

Osteoarthritis and Cartilage



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Risk factors for osteoarthritis: genetics¹

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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.

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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 1940s¹. 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 Aging³ and the Framingham Offspring Study⁴.

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 sciatica⁹, cervical spondylosis¹⁰, 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

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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 population¹⁴. 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 population¹⁵. 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 Registry¹⁶. 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 phenotypes¹⁷.

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 study¹⁸. 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 disease²⁰ 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.

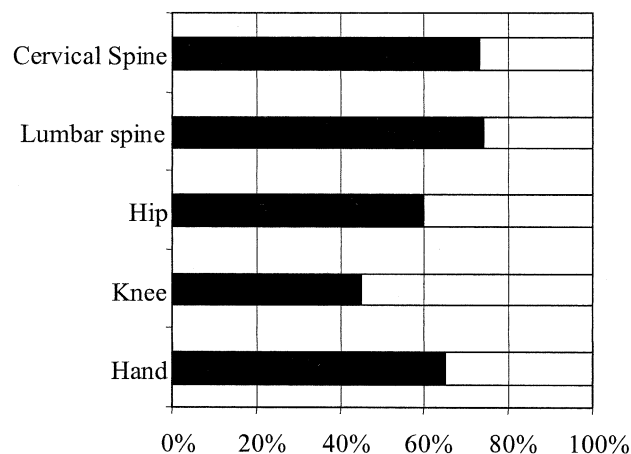


Fig. 1. Estimated heritability of osteoarthritis at different sites.

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 disorders²³; 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 collagen³¹.

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 factors³². However, as with most segregation analyses, other explanations and interpretations are possible³³.

Linkage studies have implicated quantitative trait loci (QTL) regions on chromosomes 2q, 9q, 11q, and 16p, among others (Table 1)^{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 11q⁴⁰. 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 <i>et al.</i> ³⁶
2q31-32, 4q 12-21, 6p/6q, 16p, Col 9A1 (THR†)	Loughlin <i>et al.</i> ³⁵ ; Mustafa <i>et al.</i> ³⁹
4q27, Xp11.3, 7p22 (DIP* OA)	Leppavuori <i>et al.</i> ³⁶
16p (hip OA)	Ingvarsson <i>et al.</i> ³⁷
1p, 17,9,13,19 (hand OA scores)	Demissie <i>et al.</i> ³⁸

*DIP=distal interphalangeal joint.

†THR=total hip replacement.

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 suggested³⁹. Findings from a recent study from the Framingham group revealed a large number of suggestive linkages to hand OA score in around 300 unselected families³⁸. 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 knee⁴².

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 symptoms⁴⁷. 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.

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 results⁴¹, and association studies have implicated different genes (e.g., VDR and COL2A1) in the occurrence of osteophytosis and joint space loss⁴⁹. 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 phenotypes⁵².

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 mass⁵³, 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 understood⁵⁴. About 75% of the variability observed in urinary collagen crosslinks (markers of bone resorption) is due to genes⁵⁵. 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.

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	COI1A1
	ANK

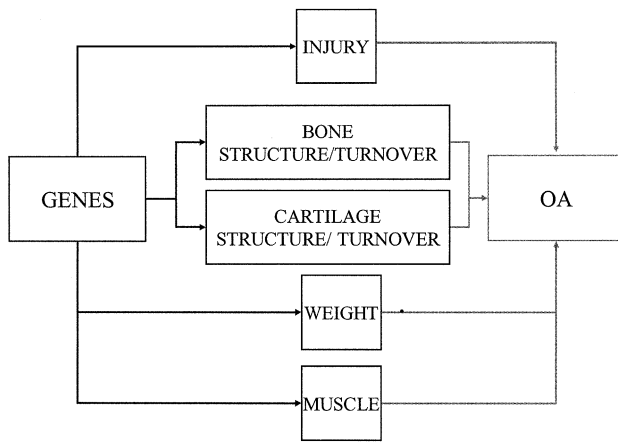


Fig. 2. The role of genes in osteoarthritis.

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 gene⁵⁸). 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.

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