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The Relationship of Estrogen Receptor-α and -β Genes with Osteoarthritis of the Hand

BARTON L. WISE, **SERKALEM DEMISSIE**, **L. ADRIENNE CUPPLES**, **DAVID T. FELSON**, **MEI YANG**, **AMANDA M. SHEARMAN**, **PIRAN ALIABADI**, and **DAVID J. HUNTER**

B.L. Wise, MD, Clinical Epidemiology Research and Training Unit, Boston University School of Medicine and Center for Healthy Aging, University of California, Davis Medical Center, Sacramento, CA; S. Demissie, PhD, MPH; L.A. Cupples, PhD, Boston University School of Public Health; D.T. Felson, MD, MPH, Clinical Epidemiology Research and Training Unit, Boston University School of Medicine; M. Yang, MSc, Clinical Epidemiology Research and Training Unit, Boston University School of Medicine and School of Public Health, Boston, MA; A.M. Shearman, PhD, Koch Institute for Integrative Cancer Research, Cambridge Institute of Technology, Cambridge, MA, and Department of Epidemiology and Genetics, Westlakes Research Institute, University of Central Lancashire, Cumbria, UK; P. Aliabadi, MD, Department of Radiology, Brigham and Women's Hospital; D.J. Hunter, MBBS, PhD, Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, and Division of Research, New England Baptist Hospital, Boston, MA

Abstract

Objective—We examined reported associations between radiographic hand osteoarthritis (OA) and single-nucleotide polymorphisms (SNP) in 2 candidate genes associated with OA in other joints: estrogen receptor alpha (*ESR1*) and beta (*ESR2*).

Methods—In 539 Framingham Offspring Study participants (49% men; mean age 61 ± 9 yrs) joint-specific radiographic hand OA was defined as Kellgren/Lawrence (K/L) scores ≥ 2 in the first carpometacarpal joint (CMC), distal interphalangeal joints (DIP), first-digit interphalangeal joint (IP), or proximal interphalangeal joints (PIP). Four SNP were genotyped for *ESR1* (PvuII-*rs2234693*, XbaI-*rs9340799*, *rs2077647*, and *rs1801132*) and 4 for *ESR2* (*rs1256031*, *rs1256034*, *rs1256059*, *rs944460*). Logistic regression analyses were performed to evaluate the relationships between genotypes and hand OA, adjusting for age, sex, height, and weight.

Results—Radiographic hand OA was identified in at least one investigated joint of DIP (39%), PIP (33%), and first CMC (40%). There was no evidence of association between OA and genotype at any polymorphism. We found no significant association between our OA phenotypes or generalized or severe generalized OA as defined by Ushiyama and heterozygosity for *rs2234693* and *rs9340799*, although in metaanalysis with the former study this heterozygosity remained significantly associated with generalized or severe generalized OA.

Conclusion—We found no significant association between hand OA and the investigated polymorphisms of *ESR1* or *ESR2* despite published reports of association and a priori hypotheses implicating their potential roles. However, we could not absolutely exclude associations with *rs2234693*, *rs9340799*, or *rs944460*.

Address correspondence to Dr. B. Wise, Center for Healthy Aging, University of California, Davis Medical Center, 4800 2nd Avenue, Suite 2600, Sacramento, CA 95817..

Keywords

OSTEOARTHRITIS; FRAMINGHAM OSTEOARTHRITIS STUDY; ESTROGEN RECEPTOR GENES HAND

Osteoarthritis (OA) is a common, painful, and often debilitating condition, with hand OA an important component of its morbidity. Among subjects aged 71–100 years of age in the Framingham Study[1], prevalence of symptomatic hand OA was 26.2% in women and 13.4% in men. Although there is already a significant burden of hand OA in the United States and other economically developed countries, its prevalence is likely to grow as their populations age. Thus, understanding the etiology of the disease is important.

OA of the hands is in significant portion a heritable disorder. Work by Stecher, *et al* as early as the 1940s demonstrated a strong heritable basis for Heberden's nodes in women, and he later observed these as having autosomal dominant inheritance[2,3]. Kellgren and Lawrence in the 1960s found a 2-fold increase in risk for generalized OA in first-degree relatives of those with the disorder[4]. Although these studies had limitations, they remain important early indicators of the genetic nature of the condition. More recently, in a twin study of radiological OA, Spector, *et al*[5] estimated that 39%–65% of hand OA could be attributed to genetic influences, the percentage depending on specific features. However, despite the demonstrable contribution of genetics to the development of OA, the specific genetic mechanisms by which this is effected remain elusive.

Among the candidate genes that have been considered in OA etiopathogenesis are those for the 2 known estrogen activated transcription factors: estrogen receptor alpha (*ESR1*) and estrogen receptor beta (*ESR2*). Estrogen is believed to play an important role in OA, based on the observation that it is particularly prevalent in women, especially postmenopausal women. Radiographic knee OA in those under age 45 years is more prevalent in men, while in those 45 years or older it is predominantly a women's disease[6]. Nevitt, *et al*[7] reported that hip OA has a decreased prevalence in women taking estrogen replacement therapy, and Zhang, *et al*[8] found a similar decrease in the incidence of radiographic knee OA in subjects using hormone replacement. Other studies have been equivocal[9,10] on the question of association of estrogen use and symptomatic OA. Nonetheless, estrogen and its receptor genes remain important arenas for OA research based on putative physiological mechanisms as well as the above studies.

ESR1 has been investigated in several genetic studies of OA. Valdes, *et al* found a nonsignificant association with change in osteophyte grade in knee progression[11] and a significant association with clinical knee OA in women but not men[12]. Bergink, *et al* found an association between *ESR1* and radiographic knee OA[13]. However, hand OA has been studied very little in this context.

In one study investigating the *ESR1* gene and its relation to hand OA, Ushiyama, *et al* examined the *PvuII* (*rs2234693*) and *XbaI* (*rs9340799*) restriction fragment length polymorphisms of *ESR1* and their relation to “generalized [hand] osteoarthritis” in a group of 65 Japanese women as well as 318 healthy controls[14]. The investigators found that for subjects heterozygous for both *rs2234693* and *rs9340799*, there were odds ratios of 1.86 (95% CI 1.03–3.24) for generalized OA and 2.21 (95% CI 1.15–4.24) for severe generalized OA. Other analyses were negative, including for those subjects homozygous for minor alleles for both *rs2234693* and *rs9340799*. Before any firm conclusions can be drawn from this work replication is necessary.

The purpose of our work on radiographic hand OA in the Framingham Study was to investigate associations between OA and SNP in *ESR1* and *ESR2*. A secondary more specific goal was to replicate the finding of Ushiyama, *et al* that the *ESR1* genotype heterozygous for both *rs2234693* and *rs9340799* was associated with radiographic hand OA in women.

MATERIALS AND METHODS

The Framingham Heart Study is a longitudinal cohort study established in 1948 to examine risk factors for heart disease[15]. A study of the offspring of the original cohort was initiated in 1971, and members of this cohort participated in a study on the inheritance of OA between 1992 and 1994 from which data for this analysis are derived.

The Framingham Offspring cohort encompassed a total of 5124 subjects. Of those, there were a total of 1268 subjects with hand radiographs performed and read; Framingham Offspring subjects were invited to participate in the radiological studies if either or both of their parents had previously participated in radiographic evaluation for OA as part of the original cohort[16]. There were 1811 Framingham Offspring subjects in total who had genotyping performed for *ESR1* and *ESR2*. These subjects were selected to be a maximal set of biologically unrelated individuals and to be about evenly divided along gender lines. They were not chosen for any specific trait. Of these subjects, 539 had hand radiographs. There were some individual subjects whose genotyping failed for some SNP, thus reducing slightly the number of subjects used in each of the SNP analyses.

Radiographs

Posteroanterior hand radiographs were read by a musculoskeletal radiologist who referred to an atlas of radiographic features that had been developed for the Framingham Osteoarthritis Study[17]. Fifteen joints on each hand were evaluated and graded using a modified Kellgren and Lawrence (K/L) scale, with 0 = no OA, 1 = questionable osteophyte and/or questionable joint space narrowing, 2 = definite small osteophyte(s) and/or mild joint space narrowing, 3 = definite moderate osteophyte(s) and/or moderate joint space narrowing, or 4 = large osteophyte(s) and/or severe joint space narrowing (with or without cysts or sclerosis)[17]. The individual characteristics of osteophytes, cysts, sclerosis, and joint space narrowing were also recorded. The intraobserver reliability (kappa statistic) was 0.79 for reader 1 and 0.82 for reader 2, with an interobserver kappa of 0.65 for the modified K/L grade scoring[17].

We extracted the data for distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints of digits 2 through 5, and the first-digit IP and carpometacarpal (CMC) joints of both hands and defined an “any OA versus none” categorization for each of the joint categories (e.g., DIP involvement of any joint vs none). We also defined a model for any single joint with K/L > 1 in one or more of any of PIP, DIP, or CMC (“combined index”) or K/L > 1 in 2 or more of any of PIP, DIP, or CMC (“combined index 2”).

In the Ushiyama study, “generalized OA” was defined radiographically as K/L grade 2 or more in 3 or more IP joints of each hand. Forty-seven of these women had at least one joint with K/L grade of 3 or more in at least one joint and were classified as “severe generalized osteoarthritis.” We used these definitions for the replication of the Ushiyama study.

Genotyping

DNA was extracted from whole-blood or buffy-coat specimens using a standard protocol[18,19]. Four SNP were genotyped for *ESR1*: *rs2234693*, *rs9340799*, *rs2077647*, and *rs1801132*; and for *ESR2*: *rs1256031*, *rs1256034*, *rs1256059*, and *rs944460*. Detailed information about the genotyping is published[20]. Briefly, the polymerase chain reaction was

used to amplify the section of DNA containing the polymorphism, and then restriction fragment length analysis, TaqMan, or other assay was used to detect the polymorphism.

Statistical analysis

Logistic regression analyses were performed for presence versus absence of each phenotype definition, for each SNP, in women and men separately, as well as in both sexes combined. We considered additive and general (2 degrees of freedom) models, except for *rs1256034* and *rs944460* (with < 4% minor allele frequency), where we combined the minor allele homozygote with the heterozygote genotypes. We describe the additive model results here. Covariates included in these models were age, sex, height, and weight. Significance was set at a 2-tailed $p < 0.05$.

In a further analysis replicating the Ushiyama, *et al* study[14] we looked at the same 2 SNP using our own joint-specific hand OA definition from elsewhere in our study. In replicating their reported phenotypes for “generalized OA” and “severe generalized OA” (defined as described above) we analyzed for women and men separately and together.

We calculated power to detect effects in this cohort. In Ushiyama's definition of “generalized OA,” for SNP with allele frequencies ranging from 3% to 45% (covering the minor allele frequencies in both *ESR1* and *ESR2*), with n = 539, 80% power and alpha = 0.05, detectable effects (as odds ratios) are between 1.55 and 2.95 in the additive model and between 1.85 and 3.05 in the dominant model. In “severe generalized OA,” detectable effects (as odds ratios) are between 1.65 and 3.25 in the additive model and 2.0 and 3.35 for the dominant model. For the “combined index” phenotype, detectable effects (as OR) are between 1.40 and 3.15 for the additive model and between 1.65 and 3.20 for the dominant model. Last, for the “combined index 2” phenotype, detectable effects (as OR) are between 1.40 and 2.80 for the additive model and between 1.65 and 2.85 for the dominant model.

RESULTS

Our study group included 263 men (48.8% of the total sample of 539) and 276 women (51.2%). As noted in Table 1A, the subjects are in general comparable to those in the Framingham Osteoarthritis Offspring study (FOA) who were not included, with a mean age of 61 versus 59 years in those not included. There was a slightly lower proportion of female subjects included, 51% versus 60% female in those not included. Height, weight, and body mass index are very similar. In terms of the distribution of radiographic hand OA, the included subjects had a slightly higher burden of OA in any hand joint (58% vs 52%), as well as OA in multiple joints (45% vs 40%). Raw numbers for the frequencies of various polymorphisms are given in Table 1B.

For *ESR1* SNP, *rs1801132* was not in linkage disequilibrium (LD) with any of the other *ESR1* SNP, while *rs2077647* was in LD with *rs2234693* ($r^2 = 0.66$), *rs2077647* was in LD with *rs9340799* ($r^2 = 0.48$), and *rs2234693* was in LD with *rs9340799* ($r^2 = 0.66$). For *ESR2* SNP, *rs944460* was in fairly strong LD with *rs1256034* ($r^2 = 0.86$), and *rs1256059* was in moderate LD with *rs1256031* ($r^2 = 0.76$).

In exploring the associations between the 4 *ESR1* SNP and hand OA, defined as any joint-specific OA (K/L > 1), we found no significant associations with any of the polymorphisms. This remained true after controlling for gender, height, weight, and age. All examined associations were negative, with all p values below the alpha = 0.10 level, let alone the alpha = 0.05 level we defined initially as our threshold for significance (Table 2).

The same lack of significance holds for the examination of *ESR2* SNP and joint-specific hand OA, with negative findings for all risk factor-adjusted analyses (see Table 2). The *ESR2* SNP *rs944460* provided the smallest p value for a positive association (with DIP OA; p = 0.09). However, it should be noted that *rs944460* is a rare variant (minor allele frequency = 3%); there were no subjects that were homozygous for this allele, and only 35 out of a total of 522 were heterozygous.

When we analyzed for association with more widespread disease in the additive model for "combined index" or "combined index 2," we again found largely negative results for men and women combined (Table 3). Similar results were found for men and women alone. However, we found that *rs944460* had a significant effect size of 2.29 for the "combined index 2" for the combined set of men and women; we note that *rs1256034* was not significant despite being in LD with *rs944460*. The effect noted in *rs944460* was not evident when men or women were analyzed alone.

Replicating the Ushiyama study

As the only significant associations of genes to hand OA are those in Ushiyama, *et al*[14] as described above, we attempted to replicate their positive findings. First we performed an analysis that did not replicate Ushiyama, but rather utilized our own phenotype definitions as applied in the rest of our present study. In our study population, we found 34% of the subjects to be heterozygous for both *rs2234693* and *rs9340799*. No significant association between our OA phenotypes and heterozygosity for *rs2234693* and *rs9340799* in men or women or in a combined set was identified.

We subsequently performed an analysis that replicated Ushiyama's phenotypes of "generalized OA" and "severe generalized OA" (Table 4). We found no association between *rs2234693* and *rs9340799* and either generalized OA or severe generalized OA, as either heterozygous or homozygous in women or men alone. We also found no association of either phenotype with paired heterozygosity of the 2 SNP. However, we noted that in the combined gender crude analysis, *rs2234693* was significant (p = 0.04) for increased risk of generalized OA, which disappeared in the adjusted analysis.

In examining all SNP and their relation to the Ushiyama phenotype definitions, we found that *rs1256034* was borderline significant, with a positive effect estimate of 2.6 for severe generalized OA in the gender-combined set (*rs944460* had a similar relation, but these 2 SNP are in LD). Similar results were obtained for men and women alone, except that all findings were nonsignificant for women, and we also found an association between severe generalized OA in men only and *rs1256034* with an effect size of 6.14 (95% CI 1.18, 32.0); *rs944460* was nonsignificant.

Although we report the results from the additive models here, the general model results were generally similar, except in 3 instances. First, the crude result for *rs2234693* in men and women combined had a marginally significant value (p = 0.04) for generalized OA and heterozygosity. Second, *rs9340799* had a significant value (p = 0.03) for heterozygosity in combined men and women in the adjusted general model for the combined index phenotype, although for homozygosity of *rs9340799* in this model, there was an opposite effect direction. Last, heterozygosity of *rs1256031* was borderline significantly associated (p = 0.05) with severe generalized OA in men only, although homozygosity of this SNP was not significantly associated and had an opposite effect direction.

We performed a metaanalysis combining our unadjusted results with the unadjusted results reported by Ushiyama, *et al*. The unadjusted metaanalysis showed that the positive results for paired heterozygosity of *rs2234693* and *rs9340799* that the Ushiyama group reported

remained significant after combination with the Framingham results, with an odds ratio of 1.74 (95% CI 1.16, 2.61) for generalized OA and an odds ratio of 1.67 (95% CI 1.06, 2.63) for severe generalized OA in women. A metaanalysis that used the Framingham men and women combined results with the women-only Ushiyama group also produced a significant association for paired heterozygosity with generalized OA (OR 1.56, 95% CI 1.09, 2.22) and approached significance for paired heterozygosity with severe generalized OA (OR 1.49, 95% CI 0.99, 2.24). In all cases of combining the Framingham results with the Ushiyama results, simple heterozygosity of either *rs2234693* or *rs9340799* was associated with similar odds ratios for either generalized OA or severe generalized OA, which approached but did not achieve significance (see Tables 5A and 5B).

DISCUSSION

Given the clear demographic characteristics of hand OA (largely in women, and worse in women over age 65 yrs), and given the prominence of estrogen changes as women age, there is clearly good reason to investigate estrogen as well as its receptors and their relation to hand OA. This interest in the receptors in hand OA is bolstered by the findings of other studies[14]. Although there is no well understood pathophysiological mechanism for explaining these observations, the “circumstantial evidence” is compelling.

Although other studies have suggested a significant heritable component in hand OA, and specific relation to estrogen receptor, our present study of *ESR1* and *ESR2* SNP provided no significant evidence of association. Some readers might note that *rs944460* was significant for an association with widespread “combined index 2” OA, as well as for severe generalized OA. If we corrected for multiple testing, the relatively modest significance level of these findings would not hold up. However, we cannot exclude the possibility that there is a modest association between hand OA (particularly severe generalized OA) and *rs944460.* Verifying such an association would require replication in independent samples.

In those cases described above where one step of the general model was found to be positive, we felt this to be a false-positive or an interaction not explained in the data. As noted, there was no trend observed across the 3 groups in any instance.

As regards the replication of the Ushiyama study, we were unable to identify in our data any significant association between heterozygosity for the 2 *ESR1* SNP and hand OA, either through the phenotypes used in the original study, or using the phenotypes we had defined, or even by exploring other population subgroups. However, it is very interesting that our unadjusted data reveal a pattern similar to those reported in the Ushiyama article, with similar effect sizes and effect directions for heterozygosity and minor allele homozygosity in *rs2234693* and *rs9340799* with generalized and severe generalized OA, and indeed even retain significance in metaanalysis combination. The failure to achieve significance within our own data may represent a difference from the other group's study population. Although our data do not definitively confirm the conclusions of the prior study, they also certainly do not convincingly refute those conclusions, and may be interpreted to support them.

Numerous studies examining the genetic basis of OA have failed to identify a single causative factor that explains most of the heritable risk of the disease. OA may be a disease where heritable risk derives from a large group of alleles rather than just a few, and our observation of risk in hand OA with heterozygosity of *rs2234693* and *rs9340799* (consonant with Ushiyama's findings but nonsignificant in our data) may represent one small part of a patchwork of alleles that contribute to the phenotype.

As far as we are aware this is the largest study aimed at replicating previous associations of *ESR* genotypes with hand OA. The prospective design of the Framingham Study protects it

from some of the selection biases that are inherent to case-control studies. Our findings are, however, specific to the Framingham cohort and do not exclude differing results in subjects from other ethnic groups or geographic regions. In the future, denser sets of polymorphisms and genome-wide association analyses will be used to characterize and identify genes that contribute to OA risk.

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Table 1A

Demographics of study sample compared with Framingham Osteoarthritis Offspring Study subjects not included due to lack of geno-typing data.

Characteristic	Subjects Included in Present Analysis, n = 539	Subjects Not Included, n = 729
Mean age, yrs (± SD)	61 (9)	59 (9)
Female, n (%)	276 (51)	435 (60)
Height, in (± SD)	66 (3.7)	66 (3.7)
Weight, kg (± SD)	80 (18)	79 (18)
BMI, kg/m^2, mean (SD)	28 (5.1)	28 (5.5)
K/L grade ≥ 2 in any joint, %	58	52
K/L grade ≥ 2 in 2 or more joints, %	45	40
Generalized hand OA, %	20	16
Severe generalized hand OA, %	13	11

BMI: body mass index; K/L: Kellgren Lawrence.

Table 1B

Frequencies of *ESR1* and *ESR2* polymorphisms.

SNP	Minor Allele Frequency, %	Major Allele Homozygous, n (%)	Heterozygous, n (%)	Minor Allele Homozygous, n (%)
rs2234693	44	166 (30.8)	245 (45.4)	104 (19.2)
rs9340799	35	233 (43.2)	215 (39.8)	73 (13.5)
rs2077647	44	156 (28.9)	268 (49.7)	90 (16.7)
rs1801132	23	291 (53.9)	175 (32.4)	24 (4.4)
rs1256031	46	159 (29.5)	243 (45.0)	120 (22.2)
rs1256034	4	477 (88.5)	36 (6.6)	1 (0.1)
rs1256059	44	158 (29.3)	260 (48.2)	95 (17.6)
rs944460	3	487 (90.3)	35 (6.4)	0 (0.0)

Table 2

SNP odds ratios per allele for men and women combined, adjusted for age, gender, height, and weight, in additive model for any single joint with K/L > 1 in the listed distribution. *rs1256034* and *rs944460* as listed here are analyzed in a dominant model due to their small allele sizes. Table cells list genotype counts for the common homozygote, heterozygote, and rare homozygote; counts on the first line are for unaffected and on second line for affected subjects. Totals differ slightly in some cases due to missing data.

Genotype Counts	DIP OA	PIP OA	CMC OA
ESR1 SNP			
rs2234693			
Unaffected	105/140/69	115/155/75	97/146/67
Affected	61/105/35	51/90/29	69/99/37
OR (95% CI)	1.01 (0.76, 1.35)	0.99 (0.74, 1.32)	0.87 (0.67, 1.16)
rs9340799			
Unaffected	139/129/49	154/141/54	133/135/45
Affected	94/86/24	79/74/19	100/80/28
OR (95% CI)	0.92 (0.68, 1.23)	0.88 (0.66, 1.19)	0.86 (0.65, 1.15)
rs2077647			
Unaffected	97/154/62	103/177/63	93/158/56
Affected	59/114/28	53/91/27	63/110/34
OR (95% CI)	0.97 (0.72, 1.32)	0.93 (0.69, 1.26)	1.01 (0.75, 1.35)
rs1801132			
Unaffected	182/103/16	200/113/16	171/100/19
Affected	109/72/8	91/62/8	120/75/5
OR (95% CI)	1.01 (0.70, 1.46)	1.24 (0.87, 1.78)	0.77 (0.54, 1.10)
ESR2 SNP			
rs1256031			
Unaffected	94/147/79	102/165/86	87/157/70
Affected	65/96/41	57/78/34	72/86/50
OR (95% CI)	1.00 (0.75, 1.33)	0.91 (0.69, 1.21)	1.00 (0.76, 1.32)
rs1256034			
Unaffected	301/18/0	329/21/0	289/22/0
Affected	176/19/0	148/16/0	188/15/0
OR (95% CI)	1.61 (0.73, 3.55)	1.67 (0.78, 3.57)	0.81 (0.37, 1.76)
rs1256059			
Unaffected	97/156/60	103/175/67	89/166/52
Affected	61/104/35	55/85/28	69/94/43
OR (95% CI)	1.06 (0.78, 1.43)	0.89 (0.66, 1.19)	1.02 (0.76, 1.36)
rs944460			
Unaffected	306/16/0	324/20/0	292/21/0
Affected	181/19/0	153/15/0	195/14/0
OR (95% CI)	2.00 (0.88, 4.52)	1.73 (0.79, 3.77)	0.83 (0.38, 1.84)

K/L: Kellgren Lawrence; DIP: distal interphalangeal; PIP: proximal interphalangeal; CMC: carpometacarpal.

Table 3

SNP odds ratios per allele for men and women combined, adjusted for age, gender, height, and weight, in additive model for any single joint with K/L > 1 in one or more of any PIP, DIP, and CMC combined ("combined index") or K/L > 1 in 2 or more of any PIP, DIP, and CMC combined ("combined index 2"). These numbers reflect men and women combined. *rs1256034* and *rs944460* as listed here are analyzed in a dominant model due to their small allele sizes. Table cells list genotype counts for the common homozygote, heterozygote, and rare homozygote; counts on the first line are for unaffected and on second line for affected subjects. Totals differ slightly in some cases due to missing data.

Genotype Count	Combined Index	Combined Index 2
ESR1 SNP		
rs2234693		
Unaffected	65/100/46	95/122/62
Affected	101/145/58	71/123/42
OR (95% CI)	0.90 (0.67, 1.19)	1.04 (0.78, 1.37)
rs9340799		
Unaffected	85/99/30	123/115/44
Affected	148/116/43	110/100/29
OR (95% CI)	0.84 (0.62, 1.12)	0.92 (0.69, 1.22)
rs2077647		
Unaffected	62/109/40	86/138/55
Affected	94/159/50	70/130/35
OR (95% CI)	0.96 (0.71, 1.30)	0.98 (0.73, 1.31)
rs1801132		
Unaffected	114/74/13	157/95/15
Affected	177/101/11	134/80/9
OR (95% CI)	0.70 (0.49, 1.01)	0.86 (0.61, 1.23)
ESR2 SNP		
rs1256031		
Unaffected	59/99/58	80/133/72
Affected	100/144/62	79/110/48
OR (95% CI)	0.88 (0.66, 1.17)	0.90 (0.68, 1.18)
rs1256034		
Unaffected	204/11/1	269/14/1
Affected	273/25/0	208/22/0
OR (95% CI)	1.40 (0.61, 3.21)	1.79 (0.81, 3.92)
rs1256059		
Unaffected	62/108/41	82/143/53
Affected	96/152/54	76/117/42
OR (95% CI)	0.95 (0.71, 1.29)	0.94 (0.70, 1.25)
rs944460		
Unaffected	207/11/0	274/13/0
Affected	280/24/0	213/22/0
OR (95% CI)	1.56 (0.66, 3.69)	2.29 (1.01, 5.18)

Table 4

SNP odds ratios per allele for men and women combined, adjusted for age, gender, height, and weight, in additive model for any single joint with K/L > 1 in at least 3 interphalangeal (IP) joints of each hand (generalized OA) or having the changes of generalized OA along with K/L ≥ 3 in one or more IP joints of each hand (severe generalized OA). *rs1256034* and *rs944460* as listed here are analyzed in a dominant model due to their small allele sizes. Cells list genotype counts for the common homozygote, heterozygote, and rare homozygote; unaffected on first line and affected on second line. Totals differ slightly in some cases due to missing data.

Genotype Count	Generalized OA	Severe Generalized OA
ESR1 SNP		
rs2234693		
Unaffected	134/189/91	146/208/92
Affected	32/56/13	20/37/12
OR (95% CI)	0.88 (0.61, 1.27)	1.15 (0.75, 1.76)
rs9340799		
Unaffected	185/168/65	201/184/66
Affected	48/47/8	32/31/7
OR (95% CI)	0.82 (0.56, 1.19)	0.92 (0.60, 1.41)
rs2077647		
Unaffected	124/208/77	133/230/79
Affected	32/60/13	23/38/11
OR (95% CI)	0.93 (0.64, 1.35)	1.02 (0.66, 1.58)
rs1801132		
Unaffected	237/136/23	254/148/24
Affected	54/39/1	37/27/0
OR (95% CI)	0.91 (0.58, 1.44)	0.91 (0.53, 1.56)
ESR2 SNP		
rs1256031		
Unaffected	124/197/100	131/219/102
Affected	35/46/20	28/24/18
OR (95% CI)	0.94 (0.67, 1.33)	1.00 (0.67, 1.49)
rs1256034		
Unaffected	391/25/1	417/27/1
Affected	86/11/0	60/9/0
OR (95% CI)	1.91 (0.80, 4.56)	2.62 (1.01, 6.78)
rs1256059		
Unaffected	126/207/81	132/230/82
Affected	32/53/14	26/30/13
OR (95% CI)	0.88 (0.61, 1.27)	0.89 (0.58, 1.36)
rs944460		
Unaffected	397/24/0	425/27/0
Affected	90/11/0	62/8/0
OR (95% CI)	2.25 (0.92, 5.46)	2.78 (1.04, 7.48)

Table 5A

Metaanalysis results for combining men and women together with Ushiyama results and women alone with Ushiyama results for any single joint with K/L > 1 in at least 3 interphalangeal (IP) joints of each hand (generalized OA as described by Ushiyama[14]). *rs2234693* (*PvuII*) genotype is represented by P, where P denotes the major allele, and p the minor allele. Similarly, *rs9340799* (*XbaI*) genotype is represented by X, where X denotes the major allele, and x the minor allele.

	Ushiyama Women[a]		Framingham Men + Women[b]		Metaanalysis	
Genotype	**OR**	**p**	**OR**	**p**	**OR (95% CI)**	**p**
PP	0.73	0.29	0.97	0.90	0.87 (0.60, 1.25)	0.44
Pp	1.37	0.24	1.48	0.08	1.44 (1.02, 2.02)	0.04
pp	0.93	0.85	0.52	0.04	0.68 (0.42, 1.08)	0.10
PpXx	1.86	0.039	1.41	0.13	1.56 (1.09, 2.22)	0.01
XX	0.63	0.09	1.10	0.67	0.88 (0.63, 1.24)	0.48
Xx	1.70	0.06	1.25	0.32	1.41 (1.00, 1.98)	0.05
xx	0.54	0.56	0.46	0.05	0.47 (0.23, 0.96)	0.04

	Ushiyama Women[a]		Framingham Women[c]			
PP	0.73	0.29	1.05	0.88	0.87 (0.57, 1.32)	0.51
Pp	1.37	0.24	1.55	0.12	1.46 (0.99, 2.14)	0.06
pp	0.93	0.85	0.40	0.04	0.66 (0.38, 1.14)	0.14
PpXx	1.86	0.039	1.64	0.09	1.74 (1.16, 2.61)	0.01
XX	0.63	0.09	1.09	0.77	0.82 (0.56, 1.21)	0.33
Xx	1.70	0.06	1.34	0.29	1.51 (1.03, 2.23)	0.04
xx	0.54	0.56	0.34	0.05	0.38 (0.14, 0.99)	0.05

[a] n = 383.

[b] n = 515 for *rs2234693* genotypes, 521 for *rs9340799* genotypes, and 513 for PpXx.

[c] n = 262 for *rs2234693* genotypes, 263 for *rs9340799* genotypes, and 260 for PpXx.

Table 5B

Metaanalysis results for combining men and women together with Ushiyama results and women alone with Ushiyama results for having generalized OA and also K/L grade ≥ 3 in one or more IP joints of each hand (severe generalized OA as described by Ushiyama[14]). *rs2234693* (*PvuII*) genotype is represented by P, where P denotes the major allele, and p the minor allele. Similarly, *rs9340799* (*XbaI*) genotype is represented by X, where X denotes the major allele, and x the minor allele.

	Ushiyama Women[a]		Framingham Men + Women[b]		Metaanalysis	
Genotype	**OR**	**p**	**OR**	**p**	**OR (95% CI)**	**p**
PP	0.61	0.16	0.84	0.54	0.74 (0.48, 1.14)	0.17
Pp	1.74	0.08	1.32	0.28	1.47(0.99, 2.19)	0.05
pp	0.80	0.61	0.81	0.53	0.81 (0.48, 1.36)	0.42
PpXx	2.21	0.018	1.16	0.57	1.49 (0.99, 2.24)	0.06
XX	0.58	0.08	1.05	0.86	0.82 (0.56, 1.22)	0.33
Xx	1.81	0.06	1.15	0.58	1.38 (0.93, 2.05)	0.11
xx	0.75	0.78	0.65	0.30	0.66 (0.31, 1.42)	0.29

	Ushiyama Women[a]		Framingham Women[c]			
PP	0.61	0.16	0.94	0.87	0.76 (0.46, 1.23)	0.27
Pp	1.74	0.08	1.31	0.40	1.51 (0.97, 2.35)	0.07
pp	0.80	0.61	0.68	0.38	0.74 (0.40, 1.36)	0.33
PpXx	2.21	0.018	1.28	0.45	1.67 (1.06, 2.63)	0.03
XX	0.58	0.08	1.07	0.84	0.78 (0.50, 1.21)	0.27
Xx	1.81	0.06	1.17	0.63	1.46 (0.94, 2.26)	0.10
xx	0.75	0.78	0.57	0.31	0.60 (0.23, 1.59)	0.31

[a] n = 365.

[b] n = 515 for *rs2234693* genotypes, 521 for *rs9340799* genotypes, and 513 for PpXx.

[c] n = 262 for *rs2234693* genotypes, 263 for *rs9340799* genotypes, and 260 for PpXx.