

PERSPECTIVES

The Genetic Predisposition to Osteoarthritis

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Abstract

Osteoarthritis (OA) is the most prevalent form of arthritis in the elderly. A large body of evidence, including familial aggregation and classical twin studies, indicates that primary OA has a strong hereditary component that is likely polygenic in nature. In recent years several linkage analysis and candidate gene studies have been carried out. However, only a handful of genes, such as *FRZB*, *DIO2*, and *GDF5*, have been found to be consistently associated with OA. In addition, a recent genome-wide association study (GWAS) found the prostaglandin-related genes *PTGS2* and *PLA2G4A* to be associated with knee OA. In this *Perspective*, the molecular pathways affected by these genes and the impact that future genome-wide association scans can have on our understanding of the pathogenesis of OA are discussed. *IBMS BoneKEy*. 2009 May;6(5):181-189.

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Osteoarthritis (OA) is the most common joint disorder in the United States and Western Europe and is the leading cause of disability in the elderly (1). OA is thought to begin with degradation of the articular cartilage in a localized, non-uniform manner (2). This process is followed by a subsequent thickening of the subchondral bone, new bony outgrowths at joint margins (referred to as osteophytes), and mild-to-moderate synovial inflammation. The initiating events that lead to osteoarthritis are not clearly established but are probably due to abnormal signals that alter the phenotype of the chondrocyte so that it synthesizes proteins that degrade the matrix and cause the joint to degenerate (3).

Understanding the genetic contribution to OA has two important clinical implications. First, the identification of genes involved in disease risk can improve our understanding of the molecular mechanisms involved in the pathogenesis of OA. Second, by selecting sets of genetic variants associated with risk of disease or with progression of OA, it will be possible to detect individuals at high risk and to better monitor disease progression. This *Perspective* reviews current knowledge relating to evidence for the genetic

susceptibility to OA, focusing mostly on the hip and the knee, and on four genetic regions that have been found associated in the largest number of cohorts.

Familial Aggregation and Heritability of OA

OA has been found to segregate in families. The way this is measured is by using the risk ratio for a relative of an affected individual compared with the population prevalence (4). For affected sib pairs this sib recurrence risk is termed the lambda sib (λ_s). For example, it is possible to identify subjects with clinically severe disease with symptoms severe enough to lead to total joint replacement (TJR), and to compare the prevalence of OA in their siblings (who have a genetic exposure) to that in controls who are matched as closely as possible to the siblings. A study in Nottingham (5) compared the prevalence of hip OA in siblings of individuals undergoing total hip replacement (THR) to the prevalence of severe radiographic hip OA in controls and found a sibling recurrence risk of 4.99. A similar study was carried out using total knee replacement (TKR) as the selection criterion (6) and an assessment of

radiographic knee OA found a λ s of 2.08. A strong familial aggregation for various OA-related traits was reported in all of these studies.

Familial aggregation does not result exclusively from genetic factors and may reflect environmental exposures that are shared by family members. If only a weak familial aggregation is observed it may not in and of itself constitute convincing evidence of the contribution of genetic, as opposed to environmental, factors to a disease (7).

An alternative method to assess the actual genetic contribution to a condition, in this case OA, is the use of classical twin studies, which enable investigators to quantify the environmental and genetic factors that contribute to a trait or disease. Comparing the resemblance of identical twins for a trait or disease with the resemblance of non-identical twins offers the first estimate of the extent to which genetic variation determines variation of that trait or "heritability." The heritability of OA has been calculated in twin sets after adjustment of the data for other known risk factors such as age, sex, and body mass index (BMI). Such findings show that the influence of genetic factors in radiographic OA of the hand, hip and knee in women is between 39% and 65%, independent of known environmental or demographic confounding factors. Classical twin studies and familial aggregation studies have also investigated the genetic contribution to cartilage volume and progression of disease (e.g., see (8-9)).

Linkage Analyses

Genetic linkage occurs when a locus involved in the trait of interest (in this case OA) and alleles at nearby markers are inherited jointly. At least five genome-wide linkage scans have been published to date based on small families or twins of affected relatives collected in the UK, Finland, Iceland, and the U.S. (see (10) for references). These genome-wide linkage scans have been performed on patients ascertained for hip, knee or hand OA and have identified a large number of relatively broad genomic intervals that may harbor OA susceptibility in chromosomes 2, 4, 6, 7, 11,

16, 19 and the X chromosome. Recently, Lee and co-workers (10) conducted a meta-analysis of OA whole-genome scans from 893 families with 3,000 affected individuals taking part in three studies (Iceland, UK and U.S.). Their analysis provided summarized linkage loci of OA across whole-genome scan studies and based on their data they concluded that genetic regions in 7q34–7q36.3, 11p12–11q13.4, 6p21.1–6q15, 2q31.1–2q34 and 15q21.3–15q26.1 were the most likely to harbor OA susceptibility genes.

Genetic Associations

Genetic association studies provide a means of quantifying the effects of specific gene variants on disease occurrence.

Early candidate gene studies concentrated on cartilage components, such as *COL2A1* and other extracellular matrix (ECM)-related genes such as type IX and type XI collagen genes and the aggrecan gene. These studies, however, did not find any strong or reproducible associations between genetic variants in cartilage ECM structural protein genes and primary OA (11). To date a large number of candidate genes have been tested for OA with varying results. A partial list of genetic associations with OA reported thus far is shown in Table 1. Of these, only a handful of genes have been replicated in three or more samples. The proven or putative role of these genes in OA is summarized in Fig. 1 and below we review these genes and the molecular pathways in which they are involved.

Wnt signaling, FRZB variants

Wnt proteins form a family of highly conserved secreted signaling molecules that bind to receptors of the Frizzled and LRP families on the cell surface. Through several cytoplasmic relay components, the signal is transduced to the cell nucleus to activate transcription of Wnt target genes. Evidence in the literature shows that the Wnt signaling pathway is involved in cartilage degeneration and OA (12). Recent data also suggest a role for Wnt signaling molecules in the homeostasis of articular chondrocytes (13).

Table 1. Selected published genetic associations with osteoarthritis

Symbol	Gene Name	Reported significant associations	Negative reports	Trait associated with
<i>AACT</i>	α 1 antiproteinase antitrypsin	32;33		Knee OA
<i>ADAM12</i>	a disintegrin and metalloproteinase domain 12	32;33		Knee OA
<i>ASPN</i>	asporin	15 and references therein; 34		Hip OA/Knee OA
<i>BMP2</i>	bone morphogenetic protein 2	32;33		Knee OA
<i>CILP</i>	cartilage intermediate layer protein	32;33;35		Knee OA, LDD
<i>COL2A1</i>	type II collagen	15 and references therein		Knee OA
<i>COX2 (PTGS2)</i>	prostaglandin-endoperoxide synthase 2	27 and references therein		Knee OA, Spine OA
<i>DIO2</i>	iodothyronine-deiodinase enzyme type 2	22		Hip OA, GOA
<i>DVWA</i>	double von Willebrand factor A	28	20	Knee OA
<i>EDG2</i>	endothelial differentiation, lysophosphatidic acid G-protein-coupled receptor, 2	29	30	Knee OA
<i>ESR1</i>	estrogen receptor α	32;33;36;37		Knee OA, GOA
<i>FRZB</i>	secreted frizzled-related protein 3	17 and references therein		Hip/Knee OA, GOA
<i>GDF5</i>	growth differentiation factor 5	17 and references therein; 19-21		Hip OA
<i>IL1</i> gene cluster	interleukin 1 α/β and interleukin 1 receptor antagonist	38-40		Hip/Knee OA
<i>IL6</i>	interleukin 6	41;42		Hip/Knee OA
<i>IL10</i>	interleukin 10	43;44		Knee/Hand OA
<i>TNA</i>	tetranectin	32;33		Knee OA
<i>VDR1</i>	vitamin D receptor	32;33;45		Knee OA

LDD = lumbar disc degenerative disease; PGE2 = prostaglandin 2; GOA = generalized osteoarthritis

Several studies have explored the relationship between OA and two polymorphisms in the *FRZB* gene: the Arg200Trp and Arg324Gly variants (SNP IDs rs7775 and rs288326), with some studies finding an association with hip OA (e.g., (14)) and knee OA (15) but others failing to find any association despite having sufficient statistical power (16). A recent large meta-analysis of ten independent Caucasian cohorts found evidence for an

association of rs288326 with risk of hip OA (odds ratio (OR), 1.12; 95% CI, 1.02-1.23; $p < 0.016$) but not with hand or knee OA (17).

Bone morphogenetic proteins (BMPs)

BMPs are members of the transforming growth factor (TGF)- β superfamily of signal molecules that mediate many diverse biological processes. For instance, regulatory elements from the growth and

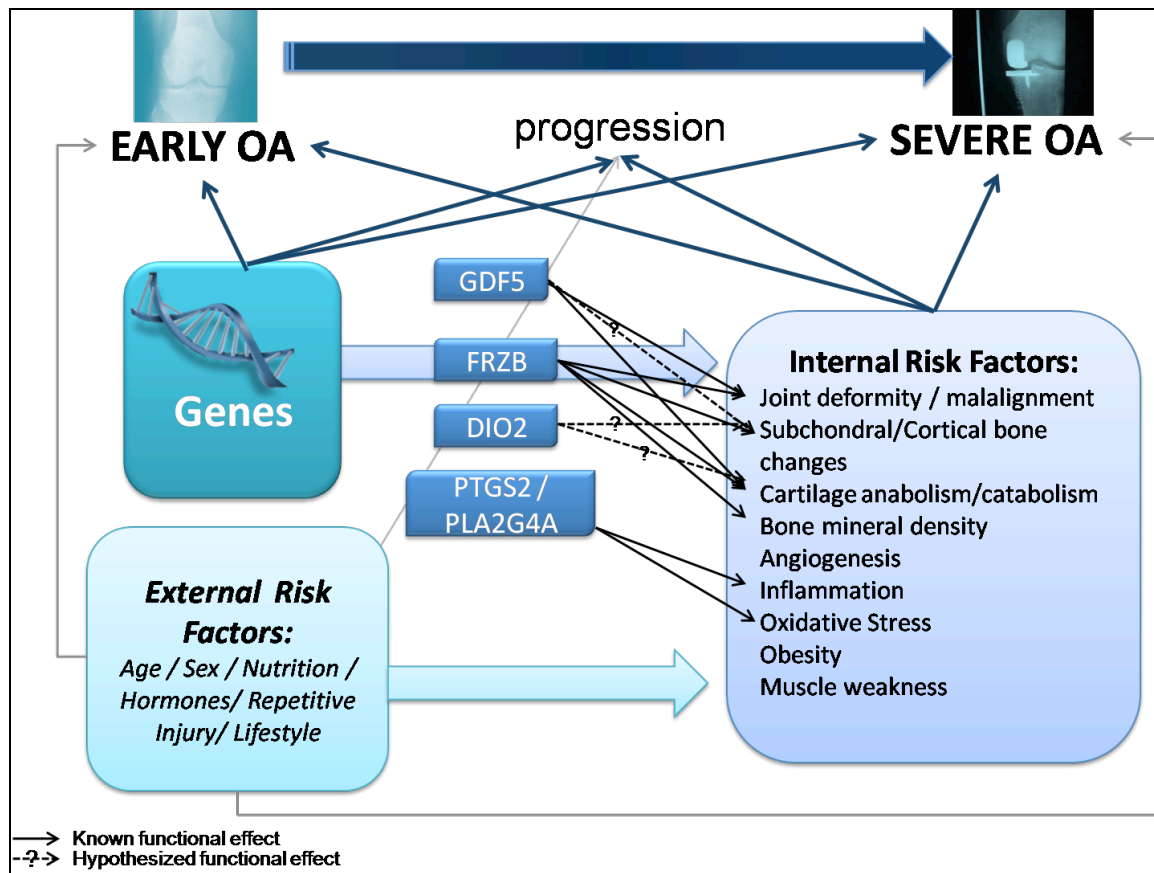


Fig. 1. Mechanisms by which selected genes can contribute to OA.

differentiation factor 5 gene (*GDF5*) can be used to inactivate other genes in joints, making it possible to identify genes and signals required for maintenance or repair of articular cartilage (18).

An association with hip and knee OA of a single SNP (rs143383, T/C) located in the 5'-UTR of *GDF5* was reported in Japanese and in Chinese case-control cohorts (19). The major, T allele of the SNP was common in Asian populations, with frequencies >70% in controls, and was at an elevated frequency in OA cases, with ORs ranging from 1.30 to 1.79 for knee and hip cases. *In vitro* cell transfection studies revealed that the T allele mediated a moderate but significant reduction in the activity of the *GDF5* promoter. The same T allele was found to be increased in hip and knee OA cases from Spain and the UK relative to controls with a very modest OR of 1.10. A smaller effect has also been observed in European samples (e.g., (17;20;21)). The

same polymorphism has also been associated with height and fracture risk (21).

A recent large-scale meta-analysis found an OR of 1.15 (95% CI, 1.09-1.22; $p=9.4 \times 10^{-7}$) for knee OA for the T allele, with no significant between-study heterogeneity across sample sets. Estimates of effect sizes for hip and hand osteoarthritis were similar to that for knee OA, but large between-study heterogeneity was observed, and statistical support was only borderline for hip ($p=0.016$) and absent for hand ($p=0.17$) OA (17).

DIO2

The deiodinase, iodothyronine, type II gene (*DIO2*) was recently identified as an osteoarthritis susceptibility gene by a genome-wide linkage scan in sibling pairs affected by OA at multiple joint sites. Combined linkage association analysis of candidate genes in the chromosomal region (14q23) of linkage revealed that this gene

explained part of the linkage present at this locus. An association with a specific haplotype, not significant in the discovery sample, was further observed in UK, Dutch, and Japanese OA studies (22). *DIO2* encodes an intracellular enzyme in the thyroid pathway, responsible for the local bioavailability of thyroid hormone in specific tissues, including the growth plate. It converts inactive thyroid pro-hormone (T₄) to active T₃ hormone, which in turn binds to thyroid receptors in the nucleus and activates thyroid hormone-responsive genes. T₃ in the growth plate stimulates specifically chondrocyte differentiation and induces hypertrophy of chondrocytes, initiating the terminal differentiation and formation of bone (23).

Inflammation and the prostaglandin pathway

OA is not considered a classical inflammatory arthropathy, due to the absence of neutrophils in the synovial fluid and the lack of systemic manifestations of inflammation (1). However, pro-inflammatory cytokines are known to be implicated as important mediators in the disease (24). Inflammation in the synovial membrane in OA is well-documented and this inflammatory response exhibits features of a T cell immune response (25). The presence of activated T cells and Th1 cytokine transcripts in chronic joint lesions of patients with OA indicates that T cells contribute to chronic inflammation in a large proportion of these patients. T cells infiltrate the synovial membrane of at least 50% of OA patients (24) and produce cytokines such as TNF- α and IL- β . Very importantly, progression of tibiofemoral cartilage damage has been found to be more severe among patients with synovial inflammation (26). In addition to inducing the synthesis of matrix metalloproteinases (MMPs) and other proteinases by chondrocytes, IL-1 and TNF- α increase the synthesis of prostaglandin E₂ (PGE₂) by stimulating the expression or activities of cyclooxygenase (COX)-2, microsomal PGE synthase-1 (mPGES-1), and soluble phospholipase A₂ (sPLA₂), and they up-regulate the production of nitric oxide via inducible nitric oxide synthetase. Interestingly, the only genome-wide scan

published to date identified variants in the 5' region of *PTGS2* (the gene encoding the COX-2 enzyme) and *PLA2G4A* (the gene encoding sPLA₂) as significantly associated with the risk of knee OA in women from five different Caucasian cohorts (27). The data did not allow the authors to determine whether the association observed was due to the gene encoding COX-2 or sPLA₂ or both, but concluded that the prostaglandin pathway has an important role in genetic susceptibility to knee OA.

Ethnic differences in genetic associations

Several genes strongly associated with OA in Asian samples have been reported to date (e.g., see (28-29)). However, a lack of reproducibility among Caucasian patients of many of these genetic associations has been observed. For example, a meta-analysis of the *EDG2* gene (30) found no evidence for association of a promoter variant with OA in individuals of European descent, although it had been previously reported to be strongly associated with knee OA in Japanese patients. Similarly, the association of the *CALM1* promoter variant was not replicated in any of the Caucasian samples tested to date (15). More recently, a novel gene, the double von Willebrand factor A (*DVWA*) was discovered (28). The common variants at two non-synonymous polymorphisms in the *DVWA* gene, rs11718863 and rs7639618, were reported in Japanese and Chinese patients to be very strongly associated with the risk of knee OA (OR, 1.43; $p < 7 \times 10^{-11}$) and to influence the binding of the DVWA protein to β -tubulin. However these alleles associated with higher risk of knee OA in Chinese and Japanese patients, were, on the contrary, associated with lower risk of TKR and not associated at all with hip OA in a sufficiently powered UK study (20). Such lack of reproducibility of Asian associations in Caucasian patients may have a number of explanations, including genetic or even environmental differences between Asians and Europeans with regard to their risk of OA. These observations highlight the difficulties in identifying genes consistently associated with the risk of OA.

Genome-Wide Association Studies

Genome-wide association studies (GWAS), if successful, can find variants in specific genes, or narrow genomic regions, that are associated with the presence or severity of a specific clinical condition.

At the time of this writing no GWAS on hip OA have been reported and only a pooled large-scale (500,000 markers) GWAS has been published (27) on knee OA. The variants identified by this scan that were subsequently replicated in independent cohorts fell in the 5' region of the gene encoding the COX-2 and the cytosolic phospholipase enzymes, both involved in prostaglandin synthesis. The importance of such molecules in OA has already been discussed above

Several other GWAS are currently being carried out on various OA-related traits, including a UK study funded by the arthritis research campaign investigating THR and TKR, and several large cohorts (e.g., Rotterdam, Framingham, TwinsUK, Iceland) with radiographic OA features are also currently being tested in a combined meta-analysis. Once the individual genes involved are identified it is likely that the OA field will have a long list of genes relating to a variety of processes that may relate to the health of joint tissues.

Combining genetic variants

A greater understanding of the pathogenesis of OA is not the only valuable contribution of GWAS results. To date, no single large genetic effect has been found. Rather, the increased risks for carrying a predisposing genetic variant appear to be fairly modest, with most variants carrying ORs between 1.1 and 1.6 (e.g., *GDF5*). One obvious question, then, is: if an individual carries risk variants at several genes does his or her risk of OA increase in proportion? Our group has investigated this possibility by computing a genetic risk variable combining variants from 10 different genes that had been implicated in the risk of knee or hip OA in other populations. When the top and bottom quartiles of this variable were used the ORs became 8.68 (95% CI, 5.20-14.49;

$p < 2 \times 10^{-16}$) for women and 5.06 (95% CI, 3.10-8.27; $p < 1 \times 10^{-10}$) for men (31). The ORs obtained using the genetic risk variable were comparable to those reported for obesity or knee injury by some studies. Such data indicate that it is possible to identify individuals at high risk of knee OA by combining genotype data from several loci and that the genetic risk for knee OA is likely to be due to the sum of many loci, each making a small contribution. The same may hold true for hip or generalized OA. The next step, once GWAS results appear, will be to conduct gene-gene and gene-environment interaction studies necessary to enlarge our understanding of the manner in which the individual genes implicated in OA exert their effect.

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