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Genetic epidemiology of osteoarthritis: recent developments and future directions

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Abstract

Purpose of review—Despite the high prevalence of osteoarthritis and its enormous public health impact, the cause of the disease remains largely obscure. The identification of genes associated with osteoarthritis can help reveal underlying biological mechanisms that may lead to development of new therapeutic targets or biomarkers for early detection and risk stratification. The goal of this short review is to provide a brief overview of the current status of genetics of osteoarthritis with an emphasis on developments generated in the last year.

Recent findings—This review focuses on the following areas: identification of new genes through genetic association studies, including genome-wide association studies; family-based studies and extreme osteoarthritis phenotypes; endophenotypes and pain; and overlap of osteoarthritis with other age-related disorders.

Summary—Although recent genetic discoveries have produced innovative findings with respect to the pathophysiology of osteoarthritis, we have yet to realize new treatments to improve the quality of life of patients with osteoarthritis.

Keywords

endophenotypes; genes; osteoarthritis; sequencing; single nucleotide polymorphisms

INTRODUCTION

Osteoarthritis is the most common form of arthritis and affects millions of individuals aged 55 years and above, often leading to physical disability and reduced quality of life [1]. The disease is characterized structurally by articular cartilage degradation and remodeling of the subchondral bone, and is accompanied by symptoms of joint pain and stiffness, preventing individuals from performing normal daily activities. There is currently no cure for osteoarthritis and treatment focuses on relieving pain and improving function of the affected joints [2,3]. A better understanding of the cause of the disorder offers the hope for developing prevention strategies and/or more effective treatments. In this context, identification of genes associated with osteoarthritis can help reveal underlying biological mechanisms that may lead to development of new therapeutic targets or biomarkers for early detection and risk stratification.

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Conflicts of interest
No conflicts of interest.

The goal of this review is to summarize the major highlights and discoveries that have occurred over the past year in the genetic epidemiology of osteoarthritis. We will focus this review on the following areas: identification of new genes through genetic association studies, including genome-wide association studies (GWAS); family-based studies and extreme osteoarthritis phenotypes; endophenotypes and pain; and overlap of osteoarthritis with other age-related disorders. This review is meant to update/supplement other recent reviews of osteoarthritis genetics (e.g., [4,5'']).

GENES ASSOCIATED WITH OSTEOARTHRITIS

A strong genetic component to osteoarthritis has been firmly established for over half a century [6], with genetic factors estimated to account for up to half of the risk for developing osteoarthritis [7,8]. To identify the genes involved in the development of osteoarthritis, numerous candidate gene studies have been published in recent years, although few positive results have been firmly replicated across multiple populations. As with numerous other complex diseases, GWAS have recently been carried out that test associations of millions of single nucleotide polymorphisms (SNPs) across the human genome with osteoarthritis in an agnostic (i.e. not hypothesis driven) fashion. This past year saw the publication of final results from the Arthritis Research UK Osteoarthritis Genetics (arcOGEN) Consortium of the largest GWAS carried out to date, with a two stage design consisting of discovery in 7410 osteoarthritis cases, 80% ascertained at the time of total joint replacement (TJR) and 11 009 population-based controls in stage 1, and an in-silico replication of 129 prioritized SNPs with $P < 10^{-5}$ from the discovery cohort in an independent set of 5064 cases and 40 619 controls for stage 2 [9''].

In an interim report including 44% of their full GWAS sample published in 2011, no novel osteoarthritis loci were detected [10]. In this updated report, the authors identified 28 SNPs representing 12 independent signals associated with osteoarthritis at $P < 1 \times 10^{-5}$. After replication, six SNPs from five loci reached genome-wide levels of significance ($P < 5 \times 10^{-8}$) and an additional three SNPs were close to genome-wide significance. The nine SNPs are shown in Table 1 [9'',11–17]. The strongest signals were in the chromosome 3p21.1 region from two SNPs that were in perfect linkage disequilibrium (LD) with each other (rs11177 and rs6976) and associated with TJR ($P = 7.24 \times 10^{-11}$) and all osteoarthritis ($P = 6.56 \times 10^{-9}$). These SNPs have biological plausibility. Rs11177 is a missense variant in *GNL3* that codes for nucleostemin, which the arcOGEN investigators measured in cultured articular chondrocytes from controls and osteoarthritis patients, finding higher expression of nucleostemin in osteoarthritis chondrocytes. Rs6976 is located in the 3′ untranslated region (UTR) of *GLT8D1* (glycosyltransferase eight domain containing one) that may affect the glycosylation of cartilage extracellular matrix proteins. The other genome-wide significant meta-analysis hits came from the hip osteoarthritis strata and lie within or nearby genes that may be of biological importance to osteoarthritis (*ASTN2*, astrotactin 2; *FILIP1*, filamin A interacting protein; *SENP6*, sentrin specific peptidase 6; *KLHDC5*, Kelch domain containing 5; *PTHLH*, parathyroid hormone-like hormone; and *CHST11*, carbohydrate sulfotransferase 11), although further functional studies would be needed to identify the causal variant and its role in osteoarthritis pathogenesis. Although this is the largest osteoarthritis genetics study to date with about 15 000 cases, the effect sizes for the eight most significant SNPs are small (1.11–1.20). Additional large GWAS from North American cohorts, including the Osteoarthritis Initiative and Johnston County Osteoarthritis Study, are forthcoming and will likely add additional genetic variants to the collection of osteoarthritis candidate genes.

The new genetic associations reported by the arcOGEN Consortium add to the three previously established genome-wide significant associations of SNPs in the *GDF5* [11] and

MCF2L [13] genes as well as a region on chromosome 7q22 [12,17] that have been robustly associated with osteoarthritis. Functional studies have focused on the mechanisms underlying the association of *GDF5* with osteoarthritis [18''']. Recent studies from the Loughlin group at Newcastle University have shown that expression of *GDF5* can be regulated epigenetically by differential methylation [19''] and that binding of transcription factors to GDF-5 may be regulated by a functional rare variant in the 5′-UTR of the gene [20,21''].

Day-Williams *et al.* [13] identified a genome-wide significant association of rs11842874 that is located in intron 4 of the *MCF2L* gene on chromosome 13q34 that was associated with hip and knee osteoarthritis with an odds ratio of 1.17 (1.11–1.23) with $P = 2.07 \times 10^{-8}$ in a fixed effects meta-analysis that included 19 041 cases and 24 504 controls. The MCF2L protein is a member of the nerve growth factor (NGF) family and regulates neurotrophin-3-induced cell migration in Schwann cells. Given the efficacy of tanezumab, a monoclonal antibody to NGF, in treatment of pain in patients with moderate-to-severe hip and knee osteoarthritis, it is likely that the association of the *MCF2L* gene with osteoarthritis is mediated by its effects on pain rather than structure.

Evangelou *et al.* [12] extended the previously reported association of a locus in the region on chromosome 7q22 with osteoarthritis. They conducted a meta-analysis of four GWAS and then replicated the top hits in 10 additional cohorts with a cumulative sample size of 6709 cases and 44 439 controls. Rs4730250 was associated with knee osteoarthritis with odds ratio of 1.17 (1.11–1.24) with $P = 9.2 \times 10^{-9}$. Whereas this SNP is located in intron 3 in the *DUS4L* gene, the associated signal at 7q22 is located within a large (300 kb) LD block that contains six genes: *PRKAR2B* (protein kinase, cAMP-dependent, regulatory, type II, β), *HPB1* (HMG-box transcription factor 1), *COG5* (component of oligomeric golgi complex 5), *GPR22* (G protein-coupled receptor 22), *DUS4L* (dihydrouridine synthase 4-like), and *BCAP29* (B cell receptor-associated protein 29). Recent studies of joint tissue specimens from 156 patients with osteoarthritis and 25 controls with hip fractures showed that all of these genes except *GPR22* were detected in osteoarthritis cartilage and that carriers of the osteoarthritis-associated allele in rs4730250 had reduced expression of *HBP1* in both cartilage and synovium and *DUS4L* in the fat pad [22].

Numerous candidate genes have been studied for their relationship to osteoarthritis. Chapman and Valdes [23''] identified a group of seven candidate genes that were significantly associated with osteoarthritis which shared the following characteristics: data were available from not only the discovery cohort but also at least one replication cohort and the *P* value was less than 5×10^{-4} after adjustment for multiple testing. These seven included rs143383 in *GDF5*, the D14 allele in the VNTR of *ASPN*, rs10980705 in *EDG2*, the haplotype rs225014-rs12885300 in *DIO2*, rs12901499 in *SMAD3*, the haplotype rs419598-rs315952-rs9005 in *IL1RA*, and rs8065080 in *TRPV1*. Other investigators also have examined the association between SNPs in the genes for interleukin-1 β (*IL1*β) and IL 1 receptor antagonist (*IL1RN*) and severity of radiographic knee osteoarthritis [24,25].

FAMILY-BASED STUDIES AND EXTREME OSTEOARTHRITIS PHENOTYPES

Resequencing, either by Next Generation or Sanger approaches, is also being applied to osteoarthritis, as it is for many other complex diseases. As one such application, it has become increasingly apparent that common variants identified by GWAS point to loci harboring additional, often rare, variants for complex disease [26]. Because of its established association with osteoarthritis, Dodd *et al.* [20] resequenced the *GDF5* gene in 992 TJR cases and 944 controls from three European cohorts to identify rare variants additionally associated with osteoarthritis susceptibility that would not have been detected through

GWAS. The common, known variants were not associated with osteoarthritis in this sample and only six novel variants, each present in only a single case or control, were identified. Functional follow-up of a proximal promoter variant identified in a control from this sequencing project increased GDF5 expression, even in the haplotype context of the T risk allele of the common rs143383 variant that is known to reduce GDF5 expression [21'',27].

Sequencing is also being used in the context of trying to identify highly penetrant rare variants with large effects, which have traditionally been mapped through family-based linkage studies. As a recent example, three pathogenic mutations in *SMAD3* were identified in three unrelated Dutch families with syndromic familial aneurysm marked by early-onset osteoarthritis (coined Aneurysms–Osteoarthritis Syndrome) [28]. Follow-up sequencing studies, including one utilizing whole exome sequencing, were then carried out in families with syndromic aneurysms of unknown cause. Although these studies identified additional rare variants in *SMAD3*, not all of the families included presented with osteoarthritis [29,30].

Mu *et al.* [31] reported in 2011 the follow-up of a linkage signal that had previously been mapped to chromosome 19p in a six-generation Taiwanese family with early-onset osteoarthritis. These investigators identified through sequencing of candidate genes in this region a nonconservative substitution mutation in the *COMP* gene. Twenty-one of 26 carriers for this mutation had early-onset osteoarthritis with the other five carriers being young enough that symptoms may not have developed yet. Although functional data were not present on this mutation, it is located in a highly conserved region of the gene and was not detected in 96 Taiwanese reference samples.

In contrast to the above examples in which targeted sequencing has been applied to specific chromosomal regions to address very specific hypotheses, whole genome or exome sequencing is starting to be applied in an agnostic manner to detect rare disease-causing variants for a variety of complex diseases. The success of these efforts remains to be determined. To date, the most striking successes of whole genome or exome sequencing efforts have generally involved selected cases of very severe diseases, usually early-onset cases, or cases segregating in families and exhibiting evidence for major gene effects. For instance, whole-exome sequencing was done on eight patients with Hall type spondyloepimetaphyseal dysplasia with joint laxity, an autosomal dominant skeletal dysplasia disorder that includes early-onset osteoarthritis, and identified five novel sequence variants in the *KIF22* gene [32]

The decrease in the cost for next-generation sequencing means that incorporating whole genome sequencing into clinical care has moved from science fiction to scientific reality. Although the discovery of disease-associated variants for osteoarthritis has trailed other complex diseases, the prevalence of osteoarthritis may keep it poised for attention in the study of personal genomes. In a recent example, Ashley *et al.* [33] evaluated a personal genome of a 40-year-old man with a family history of coronary artery disease and sudden death. This patient also had a prominent family history of osteoarthritis and knee pain and was in fact a carrier of the R200W mutation in *FRZB*.

ENDOPHENOTYPES AND PAIN

As with many other complex diseases, osteoarthritis-related endophenotypes are increasingly being used as endpoints for analyses to uncover the genetic architecture of osteoarthritis. Castaño Betancourt *et al.* [34], for example, conducted a GWAS on radiographically measured jointspace width in the hip, as a proxy for cartilage thickness, and identified an association meeting genome-wide statistical significance with SNP rs12982744 in *DOT1L*, the gene encoding DOT1-like histone H3 methyltransferase, an enzyme involved

in chondrogenic differentiation, possibly through its role in canonical Wnt-signaling. The minor G allele of rs12982744 was associated with an increase in joint space width of 0.09 mm per copy; this suggests that homozygous carriers of the G allele would have approximately 5% thicker cartilage than controls. Interestingly, this allele was also associated with a 12% reduced odds of radiographic hand osteoarthritis with $P = 1.5 \times 10^{-4}$.

Several recent studies [35,36] have used shape modeling to identify joint shapes that are associated with hip osteoarthritis development. Waarsing *et al.* [36] used data from the Genetics, Osteoarthritis and Progression study to evaluate SNPs in *GDF5*, *FRZB*, and *DIO2* for association with hip shape. Although none of these SNPs was associated with shape phenotypes *per se*, authors did observe a significant interaction between SNP rs12885300 in *DIO2* and hip osteoarthritis for one of the hip shapes, suggesting that the *DIO2* risk allele may increase the vulnerability of cartilage in those with less favorable bone shapes. Similarly, within the past year, Baker-LePain *et al.* [37] reported that SNPs within *FRZB*, a Wnt antagonist, are associated with proximal femur shape among participants of the Study of Osteoporotic Fractures, and that the risk allele at one of these SNPs (rs288326) modified the relationship between hip shape and incident radiographic hip osteoarthritis. Taken together, these two studies suggest that the association of SNPs in *DIO2* and *FRZB* with hip osteoarthritis may be mediated by their relationship with shape of the femoral head rather than metabolism of articular cartilage.

Other clinically relevant osteoarthritis-related phenotypes, such as joint pain, are also beginning to receive increased attention in genetic studies. Peters *et al.* [38] recently carried out a GWAS meta-analysis of chronic widespread pain among women and identified an associated SNP near *CCT5* and *FAM173B*. Notably, this locus was particularly associated with joint pain. Moreover, both genes are plausible candidate genes for pain, and indeed, a previously identified *CCT5* mutation is an established cause of hereditary sensory neuropathy [39]. Beginning with a genome-wide linkage screen in mice, Sorge *et al.* [40] recently mapped a gene associated with chronic pain sensitivity to the P2X7 receptor (*P2X7R*), which are members of a family of ionotropic ATP-gated receptors. They further identified an amino acid changing mutation in this gene that was associated with chronic pain sensitivity in two human cohorts, including one with osteoarthritis.

OVERLAP OF OSTEOARTHRITIS WITH OTHER AGE-RELATED DISORDERS

Several recent studies have assessed the overlap between osteoarthritis and other age-related traits. In the population-based Rotterdam Study, for example, Hoeven *et al.* [41] reported an association between carotid intima–media thickness, a measure of subclinical atherosclerosis, and radiographically defined knee osteoarthritis, suggesting a potential vascular component to the cause of osteoarthritis. Elliott *et al.* [42] performed a systematic analysis to determine the overlap between SNPs associated with osteoarthritis and SNPs associated with height or BMI by comparing GWAS results obtained from the arc-OGEN Study (for osteoarthritis) and from the Genetic Investigation of Anthropometric Traits Consortium (for height and BMI). They reported that 17 SNPs exceeding a *P* value for suggestive statistical significance with osteoarthritis in arcOGEN also showed evidence for association with height and that another four showed evidence for association with BMI. However, only one of the SNPs showing joint associations of osteoarthritis with height/BMI could be replicated in a second set of osteoarthritis cases (SNP rs12149832 in the well known *FTO* gene). Further analyses revealed the association with osteoarthritis to be attenuated following adjustment for BMI, suggesting that this SNP influences osteoarthritis susceptibility via a primary effect on BMI, a well recognized risk factor for osteoarthritis.

Motivated by the fact that high bone mineral density (BMD) is a newly identified risk factor for osteoarthritis [43], we recently presented at the American Society for Bone and Mineral Research Scientific meetings (12–15 October 2012, Minneapolis, Minnesota, USA) a meta-analysis of the Osteoarthritis Initiative and Johnson County Osteoarthritis Project cohorts testing whether SNPs previously identified with BMD are also associated with osteoarthritis susceptibility. We identified five (of 56) SNPs nominally associated with osteoarthritis, with the high-BMD risk allele associated with greater osteoarthritis prevalence. Two of these were in the Wnt-signaling pathway, reinforcing the potential role of this pathway in osteoarthritis.

CONCLUSION

Genomic approaches directed toward unraveling the genetic underpinnings of osteoarthritis are moving forward in multiple directions. Several new large GWAS studies of radiographicaly confirmed osteoarthritis will soon become available, including from the Osteoarthritis Initiative, Johnson County Osteoarthritis Project, Genetics of Generalized Osteoarthritis, and Multicenter Osteoarthritis studies. Meta-analysis of these with the arcoGEN and other existing studies supported by the TREAT-Osteoarthritis Consortium will almost certainly lead to the identification of additional small effect size loci. Beyond these and any additional studies that are already in the GWAS pipeline, it seems unlikely that additional samples of radiographically characterized osteoarthritis cases will materialize in sufficient number any time soon given the effort and expense required. However, recent availability of large clinically based biobanks, such as Vanderbilt's BioVU or Kaiser Permanente's Research Program on Genes, Environment and Health that link electronic medical records with biospecimens [44] may provide rich opportunities for assembling large numbers of cases with clinically based endpoints, such as joint replacement or pain.

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KEY POINTS

- There is a strong genetic predisposition to osteoarthritis, particularly the endophenotypes assessed by imaging modalities.
- Several genes have been identified to be associated with osteoarthritis in GWAS; however, the magnitude of these associations is weak.
- At this time, although this body of research has produced innovative findings with respect to the pathophysiology of osteoarthritis, we have yet to realize new treatments to improve the quality of life of patients with osteoarthritis.

Table 1

Loci associated with osteoarthritis

Locus	Chr	Nearest gene(s)	Effect allele	Freq of effect allele in controls	OR for effect allele (95% CI)	P-value	Reference
Genome-wide significant (or near significant) associations from arcOGEN*							
rs6976/rs11177	3	*GLT8D1 GNL3*	T A	0.37 0.38	1.12 (1.08–1.16) 1.12 (1.08–1.16)	7.24×10^{-11} 1.25×10^{-10}	[9'']
rs12107036	3	*TP63*	G	0.52	1.21 (1.13–1.29)	6.71×10^{-8}	[9'']
rs10948172	6	*SUPT3H; CDC5L*	G	0.29	1.14 (1.09–1.20)	7.92×10^{-8}	[9'']
rs9350591	6	*FILIP1; SENP6*	T	0.11	1.18 (1.12–1.25)	2.42×10^{-9}	[9'']
rs4836732	9	*ASTN2*	C	0.47	1.20 (1.13–1.27)	6.11×10^{-10}	[9'']
rs10492367	12	*KLHDC5; PTHLH*	T	0.19	1.14 (1.09–1.20)	1.48×10^{-8}	[9'']
rs835487	12	*CHST11*	G	0.34	1.13 (1.09–1.18)	1.64×10^{-8}	[9'']
rs8044769	16	*FTO*	C	0.50	1.11 (1.07–1.15)	6.85×10^{-8}	[9'']
Other established associations							
rs143383**	20	*GDF5*	T	0.59–0.75	1.17 (1.12–1.23)**	6.2×10^{-11}	[11]
rs10953541***	7q22	*DUS4L*	G	0.17	1.17 (1.11–1.24)	9.2×10^{-9}	[12]
rs11842874	13	*MCF2L*	A	0.927	1.17 (1.11–1.23)	2.1×10^{-8}	[13]

arcOGEN, Arthritis Research UK Osteoarthritis Genetics; Chr, chromosome; CI, confidence interval; Freq, frequency; OR, odds ratio.

* Table is modified from arcOGEN, 2012. Most current meta-analysis p-values are reported.

** Value reported for knee osteoarthritis in meta-analysis with Whites and Asian cohorts. Association has been previously reported for hip osteoarthritis and in Asian cohorts [14–16].

*** Value reported for knee OA. Most significant signal is located in an LD block in 7q22 that also includes *COG5, HBP1, PRKAR2B, GPR22, and BCAP29*. Region is also associated with hand osteoarthritis [17].