeneAmp PCR system 2700 (Applied Biosystems, Foster, CA, USA). PCR products were digested under the conditions specified by the enzyme supplier (New England Biolabs Inc, Beverly, MA, USA). Restriction fragments were separated by agarose gel electrophoresis and ethidium bromide staining.

Statistical analysis

For the case–control association study, the significance of differences in allelic and genotypic frequencies between OA patients and control populations was determined using standard χ² tests. We used the EH program [23] to investigate the relative risks associated with haplotypes. P < 0.05 was considered statistically significant.

Results

Distribution of estrogen receptor-α gene polymorphisms in osteoarthritis patients and control individuals

As shown in Table 4, the observed genotype distribution (P = 0.04) and allele frequency (OR = 1.89, 95% CI = 1.15–3.11; P = 0.01) for the exon 8 G/A BglI polymorphism were significantly different between male OA patients and male control individuals, whereas those in females exhibited no significant difference. We compared genotype distributions and allele frequencies for the intron 1 T/C PvuII and the intron 1 A/G XbaI polymorphisms. There were no significant differences in the polymorphisms between OA patients and controls of the same sex.

Estrogen receptor-α gene polymorphisms and sex of osteoarthritis patients

Late onsets OA patients were defined as those with disease onset at age above 52 years, whereas early onset OA patients had their disease onset at age under 52 years. When comparing allele frequency of the exon 8 G/A BglI polymorphism between late onset OA patients and control individuals, a significant difference was observed (OR = 1.62, 95% CI = 1.07–2.46; P = 0.021). However, the genotype distribution did not exhibit a significant difference between OA patients and control individuals (P = 0.06). The genotype distributions and allele frequencies of the intron 1 T/C PvuII and the intron 1 A/G XbaI polymorphisms were not significantly different between late onset OA patients and control individuals. When comparing genotype distributions and allele frequencies of the intron 1 T/C PvuII, the intron 1 A/G XbaI, and the exon 8 G/A BglI polymorphisms between early onset OA patients and control individuals, no significant difference was observed (Table 4).

Estrogen receptor-α gene polymorphisms and risk for radiographically severe osteoarthritis

Patients with radiographically severe OA were defined as those whose Kellgren-Lawrence grade was 3 or 4, whereas
radiographically mild OA was defined as Kellgren-Lawrence grade 1 or 2. When comparing genotype distributions and allele frequencies of the intron 1 T/C \textit{Pvu}\textit{II}, the intron 1 A/G \textit{Xba}\textit{I}, and the exon 8 G/A \textit{Btg}\textit{I} polymorphisms between patients with mild OA and control individuals, no significant difference was observed (Table 4). The genotype distributions and allele frequencies of the intron 1 T/C \textit{Pvu}\textit{II}, the intron 1 A/G \textit{Xba}\textit{I}, and the exon 8 G/A \textit{Btg}\textit{I} polymorphisms did not exhibit significant differences between patients with severe OA and control individuals (Table 4).

Estrogen receptor-α gene polymorphisms and risk for functionally poor osteoarthritis

OA patients who were functionally or symptomatically poor (poor index) were defined as those who with a Lequesne’s functional index score over 10, whereas those who were functionally or symptomatically good (good index) had a Lequesne’s functional index score less than or equal to 10. Genotype distributions and allele frequencies of the intron 1 T/C \textit{Pvu}\textit{II}, the intron 1 A/G \textit{Xba}\textit{I}, and the exon 8 G/A \textit{Btg}\textit{I} polymorphisms did not exhibit significant differences between patients with severe OA and control individuals (Table 4).

Estrogen receptor-α haplotype analysis in patients with primary knee osteoarthritis

Table 5 shows the frequency of each haplotype. The difference was significant between all OA patients combined and control individuals (degrees of freedom [df] = 7, $\chi^2 = 21.48$; $P = 0.003$). There was no significant difference between female patients and female control individuals (df = 7, $\chi^2 = 8.22$; $P = 0.31$). However, there was a significant difference between male OA patients and male control individuals (df = 7, $\chi^2 = 16.76$; $P = 0.019$; Table 5).

The late onset, radiographically severe, and poor index subgroups of OA patients exhibited significant differences in haplotype distribution (Table 6). There was a significant difference between patients with late onset OA and control individuals (df = 7, $\chi^2 = 21.96$; $P = 0.002$) but not between patients with early onset OA and control individuals (df = 7, $\chi^2 = 7.42$; $P = 0.390$). When comparing patients with radiographically severe OA and control individuals, a significant difference was observed (df = 7, $\chi^2 = 23.96$; $P = 0.001$), but this was not the case in patients with radiographically mild OA (df = 7, $\chi^2 = 13.60$; $P = 0.059$). There was a significant difference between OA patients with a poor index and control individuals (df = 7, $\chi^2 = 14.66$; $P = 0.041$), but this was not the case for OA patients with a good index (df = 7, $\chi^2 = 10.96$; $P = 0.140$; Table 6).

Discussion

We report here, for the first time, on the associations of exon 8 G/A \textit{Btg}\textit{I} polymorphism (codon 594) in the ER-α gene and ER-α haplotypes of three polymorphisms (\textit{Pvu}\textit{II} in intron 1, \textit{Xba}\textit{I} in intron 1, and \textit{Btg}\textit{I} in exon 8) with primary knee OA in the Korean population. Several reports [13-15,24-26] have indicated that estrogen and its receptor

---

**Table 3**

Genotype distribution and allele frequency of estrogen receptor-α gene polymorphisms in patients with osteoarthritis and control individuals

| Groups | ER-α genotypes | ER-α alleles |
|--------|---------------|--------------|
|        | OA (%) | Control (%) | $P_a$ | OA (%) | Control (%) | $P_b$ | OR (95% CI) |
| \textit{Pvu}\textit{II} (T/C) | T | 61 (40.4) | 152 (38.3) | 0.63 | 190 (62.9) | 487 (61.3) | 0.93 (0.71–1.23) |
|       | CT | 68 (45.0) | 183 (46.1) | 0.89 | 122 (37.1) | 307 (38.7) | 0.77 (0.68–1.33) |
|       | CC | 22 (14.6) | 62 (15.6) | 0.81 | 4 (2.70) | 15 (3.80) | 0.13 |
| \textit{Xba}\textit{I} (A/G) | AA | 98 (64.9) | 256 (64.5) | 0.77 | 245 (81.1) | 638 (80.3) | 1.38 (1.01–1.88) |
|       | AG | 49 (32.4) | 126 (31.7) | 0.81 | 57 (18.9) | 156 (19.7) | 0.13 |
|       | GG | 4 (2.70) | 15 (3.80) | 0.81 | 4 (2.70) | 15 (3.80) | 0.13 |
| \textit{Btg}\textit{I} (G/A) | GG | 84 (55.6) | 257 (64.7) | 0.77 | 225 (74.5) | 636 (80.1) | 1.38 (1.01–1.88) |
|       | GA | 57 (37.8) | 122 (30.7) | 0.13 | 57 (18.9) | 156 (19.7) | 0.13 |
|       | AA | 10 (6.60) | 18 (4.60) | 0.13 | 4 (2.70) | 15 (3.80) | 0.13 |

A total of 151 patients with osteoarthritis (OA) and 397 control individuals were included in the study. aControl individuals versus patients using the $\chi^2$ test with 3 × 2 contingency table. bControl individuals versus patients using the $\chi^2$ test with 2 × 2 contingency table. CI, confidence interval; ER, estrogen receptor; OR, odds ratio.
might be involved in the etiology of OA. Until now three reports on the relationship between ER-α polymorphisms and OA had been published. Two studies [13,14] reported that a ER-α polymorphism was associated with OA. Ushiyama and co-workers [13] found an association between a genotype of PvuII and XbaI polymorphisms in intron 1 and generalized OA with severe radiographic changes in the Japanese population (65 OA patients and 318 control individuals). In a population-based study conducted in a Caucasian population (1483 subjects), Bergink and co-workers [14] reported that ER-α haplotype of PvuII and XbaI polymorphisms was associated with radiographic OA of the knee. One study showed no relationship between ER-α gene polymorphisms and OA in a Caucasian population (371 OA patients and 369 control individuals) [15].

Our study showed that the genotype distributions for the intron 1 T/C PvuII and the intron 1 A/G XbaI polymorphisms were not associated with OA, a finding similar to that reported by Loughlin and co-workers [15]. However, the allele frequency for the BtgI polymorphism was significantly different between OA and control individuals. The difference in the allele frequency was more marked in OA patients with late onset of disease and in male patients (Table 4). The haplotype of three polymorphisms was associated with OA. We conducted further analysis of OA

### Table 4

**Comparison of estrogen receptor-α gene polymorphisms in subtypes of osteoarthritis patients and control individuals**

| Clinical subtypes | Genotype distributions<sup>a</sup> | Allele frequencies<sup>b</sup> |
|-------------------|-----------------------------------|-------------------------------|
|                   | PvuII | XbaI | BtgI | T | C | A | G | A |
|                   | TT | TC | CC | AA | AG | GG | GA | AA | 128 | 68 | 161 | 35 | 149 | 47 |
| Women (n = 98)    | 13 | 42 | 64 | 33 | 35 | 57 | 6 | 128 | 68 | 161 | 35 | 149 | 47 |
|                   | (43.9) | (42.8) | (13.3) | (65.3) | (33.7) | (1.00) | (58.2) | (35.7) | (6.10) | (55.3) | (34.7) | (17.9) | (76.0) | (24.0) |
| χ² = 3.84; P = 0.15 | χ² = 1.05; P = 0.59 | χ² = 0.23; P = 0.89 | 1.15 (0.80–1.64); P = 0.45 | 0.91 (0.58–1.41); P = 0.67 | 1.10 (0.74–1.65); P = 0.63 |
| χ² = 1.69; P = 0.43 | χ² = 0.07; P = 0.96 | χ² = 6.28; P = 0.043 | 0.82 (0.53–1.27); P = 0.38 | 1.04 (0.62–1.78); P = 0.86 | 1.89 (1.15–3.11); P = 0.011 |
| Early onset<sup>c</sup> (n = 85) | 41 | 26 | 34 | 16 | 27 | 22 | 4 | 62 | 44 | 84 | 22 | 76 | 30 |
|                   | (40.0) | (48.2) | (11.8) | (61.2) | (36.6) | (2.30) | (60.0) | (34.1) | (5.90) | (58.6) | (41.5) | (79.2) | (20.8) | (71.78) | (28.3) |
| χ² = 0.82; P = 0.66 | χ² = 1.00; P = 0.60 | χ² = 0.77; P = 0.68 | 0.893 (0.63–1.29); P = 0.50 | 1.06 (0.70–1.60); P = 0.78 | 1.20 (0.80–1.78); P = 0.37 |
| Late onset<sup>c</sup> (n = 66) | 41 | 26 | 34 | 16 | 27 | 22 | 4 | 62 | 44 | 84 | 22 | 76 | 30 |
|                   | (40.0) | (48.2) | (11.8) | (61.2) | (36.6) | (2.30) | (60.0) | (34.1) | (5.90) | (58.6) | (41.5) | (79.2) | (20.8) | (71.78) | (28.3) |
| χ² = 0.82; P = 0.66 | χ² = 1.00; P = 0.60 | χ² = 0.77; P = 0.68 | 0.893 (0.63–1.29); P = 0.50 | 1.06 (0.70–1.60); P = 0.78 | 1.20 (0.80–1.78); P = 0.37 |
| Mild<sup>d</sup> (n = 90) | 44 | 33 | 13 | 67 | 21 | 2 | 50 | 33 | 7 | 121 | 59 | 155 | 25 | 133 | 47 |
|                   | (48.9) | (36.7) | (14.4) | (74.5) | (23.3) | (2.20) | (55.6) | (36.7) | (6.80) | (87.2) | (32.8) | (86.1) | (13.9) | (73.9) | (26.1) |
| χ² = 3.58; P = 0.17 | χ² = 3.32; P = 0.19 | χ² = 0.30; P = 0.19 | 0.77 (0.55–1.09); P = 0.14 | 0.66 (0.42–1.04); P = 0.07 | 1.42 (0.98–2.07); P = 0.06 |
| Severe<sup>e</sup> (n = 61) | 17 | 35 | 9 | 31 | 28 | 2 | 34 | 24 | 3 | 69 | 53 | 90 | 32 | 92 | 30 |
|                   | (27.9) | (57.4) | (14.7) | (50.8) | (45.9) | (3.30) | (55.7) | (39.3) | (4.90) | (56.6) | (43.4) | (73.8) | (26.2) | (75.4) | (24.6) |
| χ² = 2.99; P = 0.02 | χ² = 4.76; P = 0.09 | χ² = 1.92; P = 0.38 | 1.22 (0.83–1.79); P = 0.31 | 1.45 (0.94–2.26); P = 0.09 | 1.31 (0.84–2.05); P = 0.23 |
| Good index<sup>f</sup> (n = 82) | 32 | 35 | 15 | 52 | 28 | 2 | 45 | 31 | 6 | 99 | 65 | 132 | 32 | 121 | 43 |
|                   | (39.6) | (42.7) | (18.3) | (63.4) | (34.2) | (2.40) | (54.9) | (37.8) | (7.30) | (80.4) | (39.6) | (80.5) | (19.5) | (73.8) | (26.2) |
| χ² = 0.68; P = 0.78 | χ² = 0.48; P = 0.78 | χ² = 3.16; P = 0.21 | 1.04 (0.74–1.47); P = 0.02 | 0.99 (0.65–1.51); P = 0.07 | 1.43 (0.97–2.11); P = 0.07 |
| Poor index<sup>e</sup> (n = 68) | 29 | 33 | 17 | 48 | 21 | 2 | 39 | 26 | 4 | 91 | 47 | 113 | 25 | 104 | 34 |
|                   | (42.0) | (47.8) | (10.2) | (66.7) | (30.4) | (2.90) | (56.5) | (37.7) | (5.80) | (55.9) | (34.1) | (81.9) | (16.1) | (75.4) | (24.6) |
| χ² = 1.44; P = 0.49 | χ² = 0.20; P = 0.90 | χ² = 1.72; P = 0.42 | 0.82 (0.58–1.20); P = 0.30 | 0.90 (0.57–1.44); P = 0.57 | 1.32 (0.86–2.01); P = 0.20 |

<sup>a</sup>Control versus patients using the χ² test with 3 × 2 contingency table.  
<sup>b</sup>Control versus patients using the χ² test with 2 × 2 contingency table.  
<sup>c</sup>Early onset osteoarthritis OA patients were defined as those with disease onset at age under 52 years, whereas late onset OA patients were those with onset at age over 52 years. Based on radiographic findings, OA patients were classified into mild (Kellgren-Lawrence grade 1 or 2) or severe (Kellgren-Lawrence grade 3 or 4).  
<sup>d</sup>Based on Lequesne’s functional index score, poor OA patients were defined as those with an index score over 10, whereas good OA patients had an index score less than or equal to 10.
patients subdivided by clinical parameters and found that the haplotype exhibited a strong association with late onset, radiographically severe, and functionally poor OA of the knee, and in particular with male sex (Tables 5 and 6). However, the TAA and CAG haplotypes exhibited differences between female and male control individuals (Table 5). Haplotype TAA had frequencies of 0.12 and 0.05 in female and male control individuals, but its frequencies in male and female OA patients were 0.18 and 0.14, respectively. Haplotype CAG had a frequency of 0.18 in female control individuals, 0.18 in female patients and 0.18 in male patients, but its frequency in the male control individuals was 0.31. This discrepancy may be due to the small numbers of male control individuals (n = 190) and male OA patients (n = 53).

The genotype distribution of the Pvu II and Xba I polymorphisms in the ER-α gene was reported to differ between racial and ethnic groups [13-15]. In the present study, genotype and allele frequencies in control individuals were similar to previously reported distributions in the Chinese population [27]. Interestingly, the exon 8 G/A BtgI polymorphism was not significantly associated with OA in the Chinese population.
orphism and haplotype of three polymorphisms (PvuII in intron 1, XbaI in intron 1, and BglI in exon 8) were associated with OA in men but not in women.

Our sample size was relatively small and our data were subjected to a number of uncorrected tests, and therefore our positive results may represent false-positive findings. To confirm the association between ER-α polymorphisms and OA, additional studies are required.

**Conclusion**

In conclusion, we found that ER-α gene haplotype may be associated with primary knee OA in the Korean population, and that genetic variations in the ER-α gene might play a role in susceptibility to OA.

**Competing interests**

None declared.

**Acknowledgements**

This study was supported by an Oriental Medicine Research Center for Bone and Joint Disease grant from the Ministry of Health and Welfare of the Republic of Korea (03-PJ9-PG6-SO01-0002).

**References**

1. Ghosh P, Cheras PA: Vascular mechanisms in osteoarthritis. *Best Pract Res Clin Rheumatol* 2001, 15:693-709.
2. Reginato AM, Olsen BR: Estrogen receptor gene polymorphism and generalized osteoarthritis. *J Rheumatol* 2003, 30:1266-73.
3. Aigner T: Articular cartilage and changes in arthritis. An introduction: cell biology of osteoarthritis. *Arthritis Res* 2001, 3:107-113.
4. Evans RM: The steroid and thyroid hormone receptor superfamily. *Science* 1998, 280:889-905.

**Available online** http://arthritis-research.com/content/6/5/R415

...graphic osteoarthritis of the knee in elderly men and women. *Arthritis Rheum* 2003, 48:1913-1922.

15. Loughlin J, Sinaheimer JS, Mustafa Z, Carr AJ, Clipsham K, Bloomfield VA, Chinnavis J, Bailey A, Sykes B, Chapman K: Association analysis of the vitamin D receptor gene, the type I collagen gene COL1A1, and the estrogen receptor gene in idiopathic osteoarthritis. *J Rheumatol* 2000, 27:779-784.