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, 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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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; from animal models of inherited skeletal disorders; and from rare examples of familial OA, which have tended to implicate genes for collagen and other structural proteins. 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, other studies have indicated that this gene is not the disease locus in other families with common OA. 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.

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

Linkage studies have implicated quantitative trait loci (QTL) regions on chromosomes 2q, 9q, 11q, and 16p, among others. 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; and the so-called “high bone mass locus” and the matrix metalloproteinase (MMP) gene cluster on chromosome 11q. 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.
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. 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. 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. 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 OA.

Genes implicated in association studies to date are seen in Table II. The most consistent finding is that of the involvement of the VDR gene, but this has not been replicated in family candidate linkage studies. 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 radiographic change is inexact. For example, abnormal radiographs of the type III vertebrae may not be accompanied by clinical symptoms, and it is well known that the overlap between pain and radiographic change is inexact. For example, abnormal radiographs of the type III vertebrae may not be accompanied by clinical symptoms, and it is well known that the overlap between pain and radiographic change is inexact. For example, abnormal radiographs of the type III vertebrae may not be accompanied by clinical symptoms.

### Table I

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<thead>
<tr>
<th>Chromosome</th>
<th>Reference</th>
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<tbody>
<tr>
<td>2q23-35 (nodal OA)</td>
<td>Wright, 1998</td>
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<tr>
<td>2q12-14 (DIP* OA)</td>
<td>Leppävuori et al.</td>
</tr>
<tr>
<td>2q31-32, 4q 12-21, 6p6q, 16p, Col 9A1 (THR1)</td>
<td>Loughlin et al.</td>
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<tr>
<td>4q27, Xp11.3, 7p22 (DIP* OA)</td>
<td>Mustafa et al.</td>
</tr>
<tr>
<td>16p (hip OA)</td>
<td>Leppävuori et al.</td>
</tr>
<tr>
<td>1p, 17,9,13,19 (hand OA scores)</td>
<td>Ingvason et al.</td>
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<td>Demissie et al.</td>
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* † THR=total hip replacement.

### Table II

<table>
<thead>
<tr>
<th>Genes implicated in osteoarthritis in association studies</th>
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<tr>
<td>VDR CRTM (cartilage matrix protein)</td>
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<tr>
<td>Col2A CRTL (cartilage link protein)</td>
</tr>
<tr>
<td>AGC1 A1ACT</td>
</tr>
<tr>
<td>IGF-1 COL9A1</td>
</tr>
<tr>
<td>ER alpha COL1A1</td>
</tr>
<tr>
<td>TGF beta COH1A1</td>
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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, 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. About 75% of the variability observed in urinary collagen crosslinks (markers of bone resorption) is due to genes. These markers are also elevated in OA. 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.

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. Site-specificity of genetic effects has been suggested in recent linkage results, and association studies have implicated different genes (e.g., VDR and COL2A1) in the occurrence of osteophytosis and joint space loss. 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 relationships 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. 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%. 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.

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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 phenotypic, 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 mouse model). 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

24. Ala-Kokko L, Baldwin CT, Moskowitz RW, Prockop DJ. Single base mutation in the type II procollagen gene...


