Osteoarthritis-Susceptibility Locus on Chromosome 11q, Detected by Linkage

Kay Chapman,[1,2] Zehra Mustafa,[1,2] Catherine Irven,[2] Andrew J. Carr,[3] Kim Clipsham,[3] Anne Smith,[1,2] Jai Chitnavis,[3] Janet S. Sinsheimer,[5] Victoria A. Bloomfield,[3] Mary McCartney,[4] Olive Cox,[3] Lon R. Cardon,[1] Bryan Sykes,[2] and John Loughlin[1,2]

[1]Wellcome Trust Centre for Human Genetics and [2]Cellular Genetics Group, Institute of Molecular Medicine, University of Oxford, and [3]Nuffield Orthopaedic Centre, Oxford; [4]Musgrave Park Hospital, Belfast; and [5]Departments of Biomathematics and Biostatistics, University of California, Los Angeles

Summary

We present a two-stage genomewide scan for osteoarthritis-susceptibility loci, using 481 families that each contain at least one affected sibling pair. The first stage, with 272 microsatellite markers and 297 families, involved a sparse map covering 23 chromosomes at intervals of ~15 cM. Sixteen markers that showed evidence of linkage at nominal $P \leq .05$ were then taken through to the second stage, with an additional 184 families. This second stage confirmed evidence of linkage for markers on chromosome 11q. Additional markers from this region were then typed to create a denser map. We obtained a maximum single-point LOD score, at D11S901, of 2.40 ($P = .0004$) and a maximum multipoint-LOD score of 3.15, between markers D11S1358 and D11S35. A subset of 196 of the 481 families, comprising affected female sibling pairs, generated a corrected LOD score of 2.54 ($P = .0003$) for marker D11S901, with evidence for linkage extending 12 cM proximal to this marker. When we stratified for affected male sibling pairs there was no evidence of linkage to chromosome 11. Our data suggest that a female-specific susceptibility gene for idiopathic osteoarthritis is located on chromosome 11q.

Introduction

Osteoarthritis (MIM 165720) is a common debilitating disease involving degeneration of the articular cartilage of synovial joints (Creamer and Hochberg 1997). Early-onset forms of the disease are associated with several osteochondrodysplasias—rare diseases involving abnormal bone and cartilage development that are transmitted as Mendelian traits (Horton 1996). The osteoarthritis in these conditions is secondary to the main dysplastic phenotype. The common late-onset form of the disease (idiopathic osteoarthritis) often has no obvious environmental or characteristic physical cause. Although idiopathic osteoarthritis has long been considered an inevitable consequence of aging, a strong genetic component has been demonstrated (Felson et al. 1998; Hirsch et al. 1998). A twin study has estimated that the heritability of radiographic osteoarthritis of the hand and knee shows a range of 39%–65% (Spector et al. 1996), and relative-risk calculations have revealed that first-degree relatives of individuals who have had hip- or knee-joint–replacement surgery for osteoarthritis have a ≤2.3-fold increased risk of developing end-stage disease (Chitnavis et al. 1997). Idiopathic osteoarthritis does not demonstrate a clear mode of inheritance and can be classified as a complex multifactorial disease.

A number of candidate genes have been proposed as potential susceptibility loci for idiopathic osteoarthritis, but the results from different studies have tended to be conflicting (Vikkula et al. 1993; Loughlin et al. 1994; Uitterlinden et al. 1997; Aerssens et al. 1998). This may simply be a reflection of the complexity of the disease. Alternatively, this conflict may highlight the limited power of some of the studies performed. The pathophysiology of osteoarthritis is complex, and the choice of candidate genes is prone to personal bias. Overall, therefore, we felt that the genetic dissection of idiopathic osteoarthritis merited a systematic genome screen using anonymous polymorphic microsatellite markers. To test for linkage, we used an affected sibling–pair approach and recruited affected sib pairs, using joint-replacement surgery resulting from idiopathic osteoarthritis as our ascertainment criterion. Our aim was to use families whose idiopathic osteoarthritis was severe and therefore more likely to have a genetic component. We used a two-stage approach, similar to that proposed by Hol-

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Address for correspondence and reprints: Dr. John Loughlin, Cellular Genetics Group, Institute of Molecular Medicine, University of Oxford, Oxford, OX3 9DS, United Kingdom. E-mail: john.loughlin@well.ox.ac.uk

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mans and Craddock (1997). In stage 1 we genotyped 272 microsatellite markers in 297 of 481 families. In stage 2, microsatellites that demonstrated evidence for linkage at nominal $P \leq .05$ in these 297 families were then analyzed in the remaining 184 families. This two-stage approach demonstrated linkage of markers on 11q to idiopathic osteoarthritis. Additional 11q markers were then typed to create a finer linkage map of this region. Stratification revealed that linkage was restricted to affected female sib pairs.

Families and Methods

Osteoarthritis Families

Families with at least two siblings each of whom had undergone one or more replacements of the total hip (THR), the total knee (TKR), or both, for primary idiopathic osteoarthritis, were recruited (table 1). Of the 790 individuals who had undergone only THR, 31.4% had undergone THR of the right hip and 22.7% had undergone THR of the left hip, whereas 45.9% had undergone bilateral THR. Of the 198 individuals who had undergone only TKR, 30.0% had undergone TKR of the right knee and 23.5% had undergone TKR of the left knee, whereas 46.5% had undergone bilateral TKR. Of the 66 individuals who had undergone hip and knee replacement, only 9 (13.6%) had undergone bilateral THR and bilateral TKR. Heberden's nodes were present in 38.5% of our affected individuals. The majority (58.3%) of these individuals had at most three nodes.

The collection of families was undertaken through the Nuffield Orthopaedic Centre in Oxford, the Musgrave Park Hospital in Belfast, and the Wishbone Trust Charity, which is part of the British Orthopaedic Association. The patients were reviewed and examined by trained clinical research nurses. Radiographs and, when available, histological samples were reviewed. We excluded all cases other than primary idiopathic osteoarthritis. Idiopathic osteoarthritis is typically a late-onset disease, and parents of affected siblings are rarely available. Of the 481 families recruited, only 3 had a parent who was able to participate. We therefore collected additional siblings who had not undergone THR or TKR, to assist in the determination of identical-by-descent (IBD) allele transmittance. The 481 families comprised 1,054 affected individuals plus 302 additional siblings. Of the affected individuals 625 (59.3%) were women and 429 (40.7%) were men. The average age of the affected individuals at the time of their first operation was 66 years (SD = 9.0 years), with an average age of 66 years (SD = 9.3 years) in affected women and an average age of 65 years (SD = 8.6 years) in affected men. From each individual, 25 ml of venous blood was collected into EDTA tubes, and DNA was extracted by conventional techniques. Ethical approval for the study was obtained from the Central Oxford Research Ethics Committee, and informed consent was obtained from all subjects.

Table 1

Family Structures

Family Structure and Type of Affectation	Stage 1	Stage 2	Total
Total no. of families:	297	184	481
With affected sibling pairs	265	149	414
With affected sibling trios	23	28	51
With affected sibling quartets	7	5	12
With other[a]	2	2	4
Stratified:			
Total no. of women	132	64	196
Pair	120	57	177
Trio	12	7	19
Total no. of men	60	42	102
Pair	55	37	92
Trio	4	5	9
Other[a]	1	0	1
Total no. of THR	194	117	311
Pair	170	94	264
Trio	17	19	36
Quartet	5	2	7
Other[a]	2	2	4
Total no. of TKR	34	20	54
Pair	33	19	52
Trio	1	1	2
Total no. of female THR	85	47	132
Pair	77	46	123
Trio	8	1	9
Total no. of female TKR	16	5	21
Pair	16	5	21
Total no. of male THR	44	27	71
Pair	40	25	65
Trio	3	2	5
Other[a]	1	0	1
Total no. of male TKR	4	4	8
Pair	4	4	8
Total no. of affected individuals:	641	413	1,054
Women	394	231	625
Men	247	182	429
Stratified:			
No. of THR	479	311	790
No. of TKR	121	77	198
No. of hip and knee	41	25	66
No. of female THR	287	173	460
No. of female TKR	77	42	119
No. of female hip and knee	30	16	46
No. of male THR	192	138	330
No. of male TKR	44	35	79
No. of male hip and knee	11	9	20
No. of additional siblings:	211	91	302
Women	107	49	156
Men	104	42	146

[a] Pairs of relatives, such as cousins, uncles, and aunts.

Markers and Genotyping

Our initial screening panel consisted of 292 microsatellite markers and was essentially the panel used by

Reed et al. (1994). Twenty (7%) of these markers amplified unreliably and were eliminated from the study. These 20 markers were spread across 14 of the 23 chromosomes. The additional microsatellite markers used to provide denser coverage of chromosome 11 were obtained from the Genome Database or from the Prism Linkage Mapping Set (version 2; Applied Biosystems). The markers were amplified with either the forward or the reverse primer in a PCR pair fluorescently labeled. The amplification products were electrophoresed through 6% acrylamide with automated DNA sequencers (ABI model 377; Applied Biosystems). We sized alleles, using GENESCAN (2.0.2) and GENOTYPER (1.1) software (Applied Biosystems). A list of the markers used and the results obtained are available electronically from the Wellcome Trust Centre for Human Genetics website.

Linkage Analysis

Since parents were rarely available to verify IBD, extensive error-checking procedures were employed for all families, for each marker. After we identified straightforward misinheritances, more-subtle transmission errors were detected by PEDCHECK (O'Connell and Weeks 1998). The entire family-data set was tested with RELATIVE (Goring and Ott 1997). RELATIVE tests whether the proportion of alleles shared IBD at unlinked loci (on the basis of $\geqslant$50 markers) is consistent with the expected proportion for each relative pair, thus allowing the identification of probable MZ twins, half-sibs, or unrelateds (as a result of unknown adoption or laboratory error). All 481 families analyzed in the study successfully progressed through these checks. In addition, the data were scrutinized for the presence of an excess of homozygotes among the genotypes produced with each marker, on the basis of allele frequencies and Hardy-Weinberg predictions (RECODE, version 1.4; D. Weeks, personal communication). Markers considered to be unreliable were eliminated from the study.

Linkage analysis was performed with the SIBPAIR module of the ANALYZE package (Terwilliger 1996). This module is able to use data from siblings to estimate IBD allele transmittance. In the linkage analysis, siblings who had not undergone joint replacement were given a clinical status of "unknown." The SIBPAIR module produces a single-point LOD score and its asymptotic *P* value. Allele frequencies were calculated from the input data by GAS (Oxford University Computing Services). Subsequent multipoint analyses were performed with ASPEX, which calculates its own allele frequencies from the data set by use of a maximum-likelihood method and employs marker information across the chromosome simultaneously. ASPEX produces a maximum multipoint-LOD score (MLS) under an additive model. It also produces an exclusion map along the entire chromosome, on the basis of a fixed value for sibling relative risk (λ). To estimate the influence that allele frequencies on the linkage to chromosome 11 have, we ran the linkage analyses through the following artificially created sets of allele frequencies: (1) alleles that were of equal frequency; (2) alleles that had a frequency $< .1$, which were binned together; and (3) alleles that were assigned frequency values either on the basis of the founders from each pedigree or (where no founders existed) on the basis of individuals selected at random from the pedigree (RECODE, version 1.4).

Our linkage-analysis strategy was to genotype a sparse map in a first stage containing 297 of our 481 families. Any marker that had a nominal *P* value $\leqslant .05$ in stage 1 would then be examined in the remaining 184 families (stage 2). The aim of this strategy was to take through to stage 2 only those markers that demonstrated reasonable evidence of linkage (Holmans and Craddock 1997). In stage 2 we were not necessarily expecting to repeat any of the positive linkage results of stage 1 but, instead, were looking for further evidence of linkage, even if only moderate. If a marker's *P* value for stages one and two combined was no more than the *P* value for stage 1, then it would support linkage at that marker. There was no difference in the ascertainment criteria between the stage 1 and stage 2 families; once a reasonably large number of families had been collected, we began the first stage of our linkage strategy.

Stratification

We stratified by sex, joint replaced (hip or knee), and both sex and joint replaced. For those families with more than two affected siblings and in which the siblings were not all of the same sex, the affected sibling(s) of opposite sex to a same-sex pair were given an affected status of "unknown" in the linkage analysis.

A "hip-only pair" comprised siblings who had each undergone THR (uni- or bilateral), whereas a "knee-only pair" comprised siblings who had undergone TKR (uni- or bilateral). If an affected pair comprised one sibling who had undergone joint replacement of only one type of joint (hip or knee), whereas the affected sibling had undergone joint replacement of the hip and knee, then that pair was excluded. For an affected trio, if a pair of the siblings had undergone joint replacement of the same joint type only (hip or knee), whereas the third sibling had undergone both hip and knee replacement, then the concordant pair were used in the stratification study and the third sibling was given a status of "unknown" in the linkage analysis.

We adjusted LOD scores and *P* values to correct for the six strata tested (women only, men only, hips only, knees only, female hip, and male hip). For a corrected LOD we deducted $\log 6 = 0.78$ from the original LOD

Table 2

Markers with Evidence for Linkage in Stage 1

	Stage 1		Stage 2		Combined	
Marker	*P*	LOD Score	*P*	LOD Score	*P*	LOD Score
D2S202	.036[a]	.70	.07	.49	.009[a]	1.21
D3S1266	.017[a]	.96	.5	...	.082	.42
D4S231	.040[a]	.67	.5	...	.33	.04
D4S415	.018[a]	.95	.33	.04	.025[a]	.83
D6S260	.050[a]	.58	.5	...	.13	.29
D6S273	.016[a]	.98	.5	...	.077	.44
D6S286	.030[a]	.77	.5	...	.081	.42
D6S281	.046[a]	.61	.45	...	.062	.52
D7S669	.018[a]	.94	.25	.10	.021[a]	.90
D7S530	.006[a]	1.36	.41	.01	.013[a]	1.09
D11S907	.050[a]	.58	.12	.31	.025[a]	.84
D11S903	.017[a]	.97	.07	.49	.007[a]	1.32
D11S901	.0004[a]	2.45	.10	.37	.0004[a]	2.40
D17S807	.014[a]	1.03	.5	...	.15	.24
D17S789	.010[a]	1.16	.5	...	.071	.47
DXS1068	.024[a]	.84	.5	...	.10	.35

Note.—Nominal *P* values and LOD scores for all markers that had $P \leq .05$.

[a] $P \leq .05$.

score, whereas for a corrected *P* value we increased the original *P* value sixfold (Kidd and Ott 1984).

Results

Sixteen markers from stage 1 showed evidence of linkage at a nominal *P* value ≤.05 (table 2). These markers were then genotyped in the remaining 184 families of stage 2. None of the 16 markers had a nominal *P* value ≤.05 in this second stage, although three had $P \leq .10$: D2S202 ($P = .07$), D11S903 ($P = .07$), and D11S901 ($P = .10$) (table 2). When the data for stages 1 and 2 were combined and compared with those for stage 1 only, the combined *P* value decreased for 3 of the 16 markers: D2S202 ($P = .009$ for combined vs. $P = .036$ for stage 1), D11S907 ($P = .025$ for combined vs. $P = .05$ for stage 1), and D11S903 ($P = .007$ for combined vs. $P = .017$ for stage 1); for D11S901 the *P* value was unchanged ($P = .0004$). Increasing the number of families therefore increased or supported the evidence for linkage at these four markers. Since three of the four markers were on chromosome 11, we concentrated our analysis on this chromosome.

The three chromosome 11 markers that had nominal *P* values ≤.05 in the combined data set encompass ~55 cM of the chromosome. Most of the chromosome 11 markers from stage 1 were not taken through to stage 2 because they did not reach our linkage criterion of $P \leq .05$. Two of these markers immediately flanked the 55-cM region, and one was located within it. These three markers were genotyped in the 184 families of stage 2. To provide denser coverage of the chromosome we also genotyped 11 new markers, located within and around this 55-cM region, for all 481 families. This made a total of 17 markers covering 153 cM of chromosome 11, at a mean density of ~1 marker/9 cM (table 3). The lowest *P* value remained with marker D11S901 (.0004). A multipoint analysis gave an MLS of 3.15, distal to D11S901 and between markers D11S1358 and D11S35 (fig. 1). An estimate of the contribution of the chromosome 11 locus to osteoarthritis can be calculated from λ for this locus. The λ for D11S901 is 1.3 (mean IBD estimate of .56, with z_0 [the proportion of sib pairs sharing neither allele IBD] of .19]. In the British population the λ for osteoarthritis, ascertained through joint-replacement surgery, has been determined to be 2.3 (Chitnavis et al. 1997). Therefore, under an additive model the contribution of the chromosome 11 locus may be as large as 23% ([1.3−1.0]/[2.3−1.0]), whereas under a nonadditive model the contribution may be as large as 31% (log 1.3/log 2.3) (Risch 1990; Hager et al. 1998). A sensitivity analysis determined that the linkage on chromosome 11 was robust to misspecification of allele frequencies (data not shown).

Stratification

It has often been noted in epidemiological studies that there is a preponderance of osteoarthritis in women (Creamer and Hochberg 1997). This may be due to differential effects that environmental factors have on the two sexes. However, a Finnish study in twins has suggested that genetic susceptibility may be greater in women than in men (Kaprio et al. 1996), and this result

Table 3

Chromosome 11 Markers for Stages 1 and 2 Combined

Marker	Distance from 11p Telomere (in cM)	*P*	LOD Score	Mean IBD Estimate	PIC
D11S4046	4	.36	.03	.51	.85
D11S907	51	.025[a]	.84	.54	.67
D11S903	64	.007[a]	1.32	.55	.73
D11S4191	69	.01	.35	.52	.84
D11S1883	73	.50	...	.50	.73
D11S1314	82	.006[a]	1.36	.55	.76
D11S916	85	.012[a]	1.12	.54	.80
D11S937	89	.077	.44	.52	.89
D11S901	94	.0004[a]	2.40	.56	.80
D11S1342	101	.034[a]	.72	.54	.67
D11S1358	102	.066	.49	.53	.69
D11S35	110	.10	.36	.52	.76
D11S898	110	.058	.53	.53	.76
D11S908	121	.50	...	.50	.65
D11S925	133	.096	.37	.52	.81
D11S4089	134	.50	...	.50	.72
D11S1320	157	.50	...	.50	.59

[a] $P \leq .05$.

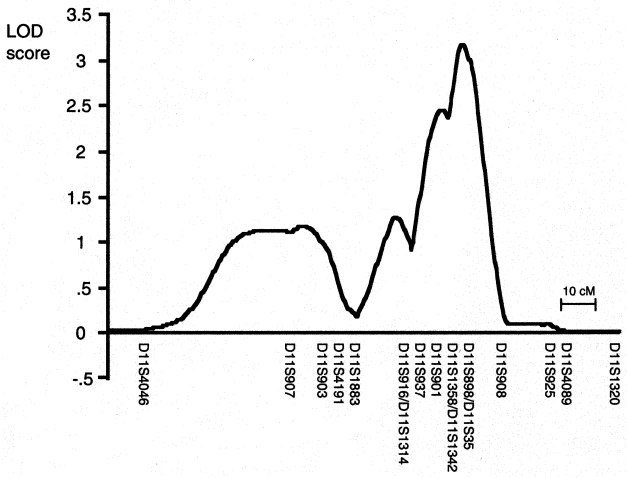

Figure 1 Multipoint analysis of chromosome 11, for stages 1 and 2 combined.

has been supported by a segregation analysis (Felson et al. 1998). Not only have differences in heritability between women and men been reported, but it also has been suggested that there are heritability differences between groups defined by type of affected joint (Lindberg 1986; Cooper et al. 1994; Chitnavis et al. 1997). These differences may be the result of genetic-locus heterogeneity. On the basis of these studies, we stratified our results for chromosome 11 into six categories: affected women only (196 families), affected men only (102 families), hips only (men, women, or both; 311 families), knees only (men, women, or both; 54 families), affected women who had undergone THR but not TKR (female THR; 132 families), and affected men who had undergone THR but notTKR (male THR; 71 families) (table 1). We did not stratify for female TKR or male TKR, because the number of families was too low (21 and 8, respectively) to allow reliable inference of linkage.

This stratification analysis revealed that the linkage to chromosome 11 was predominantly accounted for by the affected women–only pairs, with a single-point LOD score of 2.54 ($P = .0003$, mean IBD estimate of .62) for marker D11S901 (table 4) (LOD scores and P values were corrected for the six stratification tests performed). Only one marker flanking D11S901 also supported linkage in women-only pairs at $P \leq .05$: D11S1314 ($P = .036$), 12 cM proximal to D11S901. The MLS for women-only pairs was 2.81, between markers D11S901 and D11S1342 (fig. 2*A*). For affected men–only pairs there was no evidence of linkage either at D11S901 ($P = .5$) or with any of the markers distal or proximal to D11S901. At D11S901 there was much greater evidence for linkage in hip-only pairs ($P = .0024$) than in knee-only pairs ($P = .5$). Two markers proximal to D11S901 also supported linkage in hip-only pairs: D11S1314 ($P = .012$) and D11S916 ($P = .0054$). The MLS in hip-only pairs was 2.58, again between markers D11S901 and D11S1342 (fig. 2*B*). In female THR pairs the P value for D11S901 was .006, compared with .50 in male THR pairs. The MLS in female THR pairs was 3.03, between markers D11S1314 and D11S916 (fig. 2*C*). Overall, these results suggest that the linkage to chromosome 11 in our families is restricted to women with osteoarthritis. In our cohort there are a greater number of affected women–only pairs than affected men–only pairs (196 families vs. 102 families; table 1), which would provide the women-only pairs with greater power for detection of linkage; however, the difference, in LOD scores, between the two subsets is striking. Another factor that could affect power is the informativeness of the families and the degree to which IBD status can be determined, which is influenced by the number of siblings typed who are given an "unknown" clinical status. There was, however, no significant difference in these numbers between the women-only and men-only pairs (data not shown). Furthermore, the PIC values for marker D11S901 in the women-only and men-only pairs were not significantly different (.81 vs. .80). Of our 481 families, 185 were affected pairs that contained an affected brother and affected sister and so were not used in the stratification analysis. Linkage to D11S901 was not significant in these affected pairs ($P = .17$, LOD = 0.31, both uncorrected; PIC = .80). Overall, these results suggest that the specific nature of the 11q linkage, with its restriction to women-only pairs, is not an artifact of power differences between the strata. Regarding the apparent linkage differences between hip-only and knee-only pairs, there are substantially more hip-only families than knee-only families (311 vs. 54), which could account for our inability to detect linkage in our knee-only subset.

Discussion

We have identified on chromosome 11q a region that is likely to contain a osteoarthritis-susceptibility locus. We used a two-stage approach, similar to that suggested by Holmans and Craddock (1997). In the first stage we genotyped 272 microsatellite markers in 297 families with osteoarthritis. Sixteen markers that showed evidence of linkage at nominal $P \leq .05$ were then taken through to the second stage, with an additional 184 families. This second stage confirmed evidence of linkage for markers on chromosome 11q. Additional markers were then typed to create a denser map of this region. For the three genome-screen markers that supported linkage to this region in stage 1, the evidence for linkage increased (D11S907 and D11S903) or was unaltered (D11S901) when the stage 2 families were genotyped

and combined with the stage 1 families. This phenomenon was also observed for one other genome marker, D2S202. Interestingly, the chromosome 2 region to which this marker maps (2q31-q32.1) has previously been identified as a region that may harbor an osteoarthritis-susceptibility locus (Wright et al. 1996).

Our affected women–only pairs appear to account for the linkage at 11q, with a corrected *P* value of .0003 (LOD = 2.54) at D11S901, compared with .50 (LOD = 0.00) in men-only pairs. As mentioned earlier, it has been suggested that the heritability of osteoarthritis is greater in women than in men (Kaprio et al. 1996; Felson et al. 1998). This difference, if real, may be because one or more of the osteoarthritis-susceptibility loci acts in a hormonal pathway, is under some degree of hormonal regulation, or both. This observation could assist in the selection of candidate genes, once linkage to a particular region of the genome has been established. It is plausible that a hormonally regulated system, such as bone mass, is involved in osteoarthritis. Although osteoarthritis is primarily characterized by degeneration of articular cartilage, the pathophysiology of the disease is complex, with numerous cellular and extracellular changes in bone and cartilage metabolism. One finding commonly observed is an increase in the density and mass of the subchondral bone below the articulating cartilage (Lane and Nevitt 1994; Dequeker et al. 1997; Mansell and Bailey 1998). This has led to the suggestions that increased bone mass precedes any other gross changes in the osteoarthritic joint and that cartilage loss is a factor that is only secondary to this change. Under this assumption, genes that influence bone mass can be considered as candidates for osteoarthritis-susceptibility loci. Bone mass is under substantial hormonal regulation, as demonstrated by the effect that menopause has on both bone mass and the increase in osteoporotic-fracture risk in older women. A locus that is a regulator of bone mass has been mapped to chromosome 11q12-13, and this locus maps to the region where we have detected linkage (Gong et al. 1996; Johnson et al. 1997; Heaney et al. 1998; Koller et al. 1998).

A second locus that is on 11q and could be considered a candidate for osteoarthritis is a matrix metalloproteinase (MMP) gene cluster. MMPs are responsible for extracellular-matrix degradation and remodeling (Matrisian 1992). The 11q cluster consists of at least seven MMP genes (Pendas et al. 1996). However, this cluster maps to 11q22.3, which places it ⩾50 cM distal to D11S901 (11q13.2-13.3). It is unlikely therefore that this cluster represents the 11q osteoarthritis-susceptibility locus.

Deloukas et al. (1998) have reported a physical map of 30,000 human genes (GeneMap 98), which can be accessed through the World Wide Web. A search of this database reveals a large number of expressed sequence

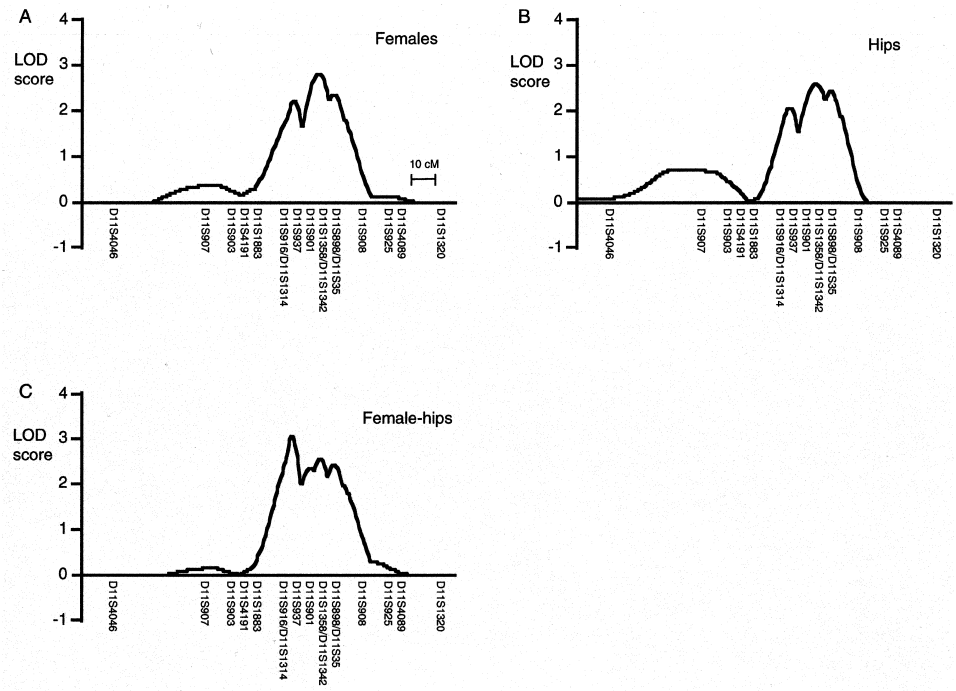

Figure 2 Multipoint analysis of chromosome 11 for stages 1 and 2 combined, with data stratified. *A*, Female-only pairs (n = 196 families). *B*, THR pairs (n = 311). *C*, female THR pairs (n = 132).

Table 4

Stratification

Marker	Distance (in cM)	Women (n = 196)		Men (n = 102)		THR (n = 311)		TKR (n = 54)		Female THR (n = 132)		Male THR (n = 71)	
		P	LOD Score	P	LOD Score	P	LOD Score	P	LOD Score	P	LOD Score	P	LOD Score
D11S4046	4	.50	...	.15	.05	.50	...	.50	...	.50	...	.03[a]	.67
D11S907	51	.50	...	.50	...	.30	...	.50	...	.50	...	.50	...
D11S903	64	.50	...	.50	...	.50	...	.50	...	.50	...	.50	...
D11S4191	69	.41	...	.50	...	.50	...	.50	...	.50	...	.50	...
D11S1883	73	.50	...	.50	...	.50	...	.50	...	.50	...	.50	...
D11S1314	82	.036[a]	.59	.50	...	.012[a]	1.04	.50	...	.012[a]	.95	.50	...
D11S916	85	.09	.24	.50	...	.0054[a]	1.34	.50	...	.024[a]	.77	.50	...
D11S937	89	.09	.25	.50	...	.09	.24	.50	...	.11	.16	.50	...
D11S901	94	.0003[a]	2.54	.50	...	.0024[a]	1.67	.50	...	.006[a]	1.26	.50	...
D11S1342	101	.11	.16	.50	...	.50	...	.26	...	.50	...	.50	...
D11S1358	102	.09	.24	.50	...	.50	...	.50	...	.13	.11	.50	...
D11S35	110	.50	...	.40	...	.50	...	.50	...	.23	...	.46	...
D11S898	110	.38	...	.50	...	.22	...	.50	...	.17	...	.50	...
D11S908	121	.50	...	.50	...	.50	...	.50	...	.50	...	.50	...
D11S925	133	.50	...	.48	...	.50	...	.50	...	.50	...	.50	...
D11S4089	134	.50	...	.26	...	.50	...	.50	...	.50	...	.12	.13
D11S1320	157	.50	...	.50	...	.50	...	.50	...	.50	...	.50	...

NOTE.—P values and LOD scores are corrected to account for the six strata tested.
[a] $P \leq .05$.

tags (ESTs) that map to 11q. These are a starting point for the identification of single-nucleotide polymorphisms, which can be used to narrow the interval and to define the osteoarthritis locus more precisely. In addition, mutation analyses of candidate genes derived from these ESTs can take place concurrently with attempts at fine mapping.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

ftp://lahmed.stanford.edu/pub/aspex (for ASPEX software)
ftp://linkage.cpmc.columbia.edu (for ANALYZE software package)
GeneMap 98, http://www.ncbi.nlm.nih.gov/genemap (for map of 30,000 human genes)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for osteoarthritis [MIM 165720])
Oxford University Computing Services, http://users.ox.ac.uk/~ayoung/gas.html (for GAS software)
Wellcome Trust Centre for Human Genetics, http://www.well.ox.ac.uk/oa/genome_screen (for complete osteoarthritis genome screen)

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