

Genetic epidemiology of hip and knee osteoarthritis

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Abstract | Osteoarthritis (OA) is the most common cause of arthritis and represents an enormous healthcare burden in industrialized societies. Current therapeutic approaches for OA are limited and are insufficient to prevent the initiation and progression of the disease. Genetic studies of patients with OA can help to unravel the molecular mechanisms responsible for specific disease manifestations, including joint damage, nociception and chronic pain. Indeed, these studies have identified molecules, such as growth/differentiation factor 5, involved in signaling cascades that are important for the pathology of joint components. Genome-wide association studies have uncovered a likely role in OA for the genes encoding structural extracellular matrix components (such as *DVWA*) and molecules involved in prostaglandin metabolism (such as *DQB1* and *BTNL2*). A ~300 kilobase region in chromosome 7q22 is also associated with OA susceptibility. Finally, the identification of individuals at a high risk of OA and of total joint arthroplasty failure might be facilitated by the use of combinations of genetic markers, allowing for the application of preventive and disease-management strategies.

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Introduction

Osteoarthritis (OA) is a disease of the musculoskeletal system that primarily involves the joints of the knee, hip, spine, hand and foot. OA is estimated to affect 40% of people >70 years of age,¹ making it more prevalent than any other form of arthritis.² Severe OA of the hip and knee cause considerable pain and physical disability and underlie an increasing need for joint replacements.³

As early as 1953 it was recognized that “what is so damaging in OA seems to be not the degeneration of the cartilage, but the vigorous and persistent attempt at repair ... which aggravates the already disordered function of the joint”.⁴ OA pathogenesis is probably affected by a combination of both genetic and environmental factors, with a continuous distribution between the extremes of predominantly genetic OA or predominantly environmental OA.¹ We are, therefore, increasing our understanding of the pathogenesis of this disease by unraveling the role of genetic variation in severe hip and knee OA susceptibility. In this Review, we discuss some of the evidence implicating genetics in the risk of hip and knee OA and summarize recent developments in the field, with particular emphasis on genetic association studies.

Genetic studies in OA

Genetic epidemiology is the study of genetic factors that influence the dynamics of diseases in populations.⁵ Genetic risk factors can influence the risk of OA and can also affect the outcomes of OA at various stages during the course of the disease. Genetic variation might influence OA risk factors such as obesity, skeletal shape,

bone mass and synovitis, although no studies have been reported regarding these mechanisms to date. In addition, it is accepted that genetic variants can affect the risk of a generalized OA phenotype,⁶ of genetic sensitivity to pain⁷ and of disease progression.⁸ Furthermore, genetic variants can influence a patient's susceptibility to periprosthetic osteolysis following total hip arthroplasty.⁹

An American College of Rheumatology task force highlighted that pain is the most common symptom of patients with rheumatic disorders, including OA.¹⁰ Pain relief in patients with severe chronic OA remains an unmet medical need and, therefore, constitutes a major reason that these individuals seek surgical intervention. The approval of a potential therapy in OA requires that either the agent be intended to improve symptoms, or, if the drug is intended to be structure-modifying, that the structural alteration be linked to some current or future clinical benefit.¹¹

Understanding the molecular pathogenesis of chronic pain and specifically OA-related pain should be of particular interest to both rheumatologists and drug developers. Van Meurs and co-workers⁷ have shown that a functional variant (V158M) in the *COMT* gene, encoding catechol-O-methyltransferase, is associated with hip pain in patients with hip OA. In addition, Reimann *et al.*¹² identified a single nucleotide polymorphism (SNP) in the *SCN9A* gene (which encodes the alpha subunit of sodium channel protein type 9) that, when present in patients with OA, is associated with higher pain scores than control patients. This *SCN9A* SNP confers an R1150W amino acid change that is associated with several forms of pain and with altered pain thresholds. This area of genetics should see considerable progress in the near future because an

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Competing interests

The authors declare no competing interests.

Key points

- Severe osteoarthritis (OA) is a cause of social, economic and personal burden and is the main cause of an increasing need for joint replacements
- Candidate gene studies and genome-wide association studies show that OA is genetically heterogeneous with each individual common gene variant contributing only modestly to the risk of OA
- Genetic studies in humans have identified molecules that are important in the development of pathological changes to articular cartilage
- The genes involved in the main clinical end points of OA, such as chronic pain and functional disability, has not yet been studied extensively
- Preliminary studies suggest that it might be possible to combine sets of genetic variants to predict which individuals will be at a higher risk of OA

improved understanding of the molecular pathways involved in pain associated with OA can have direct clinical significance for the choice of pharmacotherapy.

Twin studies

Classic twin studies, in which the resemblance of identical twins for a trait or disease is compared with the resemblance of non-identical twins, estimate the extent to which genetic variation determines variation of that trait or 'heritability'. The heritability of OA has been calculated in such twin studies and, after adjustment of the data for other known risk factors such as age, sex and BMI, the influence of genetic factors in radiographic OA of the hip or knee in women is 60% and 39%, respectively, independent of known environmental or demographic confounding factors. Classic twin studies and familial aggregation studies have also investigated the genetic contribution to longitudinal changes in knee structure, cartilage volume and radiographic progression of OA and showed that all these traits have a substantial heritability, ranging from 33% for change in lateral knee osteophyte grade to 73% for change in medial cartilage volume.^{13–15}

Familial aggregation studies

Investigation of familial aggregation indicates the disease risk for a relative of a patient compared with prevalence of a disease in the general population, and these studies are the *sine qua non* for performing the genetic analysis of a disorder. The measure commonly used to estimate the strength of familial aggregation is the sibling recurrence risk (λ_s), defined as the ratio of the prevalence among siblings of individuals with the disease to the prevalence in the general population. A UK study assessed the prevalence of hip OA in siblings of individuals undergoing total hip replacement (THR) compared with the prevalence of radiographic hip OA in control patients undergoing intravenous urograms for the investigation of a renal problem.¹⁶ Using the prevalence values reported in this study,¹⁶ we computed a λ_s of 4.99 for OA classified as Kellgren–Lawrence grade 3 or higher, a λ_s of 5.07 for minimum joint-space width and a λ_s of 8.53 for THR. A similar study by the same research group was carried out using total knee replacement (TKR) as the selection criterion,¹⁷ and a λ_s of 2.13 or 2.08 can be derived for tibiofemoral OA or any radiographic knee OA, respectively, based on the prevalences

reported. Using self-reported total-joint replacement in a smaller data set,¹⁸ a λ_s of 1.78 or 4.80 were reported for THR and TKR, respectively. In a similar study of the siblings of US patients with OA, λ_s values of 2.85 for THR and 2.92 for TKR can be derived from the reported data, although the familial aggregation for TKR was not statistically significant following adjustment for age and sex.¹⁹ Familial aggregation of specific knee OA phenotypes that correspond to lesions in the tibial plateau and preservation of cartilage of other compartments of the knee, such as anteromedial OA, have also been reported in UK populations.²⁰ Unlike other patterns of OA, cartilage degeneration in anteromedial OA is consistent with increased loading and, therefore, could be assumed to be mostly attributable to mechanical causes rather than genetic factors. However, the λ_s of 3.21 reported for this form of OA suggests that this particular type of OA has a substantial genetic component.

Linkage analysis

This approach is based on the cosegregation of a disease trait of interest with one or several genetic markers and seeks to identify disease loci at specific regions in the genome. Linkage analysis has been successful in localizing chromosomal regions containing highly-penetrant genetic variants, although regions containing genes for complex traits, such as those involved in breast cancer, were also mapped in this manner.⁵

To date, at least five genome-wide linkage scans of OA have been published based on small families or twins of affected relatives from the UK, Finland, Iceland and the US.²¹ These genome-wide linkage scans were performed using data from patients with hip, knee or hand OA and identified a large number of genomic regions that might associate with OA susceptibility in chromosomes 2, 4, 6, 7, 11, 16, 19 and the X chromosome. Although this approach has now been largely superseded by association studies, a Dutch study identified a linkage region in chromosome 12 harboring the *DIO2* gene, which was later found to be associated with hip OA in women.²²

Genetic association studies

Genetic association studies examine the effects of specific genetic variants on disease occurrence. Regions identified by linkage analysis can be investigated, or candidate gene association studies can be conducted to identify the genetic and allelic variants involved in disease risk. 'Hypothesis-free' association studies can also be carried out, which test a large number of genetic variants covering the whole genome and can identify genes and pathways for which no previous knowledge on disease risk was available.

Genome-wide association studies

The HapMap project has made it possible to test a large number of genetic markers across the genome.²³ The goal of the HapMap project is to compare the genetic sequences of different individuals in order to identify chromosomal regions where genetic variants are shared. By testing variants for association across the genome, it has become

possible to generate reliable and compelling data on the genetic contribution to complex diseases, including OA and other forms of arthritis.²⁴ Typical genome-wide association studies (GWAS) are carried out on a sample of cases (characterized for the clinical trait of interest) and controls, and these samples are genotyped for hundreds of thousands of SNPs. After several quality control steps and SNP imputation,²⁵ each SNP is tested for an association with the disease and the top SNPs—usually those with the smallest *P* values—are selected for further testing in replication cohorts. The overall evidence for association with the clinical trait of interest is then assessed (Figure 1).

One of the major challenges facing GWAS is that of multiple testing. The statistical significance threshold accepted to consider a genetic variant as being of genome-wide significance is $P < 5 \times 10^{-8}$.²⁶ To meet this threshold, a study requires either extremely large sample sizes—several thousand cases and controls—or very large genetic effects (such as an odds ratios >2.0) that are not found for common variants in a complex and highly prevalent disease like OA.

Another limitation to take into account is that GWAS that include genetic variants screened by the HapMap project are based on the ‘common disease, common variant’ hypothesis. Because of the low number of individual genomes sequenced by the HapMap project, most genetic variants detected by GWAS are likely to be common variants (defined as variants that are present in $>5\%$ of the population). Rare variants—even if strongly involved in disease—are, therefore, hard to identify by GWAS.

Rare large-effect mutations are known to cause many different common medical conditions and genome-wide screening for these mutations has been proposed as the most unbiased strategy to discover genes involved in complex illnesses.²⁷ Indeed, with this aim, the 1,000 Genomes Project has sequenced genomic samples from 1,000 individuals of diverse backgrounds and catalogued genetic variants with a frequency $<1\%$.²⁸ Some next-generation sequencing ventures are, however, going into even greater depth than the 1,000 Genomes Project. For example, the UK10K Project aims to sequence 10,000 genomes—including 2,000 individuals with an OA phenotype—in order to accurately estimate the number of variants with $>0.1\%$ frequency in the general population.²⁹ Other challenges include the influence of multiple loci on complex diseases, the possible segregation of unique loci in different populations (heterogeneity), and the interaction of multiple loci in influencing disease risk (epistasis) (Box 1).

Published genetic association studies

The Human Genome Epidemiology (HuGE) Navigator provides a comprehensive and continuously updated archive of studies assessing the relationship between genetic variants and diseases.³⁰ This repository includes all relevant studies published since 2001 and is continuously curated by selecting the relevant studies from the PubMed database. We conducted a search of the HuGE Navigator using the search term “osteoarthritis”. Studies referring to

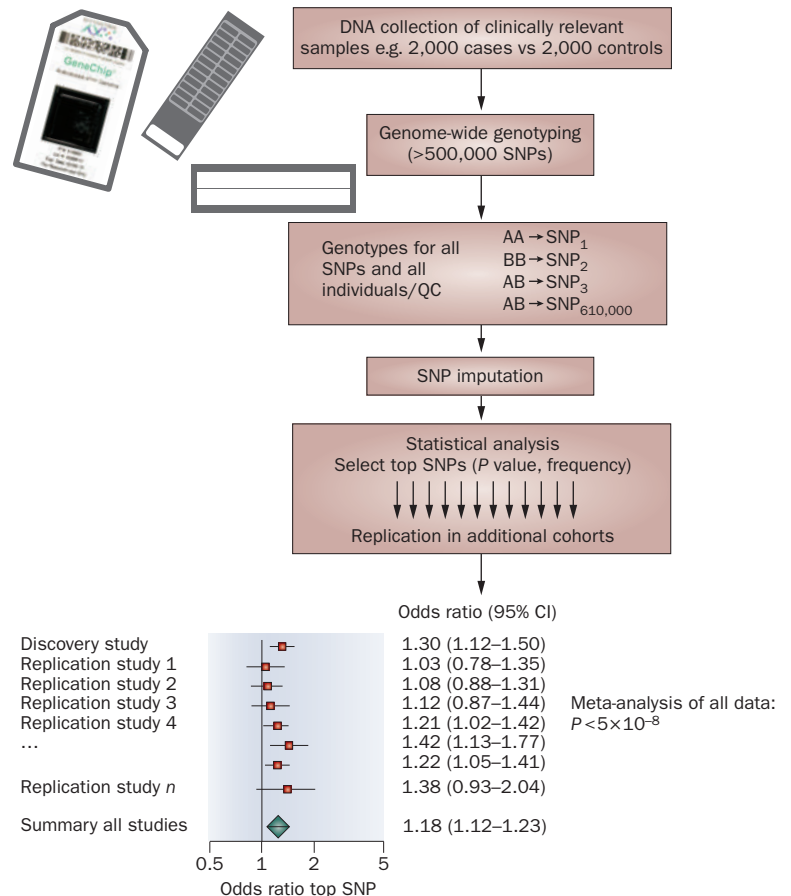


Figure 1 | Schematic representation of a genome-wide association study. DNA samples are collected from cases and controls and are typed using a genome-wide assay, such as those developed by Illumina® or Affymetrix®, which comprise genotypes for hundreds of thousands of SNPs. The genotypes for all individuals are assessed and QC procedures are applied. In addition, SNP genotypes for >2 million SNPs can be imputed using the actual genotypes observed. The genotype data is tested for genetic associations with the clinical trait under study and the most convincing association signals are tested for replication in independent study cohorts. Data from the discovery and replication cohorts is meta-analyzed and the overall evidence for genetic association is assessed. Abbreviations: QC, quality control; SNP, single nucleotide polymorphism.

Box 1 | Challenges in genetic studies of osteoarthritis

Osteoarthritis (OA) has a strong genetic component, which in the case of hip OA is comparable in strength to that of rheumatoid arthritis. Human genetic studies can unravel the molecular mechanisms responsible for joint damage, nociception and chronic pain involved in OA. The search for genes involved in the risk of OA has, however, proven very challenging owing to several factors:

- The heterogeneity observed within clinical subsets of the disease (e.g. generalized vs local)
- The heterogeneity between different ethnic groups (e.g. Asian vs European)
- OA appears to be influenced by many loci, each with a small effect (OR <1.2); very large sample sizes are, therefore, required to reliably establish such effects
- Rare large-effect mutations that are important in other common complex diseases have not yet been explored in OA

Table 1 | Candidate gene associations with knee or hip OA*

Study	SNP	Gene	OR	P value	Function	Ethnic group
Knee OA						
Valdes <i>et al.</i> ⁴⁰	rs143383	GDF5	1.16	8 × 10 ⁻⁹	Bone morphogenetic protein, joint development	European
Nakamura <i>et al.</i> ⁴⁷	Asp14 in VNTR allele	ASPN	1.95	1.3 × 10 ⁻⁶	TGF-β signaling	Asian
Valdes <i>et al.</i> ⁴⁹	rs12901499	SMAD3	1.22	7 × 10 ⁻⁶	TGF-β signaling	European
Mototani <i>et al.</i> ⁹²	rs10980705	EDG2	2.30	3 × 10 ⁻⁵	Lysophosphatidic acid receptor	Asian
Attur <i>et al.</i> ^{66†}	Haplotype: rs419598–rs315952–rs9005	IL1RA	0.15	1 × 10 ⁻⁴	Inflammation	European
Hip OA						
Miyamoto <i>et al.</i> ³⁴	rs143383	GDF5	1.79	2 × 10 ⁻¹³	Bone morphogenetic protein, joint development	Asian
Meulenbelt <i>et al.</i> ²²	Haplotype: rs225014–rs12885300	DIO2	1.79 [§]	2 × 10 ⁻⁵	Thyroid metabolism	Asian and European
Valdes <i>et al.</i> ⁴⁹	rs12901499	SMAD3	1.22	3 × 10 ⁻⁴	TGF-β signaling	European
Valdes <i>et al.</i> ⁵⁵	rs7164503	ANP32A	0.87	4 × 10 ⁻⁴	Apoptosis and Wnt signaling regulator	European

*Not identified by genome-wide association studies but replicated in at least one independent cohort and with a significance of at least $P < 5 \times 10^{-4}$ overall.

†Severe knee OA. §OR refers to a recessive model. ||Women only. Abbreviations: OA, osteoarthritis; OR, odds ratio; SNP, single nucleotide polymorphism; TGF-β, transforming growth factor β; VNTR, variable number of tandem repeats.

OA of the knee or hip, or both, (not dysplasias or other syndromes) were selected for further analysis. Genes for which data was available from at least one replication cohort were taken into consideration, with the condition that the *P* value had been adjusted for multiple testing and conferred significance of at least $P < 0.0005$. This *P* value cut-off for candidate genes represents the significance level needed to achieve 80% Bayesian posterior credibility for a genetic association that has a prior probability of being true of 0.1, and a variance for the observed effect of 0.01.³¹ The results of polymorphisms meeting these criteria as of 18th June, 2010, and not derived from GWAS, are summarized in Table 1. In addition, a few large-scale GWAS ($\geq 100,000$ markers) on knee and hip OA have been published to date. The results of those genes that achieve genome-wide significance in OA are summarized in Table 2. A large number of other genetic associations with hip or knee OA have been reported and are described in the following sections.

Bone morphogenetic proteins

The signaling pathways that involve the transforming growth factor beta (TGF-β) and bone morphogenetic protein (BMP) protein families are implicated in the development of cartilage and bone.³² The BMP growth/differentiation factor 5 (GDF-5) is involved in joint formation.³³ Miyamoto *et al.*³⁴ searched for sequence variations in *GDF5* exons and their flanking regions and identified the rs143383 SNP in the promoter region as having the strongest association with hip OA. This SNP was also associated with knee OA in Japanese and Chinese patients,³⁴ and confers a reduction in GDF-5 mRNA expression.^{34,35} Subsequently, the rs143383 functional variant was found to be associated with knee OA in white populations,^{36–39} one of only a few genetic variants to reach genome-wide significance in this setting with no interstudy heterogeneity (Table 1).⁴⁰

The association of rs143383 with hip OA has been much more controversial than its link to knee OA. Evangelou and colleagues³⁷ tested this variant in a large case–control study and found only a modest association (OR = 1.16, 95% CI 1.03–1.31, $P = 0.016$) and very large interstudy heterogeneity ($I^2 = 75\%$). In severe hip and knee OA cases stratified on the basis of generalized OA (nodal) status,⁶ an association was found between rs143383 and hip OA, but only in cases with the generalized nodal OA phenotype (OR = 1.27, 95% CI 1.11–1.45, $P < 6 \times 10^{-4}$). By contrast, this variant showed no evidence for an association with hip OA among patients with severe hip OA without the generalized OA phenotype, (OR = 1.02, 95% CI 0.92–1.14, $P < 0.56$). On the basis of these and other data, the authors concluded that generalized and non-generalized forms of severe symptomatic hip OA have different etiologies and that this heterogeneity is, in part, genetically determined.⁶

TGF-β proteins signal through the TGF-β receptors and the mothers against decapentaplegic homolog (SMAD) signaling cascade. Although chondrocytes in the growth plate undergo terminal differentiation, become hypertrophic and produce high amounts of matrix metalloproteinase (MMP)-13, cells in normal articular cartilage are prevented from this final step, and TGF-β1 is considered a major growth factor controlling hypertrophy.⁴¹ Asporin belongs to the family of TGF-β-interacting proteins that binds TGF-β1 *in vivo*. Overexpression of the gene encoding asporin, *ASPN*, leads to a decrease in TGF-β1-mediated chondrogenesis *in vitro*, as measured by expression of aggrecan core protein and collagen type II.⁴²

A variable number of tandem repeats (VNTR) allele associated with decreased TGF-β1 mediated chondrogenesis *in vitro* was reported to be associated with an increased risk of knee OA in Japanese,³⁷ Chinese^{43,44} and Korean⁴⁵ cohorts. The effect of this variant in populations

Table 2 | Genetic associations with knee OA as identified by GWAS*

Study	SNP	Gene	OR	P value	Function	Ethnic group
Miyamoto <i>et al.</i> ⁶¹	rs11718863	DVWA	1.43	7×10^{-11}	Cartilage-specific tubulin binding	Asian
Nakajima <i>et al.</i> ⁷²	rs10947262	BTNL2	1.31	5×10^{-9}	Immunomodulatory function, T-cell response	Asian and European
Nakajima <i>et al.</i> ⁷²	rs7775228	HLA-DQB1	1.34	2×10^{-8}	Antigen presentation	Asian
Evangelou <i>et al.</i> ¹¹³	rs4730250	COG5 [‡] , GPR22 [‡] , DUS4L [‡] , HBP1 [‡]	1.17	9×10^{-9}	Unknown	European

*With a significance of at least $P < 5 \times 10^{-8}$ overall. [‡]SNP is in a linkage disequilibrium block and it is currently unknown which gene is causing the association. Abbreviations: GWAS, genome-wide association studies; OA, osteoarthritis; OR, odds ratio; SNP, single nucleotide polymorphism.

of European descent has been reported to be weak or absent.⁴⁶ Indeed, a meta-analysis of the VNTR variant has shown it to be strongly associated with knee OA, but not hip OA, in Asian populations (Table 1); no overall association was found in European samples.⁴⁷

TGF- β -SMAD3 signaling is essential for maintaining articular cartilage; mutant mice homozygous for a targeted disruption of *Smad3* developed degenerative joint disease resembling human OA.⁴⁸ A polymorphism mapping to intron 1 of *SMAD3* has been reported to be associated with both hip and knee OA in four independent knee OA and two independent hip OA cohorts of European descent.⁴⁹ The resulting genetic effects on hip and knee OA (Table 1) are supportive of the relevance of this molecule *in vivo*,⁴⁸ and in chondrocyte metabolism and function *in vitro*.⁵⁰

Thyroid metabolism

The gene encoding type II iodothyronine deiodinase, *DIO2*, has been identified as an OA susceptibility gene.²² In particular, a recessive model of a haplotype containing two SNPs was found to be associated with hip OA in women (Table 1). Type II iodothyronine deiodinase is an intracellular enzyme in the thyroid pathway and is responsible for the local bioavailability of thyroid hormone in specific tissues, including the growth plate. The active thyroid hormone, triiodothyronine, has an essential role in the control of chondrocyte proliferation and differentiation and inhibits the BMP-2-induced growth of mouse rib bones. Indeed, the role of thyroid hormone regulation in the genetic risk of OA might be of clinical relevance, as well-characterized agents targeting this pathway are in use for other therapeutic indications.⁵¹ Other variants in the thyroid metabolism pathway have been tested with regards to the genetic risk of OA.⁵² A SNP in the *DIO3* gene was reported to be associated with the risk of OA, but no variants of the thyroid metabolism genes tested were associated with hip or knee or hand OA following adjustment for multiple tests, suggesting that further research is needed to assess the relevance of this pathway for genetic susceptibility to OA.⁵²

Apoptosis and mitochondrial damage

Evidence from animal models of OA indicates that inadequate control of reactive oxygen species has a role in the initiation and pathophysiology of OA.⁵³ Furthermore, data from human *ex vivo* experiments, and from animal models and *in vitro* studies, strongly indicate a role for

mitochondrial damage and apoptotic pathways in OA.⁵⁴ In fact, a higher proportion of apoptotic chondrocytes is found in samples from patients with OA than in those from age-matched controls.⁵⁴ One gene implicated in OA that is involved apoptosis is the acidic leucine-rich nuclear phosphoprotein 32 family member A gene (*ANP32A*).⁵⁵ This gene encodes a tumor suppressor molecule that has a regulatory role in apoptosis, interferes with canonical Wnt signaling *in vitro* and is associated with hip OA in women (Table 1).⁵⁵ In addition, mitochondrial DNA variation, particularly in haplogroup J, has been found to be associated with a decreased risk of hip OA (OR = 0.661, 95% CI 0.440–0.993, $P = 0.045$)⁵⁶ and knee OA (OR = 0.460, 95% CI 0.282–0.748, $P = 0.002$).⁵⁷

Extracellular matrix components

In cartilage, the extracellular matrix constitutes the majority of the tissue volume and is responsible for functions such as load bearing and, in the case of joint cartilage, allowing smooth articulation of long bones. Several extracellular matrix molecules have been implicated in genetic susceptibility to hip and knee OA, such as *COL2A1*,⁵⁸ *COL10A1*⁵⁹ and double von Willebrand factor A (*DVWA*), which some consider to be a segment of the *COL6A4* gene.⁶⁰

The strongest genetic association with knee OA identified by GWAS to date was found with *DVWA* in Asian populations following the testing of 99,295 SNPs (Table 2).⁶¹ The protein encoded by *DVWA* was observed to physically interact with tubulin β chain. Following replication and mapping, the authors identified two variants in *DVWA* that were in high linkage disequilibrium with each other, both of which encoded amino acid changes that were strongly associated with knee OA (OR = 1.43, 95% CI 1.28–1.59, $P = 7 \times 10^{-11}$) in combined Chinese and Japanese populations.⁶¹ The binding strength of the encoded protein was found to be influenced by alleles associated with these missense polymorphisms. The association of *DVWA* variants with OA was not observed in populations of European descent^{8,36,62} and strong heterogeneity is seen between these samples and those from Asian populations ($P = 7 \times 10^{-10}$).³⁶ The *DVWA* gene, therefore, illustrates one of the major challenges for identifying genetic risk factors for OA—heterogeneity between populations.

Inflammation and immune responses

Inflammatory changes observed in the synovium that can contribute to OA imply that inflammatory and

degradative activities of synoviocytes are important in the pathogenesis of OA, and suggest that enzymes produced by the cells that line the synovium can directly degrade matrix molecules.⁶³ This low-grade OA synovitis is cytokine-driven. A number of variants in interleukin (IL) genes, particularly *IL1*, *IL6* and *IL10*, have been reported to be associated with the risk of OA,⁶⁴ although some of these associations have proven to lack reproducibility when tested in large scale meta-analyses.⁶⁵ Nevertheless, variants in the gene encoding the IL1 receptor antagonist are strongly associated with OA disease severity (Table 1).⁶⁶ Several studies have implicated a role for *IL1* polymorphisms in the risk of OA, although the results are inconclusive.^{67–69}

IL-1 and tumor necrosis factor (TNF) increase the synthesis of prostaglandin E_2 (PGE₂). A GWAS identified a SNP between *PTGS2* (the gene encoding cyclooxygenase 2) and *PLA2G4A* as being significantly associated with the risk of knee OA in women from five different cohorts from the UK and the USA (Table 2).⁷⁰ In addition, another study found a strong association between a functional *PTGS2* promoter variant and the risk of both hip and knee OA.⁷¹

Another important class of molecules involved in inflammation and the immune response are those mapping the major histocompatibility complex (MHC). A large-scale Japanese GWAS identified two MHC-related SNPs to be strongly associated with knee OA.⁷² One of the markers mapped to the MHC class II gene *DQB1*, and found genome-wide significance in Japanese samples (Table 2), although an opposite effect was observed in European populations. The other marker mapped to intron 1 of the gene encoding butyrophilin-like protein 2 (*BTNL2*), which regulates T-cell activation.⁷² This SNP, termed rs10947262, was associated with OA in both Asian and European cohorts, and these associations achieved genome-wide significance (Table 2). The functional relevance of these variants, or even the HLA class II haplotypes in which they were found, were not explored. However, the presence of activated T cells and type 1 T-helper cytokine transcripts in the chronic joint lesions of patients with OA indicates that T cells contribute to chronic inflammation. Indeed, T cells and chondrocytes have been reported to interact through cell surface molecules such as MHC, CD4 and CD8 in OA, and proliferative responses of peripheral blood T cells from patients with OA are substantially higher than those of T cells from control individuals.⁷³ These observations imply that MHC has a role in OA susceptibility, in agreement with findings from the Japanese GWAS.⁷²

Other genes involved in inflammation that have been tested for association with OA include the gene encoding the C-reactive protein (*CRP*), which was shown to have no effect on knee or hip OA in a large Dutch study.⁷⁴ In addition, *TNF* failed to show an association with knee OA in a Turkish study.⁷⁵

Wnt signaling

The Wnt–Frizzled signaling pathway is vital for embryonic skeletal development and also participates in normal

adult bone and cartilage biology.⁷⁶ Several research groups have shown that polymorphisms in the gene encoding the Frizzled coreceptor, low density lipoprotein receptor-related protein 5 (LRP5), can influence human bone density.⁷⁷ Genetic variants that induce LRP5-related signaling or disrupt the interaction of LRP5 with the soluble antagonist Dickkopf-related protein 1 gradually increase bone density in adults. Complex haplotypes of *LRP5* have been implicated in susceptibility to knee OA,⁷⁸ although the results were not reproducible in two large population-based cohorts.⁷⁹

Several studies have explored the relationship between OA and two polymorphisms in the secreted Frizzled-related protein 3 gene (*FRZB*)—Arg200Trp (rs7775) and Arg324Gly (rs288326)—with some studies finding an association of these variants with hip OA⁸⁰ and knee OA,⁸¹ but others failing to find any association despite having sufficient statistical power.⁷⁹ A large meta-analysis found evidence for a weak association of rs288326 with the risk of hip OA (OR = 1.12, 95% CI 1.02–1.23, $P < 0.016$) but not with hand OA or knee OA in multiple cohorts of European descent.³⁷

Cartilage degrading enzymes

The primary cause of cartilage degradation is elevated proteolytic activity that degrades aggrecan core protein and type II collagen. Loss of aggrecan core protein is an early and crucial event in the progression of cartilage destruction and is attributed to proteolytic cleavage. Mouse models of OA have clearly demonstrated that the enzymatic activity of a disintegrin and metalloproteinase with thrombospondin motifs 5 (*ADAMTS-5*), mediates the turnover of articular cartilage (induced by aggrecan core protein) following physical or cytokine-mediated injury.^{82,83} A large genetic-association analysis of *ADAMTS5* SNPs with hip, hand and knee OA failed to find convincing evidence for an association of *ADAMTS5* genetic variation with high-risk or low-risk patients.⁸⁴ Although the role of aggrecanases might be different in mouse models of OA than in human disease, studies on the link between genetic variation of aggrecanases and metalloproteinases and the risk of OA has also failed to demonstrate any associations.⁸⁵ Nevertheless, some smaller studies have suggested a role for MMP-1⁸⁶ and disintegrin and metalloproteinase domain-containing protein (ADAM)-12.^{87,88}

Other genes implicated in OA

In addition to the genes described in the preceding sections, the following sections describe genes that have been implicated in knee or hip OA in genetic association studies published between January 2008 and May 2010.

ESR1: A number of studies tested for associations between genetic variants of the estrogen receptor gene (*ESR1*) and the risk of OA in both in Asian^{88–90} and Caucasian populations.^{91,92} Some of the studies reported an association with OA,^{88–91} whereas others could not find evidence of an association.⁹² Different variants and combinations of polymorphisms have been tested by the various studies, making it difficult to reach a definitive conclusion on whether this gene is implicated in OA.

EDG2: A functional variant of the endothelial differentiation, lysophosphatidic acid G-protein-coupled receptor 2 gene (*EDG2*) was found to be strongly associated with the risk of knee OA in Japanese patients (Table 1).⁹³ By contrast, no association was found between this SNP and the risk of OA in European samples.⁹⁴

KL: The *klotho* gene (*KL*) encodes an enzyme with an important role in calcium and phosphate homeostasis. Polymorphisms in *KL* have been implicated in the risk of knee OA in a Greek cohort.⁹⁵

PITX1: The transcription factor pituitary homeobox 1, encoded by *PITX1*, is expressed during hindlimb development in regions giving rise to cartilage joints, long bones and skeletal muscles, but is mostly absent from joint tissue from patients with OA.⁹⁶ Polymorphisms in *PITX1* are associated with the risk of knee OA in Chinese patients.⁹⁷

CALM1 and CALM2: Calmodulins are binding proteins expressed in all eukaryotic cells. A functional promoter polymorphism in *CALM1* was reported to be strongly associated with the risk of hip OA in Japanese patients.⁹⁸ Subsequent studies failed to find an association of this genetic variant in Greek⁹⁹ and Chinese populations.¹⁰⁰ In addition, a polymorphism in *CALM2* has been implicated in the risk of hip OA in Japanese patients without acetabular dysplasia.¹⁰¹

ACE: An insertion–deletion polymorphism in the angiotensin-converting enzyme gene (*ACE*) has been reported to associate with knee OA in small studies from Korea¹⁰² and Turkey.¹⁰³ However, this association was not found in a cohort from Kuwait.¹⁰⁴

CALCA: Calcitonin, encoded by *CALCA*, is produced in the thyroid, involved in bone mineral metabolism and thought to have chondroprotective effects.¹⁰⁵ A study from Mexico reported an association between polymorphisms in the *CALCA* and the risk of knee OA.¹⁰⁶

LEP: Leptin is a peptide hormone with a role in bone metabolism and rheumatic diseases that has been implicated in the pathogenesis of OA.^{107,108} Haplotypes in the gene encoding leptin, *LEP*, have been reported to be associated with an increased risk of OA in a subset of patients in a Chinese study.¹⁰⁹

Negative studies: In addition to the genetic associations outlined above, several studies have tested various candidate genes and failed to find an association with OA. Indeed, the genes encoding vascular endothelial growth factor A (*VEGF*),¹¹⁰ Rho-related GTP-binding protein RhoB (*RHOB*),¹¹¹ thioredoxin domain-containing protein 3 (*TXNDC3*)¹¹¹ and LRCH1 protein (*LRCH1*)¹¹² were all found not to be associated with OA.

Loci of unknown function

The largest OA GWAS published to date was carried out by a European consortium and found a strong association between a locus at chromosome 7q22 and knee and/or hand OA in patients of European descent (Table 2).⁸ Although the specific functions of this locus are unknown, a number of potential causative genes are located within this linkage disequilibrium block, in particular the probable G-protein-coupled receptor protein 22 gene (*GPR22*), which is present in cartilage and osteophytes and absent

in normal cartilage in mouse models of OA. This locus reached genome-wide significance with respect to an association with knee OA (OR = 1.17, 95% CI 1.11–1.24, $P = 9.17 \times 10^{-9}$) in a subsequent large-scale meta-analysis (Table 2), but this result was not replicated in Asian populations (OR = 1.03, 95% CI 0.85–1.25).¹¹³ This example illustrates the ability of GWAS to identify novel loci of unknown function that can increase our understanding of disease pathogenesis.

Future directions

The increased risk for OA conferred by carrying a predisposing genetic variant at any of the identified loci seems to be quite modest; most variants have modest effect sizes in comparison with those associated with other chronic complex diseases.¹¹⁴ Nevertheless, there are data suggesting that the computation of a genetic risk variable can result in much larger odds ratios when variants from several different genes are combined.^{115,116} These results suggest the possibility of identifying individuals who are at a high risk of hip and knee OA by combining genotyping data from several loci, and that the genetic risk to OA is likely to be attributable to the sum of many loci, each of which make a small contribution to disease risk. Moreover, the more relevant loci that are found—even of small effect—the better the predictions should be for both high and low susceptibility to OA.

Conclusions

Hip and knee OA represent a huge healthcare burden to society and a personal burden to individuals affected by the disease, in addition to being the main cause of the increasing need for joint replacements. Understanding the genetic contribution to OA, therefore, 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 the risk of disease or with the progression of OA, it will be possible to detect individuals at a high risk for clinical development, allowing clinicians to increase the monitoring of disease progression in these patients. Some genes, such as *GDF5*, are now known to be consistently associated with the risk of knee OA, highlighting some potential pathways for therapeutic intervention. However, considerable progress remains to be achieved, particularly with respect to hip OA. As our understanding of the pathogenic pathways responsible for genetic susceptibility to both OA-related pain and joint damage increase, it should become possible to develop better strategies for the treatment and prevention of the disease.

Review criteria

The PubMed database was searched for original articles focusing on osteoarthritis published between 2008 and 2010. The search terms used were “osteoarthritis”, “genetic polymorphism”, “hip” and “knee”. All papers identified were English-language full-text papers that reported genetic associations.

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Author contributions

A. M. Valdes researched the data for the article and wrote the article. A. M. Valdes and T. D. Spector provided a substantial contribution to discussions of the content and to the review and/or editing of the manuscript before submission.