OsteoArthritis and Cartilage (2004) **12,** S39–S44

doi:10.1016/j.joca.2003.09.005

Osteoarthritis and Cartilage

International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Risk factors for osteoarthritis: genetics[1]

Tim D. Spector MD, MSc, FRCP* and Alex J. MacGregor MD, MSc FRCP
Twin Research & Genetic Epidemiology Unit, St. Thomas' Hospital, London, UK

Summary

Although the multifactorial nature of osteoarthritis (OA) is well recognized, genetic factors have been found to be strong determinants of the disease. Evidence of a genetic influence of OA comes from a number of sources, including epidemiological studies of family history and family clustering, twin studies, and exploration of rare genetic disorders. Classic twin studies have shown that the influence of genetic factors is between 39% and 65% in radiographic OA of the hand and knee in women, about 60% in OA of the hip, and about 70% in OA of the spine. Taken together, these estimates suggest a heritability of OA of 50% or more, indicating that half the variation in susceptibility to disease in the population is explained by genetic factors. Studies have implicated linkages to OA on chromosomes 2q, 9q, 11q, and 16p, among others. Genes implicated in association studies include VDR, AGC1, IGF-1, ER alpha, TGF beta, CRTM (cartilage matrix protein), CRTL (cartilage link protein), and collagen II, IX, and XI. Genes may operate differently in the two sexes, at different body sites, and on different disease features within body sites. OA is a complex disease, and understanding its complexity should help us find the genes and new pathways and drug targets.

Key words: Osteoarthritis, Etiology, Genetics, Twin studies.

Evidence of a genetic influence in osteoarthritis

This paper presents a brief overview of the genetics of osteoarthritis (OA) and its relationship to bone and bone density. Although the multifactorial nature of OA is well recognized, genetic factors have been found to be strong determinants of this disease. Evidence of a genetic influence of OA comes from a number of sources, including epidemiological studies of family history and family clustering, adoption studies, twin studies, and exploration of rare genetic disorders related to OA, such as chondrodysplasias.

FAMILY STUDIES

Family studies provide an indication of the extent to which the external environment and the genetically-determined internal environment account for disease. Familial clustering of OA has been recognized since the earliest descriptions of the disease; however, its importance in terms of etiology has only recently been fully appreciated. Familial clustering of Heberden's nodes of the fingers was first formally studied by Stecher in the 1940s[1]. Family clustering of hand and knee OA has since been confirmed in epidemiological surveys in the U.K. by Kellgren *et al.*[2]. and more recently in large community-based surveys in the U.S., such as the Baltimore Longitudinal Study of Aging[3] and the Framingham Offspring Study[4].

Clustering of hip OA has been more difficult to study because of its low prevalence. The recently published community-based surveys have not included data on radiographic hip OA[3,4]. Nevertheless, studies designed to evaluate the prevalence of disease among siblings of probands who have undergone total joint replacement have shown 2- to 3-fold increases in the risk of OA relative to controls[5–8]. The 4.7-fold increase in risk observed in the study by Lanyon *et al.*[7]. is probably a slight overestimate resulting from the methods used for case selection.

These studies show that within affected families there is a clustering of cases of OA in the hands, knees, and hip, with significant increases in risk among relatives of probands. Evidence of family clustering of OA of the spine has also been presented in several radiological case reports and case series of sciatica[9], cervical spondylosis[10], and herniated discs[11–13].

Only limited information is available from family studies, in part because little family history data have been collected, and in part because data gathered by questioning patients with OA about their parents has been considered unreliable. Further, family studies have a number of shortcomings that restrict their interpretation. Chief among these is the failure to ensure that index individuals and relatives are matched with respect to age. Age matching is particularly important in diseases such as OA in which age has a crucial effect on the disease. In addition, family studies do not permit differentiation of clustering that is due to a shared environment from clustering that is caused by genetic factors. For example, environmental factors, such as patterns of exercise, that may affect the risk of OA have been shown to cluster in families and are difficult to control for in epidemiological studies. Furthermore, population data on hip and spine OA are limited, making it difficult to determine the expected rates of OA at these sites for comparative purposes.

[1] Supported by Procter & Gamble Pharmaceuticals, Mason, OH
*Address correspondence to: Tim D. Spector, MD, Twin Research & Genetic Epidemiology Unit, St. Thomas' Hospital, London, SE1 7EH, UK. Tel.: +44-207-960-5557; Fax: +44-207-922-8234; E-mail: tim.spector@kcl.ac.uk
E-mail: http://www.twin-research.ac.uk

TWIN STUDIES

Clustering of disease in families is due either to shared genetic influences or the shared family environment. The study of twins, specifically the comparison of the occurrence of disease in monozygotic (MZ) and dizygotic (DZ) twins, allows the effects of genetic factors and the shared family environment to be separated in a design that naturally allows matching for age. Because MZ twins have identical genes, any intrapair variation may be attributed to environmental factors. In contrast, DZ twins share, on average, only half of their genes, and any intrapair differences may be attributed to both environmental and genetic factors. Comparison of the occurrence of disease in MZ and DZ twins, therefore, makes it possible to quantify genetic and environmental contributions to disease and disease-related traits in a population[14]. Classic twin studies can yield a good estimate of the heritability, defined as the relative contribution of genetic variance to the liability to disease, of any disease in a population[15]. Using an MZ-discordant design (one affected co-twin) also permits ideally matched case-control studies to be performed.

In the last 10 years, we have been collecting data relating to OA from a large group of healthy twins that make up the St. Thomas' UK Adult Twin Registry[16]. The registry is a volunteer-based group of nearly 10 000 adult, mainly female, twin pairs recruited through media campaigns from the healthy UK population. These volunteers are representative of the UK population in terms of most environmental risk factors, rates of OA, and disease features and have been found to be similar to the Chingford population of age-matched singletons for a range of musculoskeletal phenotypes[17].

We first assessed the relative contribution of genetic and environmental factors to OA of the hands and knees in 130 MZ and 120 DZ female twins aged 48 to 70 years in a classic twin study[18]. The correlations of radiographic osteophytes and joint space narrowing at most sites and the presence of Heberden's nodes and knee pain were higher in the MZ pairs than in the DZ pairs. The findings from this study showed that the influence of genetic factors in radiographic OA of the hand and knee in women is between 39% and 65%, independent of known environmental or demographic confounding factors. In another study in a larger sample of twins, we found that joint space narrowing of the hip was also heritable, with an estimated heritability of 60%[19]. We also evaluated the extent of genetic influences on disc degeneration in 172 MZ and 154 DZ twins unselected for back pain or disc disease[20] using magnetic resonance images of the cervical and lumbar spine. For the overall degeneration score, heritability was 73% at the cervical spine and 74% at the lumbar spine.

Interestingly, when we examined the genetic contribution to the various individual features of OA, we found differences in genetic influence. The data on disc height and disk bulge suggested a strong genetic component, whereas disc signal intensity did not differ between the MZ and DZ pairs, suggesting that environmental factors are the predominant influence affecting this measure. These findings may provide insight into which clinical findings are actually part of OA and which are not, since it is unlikely that some aspects of the disease are genetic while others are not.

Our findings indicate that OA of the spine, hip, knee, and hand are all heritable to slightly different extents (Fig. 1). Taken together, these heritability estimates suggest that at least half the variation in susceptibility to disease in the population is explained by genetic factors.

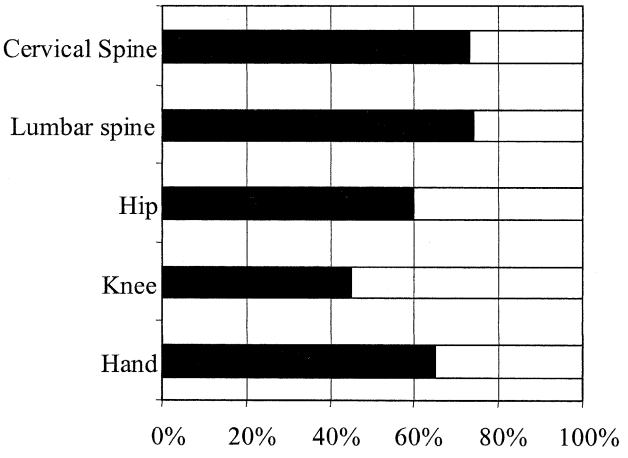

Fig. 1. Estimated heritability of osteoarthritis at different sites.

Candidate genes in the inheritance of osteoarthritis

The findings that OA is a largely heritable disease raise the question of which genes are responsible. Clues come from studies of inherited diseases in which OA forms a part and for which single-gene defects have been identified, such as chondrodysplasias, spondyloepiphyseal dysplasia, and collagen II and IX mutations[21,22]; from animal models of inherited skeletal disorders[23]; and from rare examples of familial OA, which have tended to implicate genes for collagen and other structural proteins[24–28]. Although some studies have shown the presence of mutations in the COL2A1 gene for type II procollagen in individuals affected with OA in some families[26,29], other studies have indicated that this gene is not the disease locus in other families with common OA[29,30]. These strictly familial diseases are rare, and the small number of family studies do not allow conclusions to be drawn regarding the contribution of genetics to disease in the population. In fact, there is currently little evidence that common forms of OA are due to mutations in genes for collagen[31].

From the results of segregation analyses of data from the Framingham Offspring Study, which are now sufficiently mature that the offspring of the original cohort have developed disease, Felson *et al.*[4]. inferred that there is significant genetic contribution to hand and knee OA, with a pattern most consistent with that of a major Mendelian gene and a multifactorial component. This multifactorial component may be other genes or environmental or personal factors[32]. However, as with most segregation analyses, other explanations and interpretations are possible[33].

Linkage studies have implicated quantitative trait loci (QTL) regions on chromosomes 2q, 9q, 11q, and 16p, among others (Table I)[34–38]. Candidate genes for OA on these chromosomes include those encoding for fibronectin, a glycoprotein present in the extracellular matrix of normal cartilage; the alpha-2 chain of collagen type V, a major constituent of bone; the interleukin 8 receptor, important in the regulation of neutrophil activation and chemotaxis, within the 2q23-25 region of chromosome 2;[14] and the so-called "high bone mass locus" and the matrix metalloproteinase (MMP) gene cluster on chromosome 11q[40]. The conclusions reached on the basis of these studies are limited by the small size and relatively small logarithm of the odds (Lod) scores of the studies. Loughlin *et al.*

Table I
Major chromosomal regions with linkages to osteoarthritis (OA)

Chromosome	Reference
2q23-35 (nodal OA)	Wright, 1996[34]
2q12-14 (DIP* OA)	Leppavuori *et al.*[36]
2q31-32, 4q 12-21, 6p/6q, 16p, Col 9A1 (THR†)	Loughlin *et al.*[35]; Mustafa *et al.*[39]
4q27, Xp11.3, 7p22 (DIP* OA)	Leppavuori *et al.*[36]
16p (hip OA)	Ingvarsson *et al.*[37]
1p, 17,9,13,19 (hand OA scores)	Demissie *et al.*[38]

*DIP=distal interphalangeal joint.
†THR=total hip replacment.

conducted linkage analyses in a larger study including 481 families that each contained at least one pair of siblings who had undergone knee or hip joint replacements[35,39–41]. This study included men and women and mixed-sex siblingships, and combined data from patients with hip and knee OA. As a consequence, this study did not at first reveal any meaningful information. When the data were subdivided by sex and site of OA, clearer patterns began to emerge, particularly in the female hip OA group, in which a linkage of the type IX collagen gene COL9A1 (6q12-q13) to OA was suggested[39]. Findings from a recent study from the Framingham group revealed a large number of suggestive linkages to hand OA score in around 300 unselected families[38]. The heritabilities determined in this study were lower than previously found. Unfortunately, none of these linkages clearly coincided with those areas previously reported, including the area on chromosome 2 most commonly linked with OA. Moreover a large linkage study using fine mapping failed to find any significant at 2q for hand or knee[42].

Genes implicated in association studies to date are seen in Table II[43,47]. The most consistent finding is that of the involvement of the VDR gene[44,45], but this has not been replicated in family candidate linkage studies[31,46]. One would anticipate that this list will grow, and that as analyses are repeated in larger samples and different populations, inconsistencies will become fewer. Interestingly, the list of genes associated with osteoporosis is virtually the same as that for OA, with the exception of those for cartilage. The results of these association studies, even of the best candidate, VDR, are still uncertain and remain to be confirmed in larger studies in more homogeneous populations.

Genetic influences in symptomatic osteoarthritis

Radiographs provide no information on pain or disability, and it is well known that the overlap between pain and radiological change is inexact. For example, abnormal findings on magnetic resonance images of the lumbar spine do not necessarily correlate with clinical symptoms[47]. Symptomatic OA and radiographic OA may well represent two different although related phenotypes with different underlying causes involving different genes. Studies have so far not been large enough to explore both.

Table II
Genes implicated in osteoarthritis in association studies

VDR	CRTM (cartilage matrix protein)
Col2A	CRTL (cartilage link protein)
AGC1	A1ACT
IGF-1	COL9A1
ER alpha	COL11A1
TGF beta	COl1A1
	ANK

Clustering and specificity of disease features

One has to be aware also that genes may operate differently in the two sexes, at different body sites, and on different disease features within body sites. Heritability appears to be greater in females[41,48]. Site-specificity of genetic effects has been suggested in recent linkage results[41], and association studies have implicated different genes (e.g., VDR and COL2A1) in the occurrence of osteophytosis and joint space loss[49]. Therefore, certain genes may 'turn on' bone but not cartilage, so each tissue must be examined separately to allow accurate determination of genetic linkages. Combining all individuals with OA without regard to whether they are 'bone formers' or 'cartilage losers' may make it impossible to detect a tissue-specific effect. Clearly, studies will provide more information if they are designed to examine populations representing specific aspects or different components of OA.

The relationship between osteoarthritis and osteoporosis

The question remains, are the genes for bone density and OA pleiotropic (shared)? Studies have shown that there is a difference of 6% to 8% in bone mineral density (BMD) between populations of subjects with OA and controls[50,51]. Twin studies, which allow adjustment and matching for genetic factors, have shown that MZ twins discordant for OA demonstrate discordance in BMD of the hip of only 3% to 4%[52]. The difference in the discordance of 6% to 8% at the population level and 3% to 4% in MZ twins suggests that some genes overlap both phenotypes[52].

The heritability of different osteoporosis-related phenotypes that are important independent risk factors is generally about 50% or greater. Heritability is close to 80% for spinal BMD and over 60% for muscle mass[53], both of which are important determinants in OA and osteoporosis. Hip axis length, a measure of the size of the femur, is also heritable, as is broadband ultrasound attenuation and velocity of sound of the calcaneus, a measure of bone structure not yet fully understood[54]. About 75% of the variability observed in urinary collagen crosslinks (markers of bone resorption) is due to genes[55]. These markers are also elevated in OA[56,57]. These findings suggest that most of the variation in susceptibility to osteoporosis in the population is best explained by genetic causes. Modifying these genes could be important for both diseases.

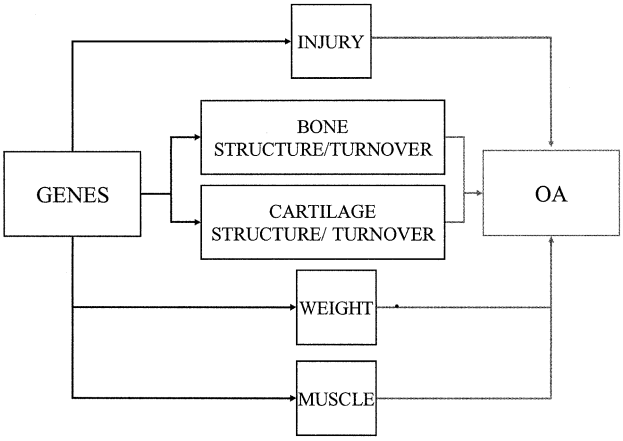

Fig. 2. The role of genes in osteoarthritis.

Conclusions

In conclusion, the epidemiological study of OA has allowed us to quantify the disease burden and the contribution of genetic and environmental risks in populations. It also allows us to quantify the importance of individual risk factors operating as potential targets for disease prevention and reveals disease mechanisms as targets for drug intervention. Genes are the strongest risk factor for OA in the general population. Fig. 2 schematically shows a simplistic picture of the role of genes in OA. Genes act through a complex web of mechanisms involving injury and its avoidance; response to injury; body weight; muscle mass; and bone structure and bone turnover or cartilage structure and cartilage turnover or, synergistically, the two together. Clearly the heritability of OA is very complex, and understanding its complexity should help us find the genes and new pathways and drug targets. To better understand the genetic component of OA in the future, larger linkage studies are needed that focus more attention on phenotype, sex, and disease site. Better and larger association studies are needed that are adequately powered and use greater numbers of genetic markers, such as either anonymous single nucleotide polymorphisms (SNPs) or specified candidates. Other techniques to increase power and reduce cost include using DNA pooling and extreme discordants, along with parallel animal studies (e.g., the study on the ANK gene[58]). Clinical and genetic programs incorporating study of both OA and osteoporosis will also provide extra power to find the genes for both disorders as well as new pathways.

References

1. Stecher RM. Heberden's nodes. Heredity in hypertrophic arthritis of the finger joints. Am J Med Sci 1941;201:801–9.
2. Kellgren JH, Lawrence JS, Bier F. Genetic factors in generalised osteoarthritis. Ann Rheum Dis 1963; 22:237–55.
3. Hirsch R, Lethbridge-Cejku M, Hanson R, Scott WW Jr., Reichle R, Plato CC, *et al.* Familial aggregation of osteoarthritis: data from the Baltimore Longitudinal Study on Aging. Arthritis Rheum 1998;41:1227–32.
4. Felson DT, Couropmitree NN, Chaisson CE, Hannan MT, Zhang Y, McAlindon TE, *et al.* Evidence for a Mendelian gene in a segregation analysis of generalized radiographic osteoarthritis: the Framingham Study. Arthritis Rheum 1998;41:1064–71.
5. Lindberg H. Prevalence of primary coxarthrosis in siblings of patients with primary coxarthrosis. Clin Orthop 1986;203:273–5.
6. Chitnavis J, Sinsheimer JS, Clipsham K, Loughlin J, Sykes B, Burge PD, *et al.* Genetic influences in end-stage osteoarthritis. Sibling risks of hip and knee replacement for idiopathic osteoarthritis. J Bone Joint Surg Br 1997;79:660–4.
7. Lanyon P, Muir K, Doherty S, Doherty M. Assessment of a genetic contribution to osteoarthritis of the hip: sibling study. BMJ 2000;321:1179–83.
8. Ingvarsson T, Stefansson SE, Hallgrimsdottir IB, Frigge ML, Jonsson H Jr., Gulcher J, *et al.* The inheritance of hip osteoarthritis in Iceland. Arthritis Rheum 2000;43:2785–92.
9. Postacchini F, Lami R, Pugliese O. Familial predisposition to discogenic low-back pain. An epidemiologic and immunogenetic study. Spine 1988;13:1403–6.
10. Yoo K, Origitano TC. Familial cervical spondylosis. Case report. J Neurosurg 1998;89:139–41.
11. Matsui H, Terahata N, Tsuji H, Hirano N, Naruse Y. Familial predisposition and clustering for juvenile lumbar disc herniation. Spine 1992;17:1323–8.
12. Varlotta GP, Brown MD, Kelsey JL, Golden AL. Familial predisposition for herniation of a lumbar disc in patients who are less than twenty-one years old. J Bone Joint Surg Am 1991;73:124–8.
13. Scapinelli R. Lumbar disc herniation in eight siblings with a positive family history for disc disease. Acta Orthop Belg 1993;59:371–6.
14. Cicuttini FM, Spector TD. What is the evidence that osteoarthritis is genetically determined? Baillieres Clin Rheumatol 1997;11:657–69.
15. MacGregor AJ, Spector TD. Twins and the genetic architecture of osteoarthritis [editorial]. Rheumatology (Oxford) 1999;38:583–8.
16. Boomsma DI. Twin registers in Europe: an overview. Twin Res 1998;1:34–51.
17. Andrew T, Hart DJ, Snieder H, de Lange M, Spector TD, MacGregor AJ. Are twins and singletons comparable? A study of disease-related and lifestyle characteristics in adult women. Twin Res 2001;4:464–77.
18. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. BMJ 1996;312:940–3.
19. MacGregor AJ, Antoniades L, Matson M, Andrew T, Spector TD. The genetic contribution to radiographic hip osteoarthritis in women: results of a classic twin study. Arthritis Rheum 2000;43:2410–6.
20. Sambrook PN, MacGregor AJ, Spector TD. Genetic influences on cervical and lumbar disc degeneration: a magnetic resonance imaging study in twins. Arthritis Rheum 1999;42:366–72.
21. Olsen BR. Mutations in collagen genes resulting in metaphyseal and epiphyseal dysplasias. Bone 1995; 17(2 Suppl):45S–49S.
22. Cicuttini FM, Spector TD. Genetics of osteoarthritis. Ann Rheum Dis 1996;55:665–7.
23. Li Y, Olsen BR. Murine models of human genetic skeletal disorders. Matrix Biol 1997;16:49–52.
24. Ala-Kokko L, Baldwin CT, Moskowitz RW, Prockop DJ. Single base mutation in the type II procollagen gene

(COL2A1) as a cause of primary osteoarthritis associated with a mild chondrodysplasia. Proc Natl Acad Sci USA 1990;87:6565–8.
25. Palotie A, Vaisanen P, Ott J, Ryhanen L, Elima K, Vikkula M, *et al.* Predisposition to familial osteoarthrosis linked to type II collagen gene. Lancet 1989; 1:924–7.
26. Vikkula M, Palotie A, Ritvaniemi P, Ott J, Ala-Kokko L, Sievers U, *et al.* Early-onset osteoarthritis linked to the type II procollagen gene. Detailed clinical phenotype and further analyses of the gene. Arthritis Rheum 1993;36:401–9.
27. Chapman KL, Mortier GR, Chapman K, Loughlin J, Grant ME, Briggs MD. Mutations in the region encoding the von Willebrand factor A domain of matrilin-3 are associated with multiple epiphyseal dysplasia. Nat Genet 2001;28:393–6.
28. Czarny-Ratajczak M, Lohiniva J, Rogala P, Kozlowski K, Perala M, Carter L, *et al.* A mutation in COL9A1 causes multiple epiphyseal dysplasia: further evidence for locus heterogeneity. Am J Hum Genet 2001;69:969–80.
29. Williams CJ, Jimenez SA. Heritable diseases of cartilage caused by mutations in collagen genes. J Rheumatol Suppl 1995;43:28–33.
30. Loughlin J, Irven C, Fergusson C, Sykes B. Sibling pair analysis shows no linkage of generalized osteoarthritis to the loci encoding type II collagen, cartilage link protein or cartilage matrix protein. Br J Rheumatol 1994;33:1103–6.
31. Baldwin CT, Cupples LA, Joost O, Demissie S, Chaisson C, Mcalindon T, *et al.* Absence of linkage or association for osteoarthritis with the vitamin D receptor/type II collagen locus: the Framingham Osteoarthritis Study. J Rheumatol 2002;29:161–5.
32. Felson DT, Myers R. Reply. Arthritis Rheum 1999; 42:1069–70.
33. Spector TD, Snieder H, Keen R, Lewis C, MacGregor A. Interpreting the results of a segregation analysis of generalized radiographic osteoarthritis: comment on the article by Felson et al. Arthritis Rheum 1999; 42:1068–70.
34. Wright GD, Hughes AE, Regan M, Doherty M. Association of two loci on chromosome 2q with nodal osteoarthritis. Ann Rheum Dis 1996;55:317–9.
35. Loughlin J, Mustafa Z, Smith A, Irven C, Carr AJ, Clipsham K, *et al.* Linkage analysis of chromosome 2q in osteoarthritis. Rheumatology (Oxford) 2000; 39:377–81.
36. Leppavuori J, Kujala U, Kinnunen J, Kaprio J, Nissila M, Heliovaara M, *et al.* Genome scan for predisposing loci for distal interphalangeal joint osteoarthritis: evidence for a locus on 2q. Am J Hum Genet 1999; 65:1060–7.
37. Ingvarsson T, Stefansson SE, Gulcher JR, Jonsson HH, Jonsson H, Frigge ML, *et al.* A large Icelandic family with early osteoarthritis of the hip associated with a susceptibility locus on chromosome 16p. Arthritis Rheum 2001;44:2548–55.
38. Demissie S, Cupples LA, Myers R, Aliabadi P, Levy D, Felson DT. Genome scan for quantity of hand osteoarthritis: the Framingham Study. Arthritis Rheum 2002;46:946–52.
39. Mustafa Z, Chapman K, Irven C, Carr AJ, Clipsham K, Chitnavis J, *et al.* Linkage analysis of candidate genes as susceptibility loci for osteoarthritis-suggestive linkage of COL9A1 to female hip osteoarthritis. Rheumatology (Oxford) 2000; 39:299–306.
40. Chapman K, Mustafa Z, Irven C, Carr AJ, Clipsham K, Smith A, *et al.* Osteoarthritis-susceptibility locus on chromosome 11q, detected by linkage. Am J Hum Genet 1999;65:167–74.
41. Loughlin J, Mustafa Z, Irven C, Smith A, Carr AJ, Sykes B, *et al.* Stratification analysis of an osteoarthritis genome screen-suggestive linkage to chromosomes 4, 6, and 16. Am J Hum Genet 1999; 65:1795–8.
42. Gillaspy E, Sprekley K, Wallis G, Doherty M, Spector TD. Investigation of linkage on chromosome 2q and hand and knee osteoarthritis. Arthritis Rheum 2002; 46:3386–7.
43. Keen RW, Snieder H, Molloy H, Daniels J, Chiano M, Gibson F, *et al.* Evidence of association and linkage disequilibrium between a novel polymorphism in the transforming growth factor b1 gene and hip bone mineral density: a study of female twins. Rheumatology 2001;40:48–54.
44. Keen RW, Hart DJ, Lanchbury JS, Spector TD. Association of early osteoarthritis of the knee with a Taq I polymorphism of the vitamin D receptor gene. Arthritis Rheum 1997;40:1444–9.
45. Uitterlinden AG, Burger H, Huang Q, Odding E, Duijn CM, Hofman A, *et al.* Vitamin D receptor genotype is associated with radiographic osteoarthritis at the knee. J Clin Invest 1997;100:259–63.
46. Loughlin J, Sinsheimer JS, Mustafa Z, Carr AJ, Clipsham K, Bloomfield VA, *et al.* 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; 27:779–84.
47. Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. N Engl J Med 1994;331:115–6.
48. Kaprio J, Kujala UM, Peltonen L, Koskenvuo M. Genetic liability to osteoarthritis may be greater in women than men [letter]. BMJ 1996;313:232.
49. Uitterlinden AG, Burger H, van Duijn CM, Huang Q, Hofman A, Birkenhager JC, *et al.* Adjacent genes, for COL2A1 and the vitamin D receptor, are associated with separate features of radiographic osteoarthritis of the knee. Arthritis Rheum 2000; 43:1456–64.
50. Nevitt MC, Lane NE, Scott JC, Hochberg MC, Pressman AR, Genant HK, *et al.* Radiographic osteoarthritis of the hip and bone mineral density. The Study of Osteoporotic Fractures Research Group. Arthritis Rheum 1995;38:907–16.
51. Hart DJ, Mootoosamy I, Doyle DV, Spector TD. The relationship between osteoarthritis and osteoporosis in the general population: the Chingford Study. Ann Rheum Dis 1994;53:158–62.
52. Antoniades L, MacGregor AJ, Matson M, Spector TD. A cotwin control study of the relationship between hip osteoarthritis and bone mineral density. Arthritis Rheum 2000;43:1450–5.
53. Arden NK, Spector TD. Genetic influences on muscle strength, lean body mass, and bone mineral density: a twin study. J Bone Miner Res 1997;12: 2076–20781.

54. Arden NK, Baker J, Hogg C, Baan K, Spector TD. The heritability of bone mineral density, ultrasound of the calcaneus and hip axis length: a study of postmenopausal twins. J Bone Miner Res 1996;11: 530–4.
55. Hunter D, De Lange M, Snieder H, MacGregor AJ, Swaminathan R, Thakker RV, *et al.* Genetic contribution to bone metabolism, calcium excretion, and vitamin D and parathyroid hormone regulation. J Bone Miner Res 2001;16:371–8.
56. Bettica P, Hart DJ, Cline G, Meyer J, Spector TD. Increased bone turnover in progressive osteoarthritis: the Chingford study. Arthritis Rheum 2002: in press.
57. Hunter DJ, Hart D, Snieder H, Bettica P, Swaminathan R, Spector TD. Evidence of altered bone turnover, vitamin D and calcium regulation with knee osteoarthritis in female twins. Rheumatology (Oxford) 2003, Jul 16 (epub ahead of print).
58. Ho AM, Johnson MD, Kingsley DM. Role of the mouse ank gene in control of tissue calcification and arthritis. Science 2000;289:265–70.