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Osteoarthritis susceptibility genes continue trickling in

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Osteoarthritis is the most common form of arthritis, with the small joints of the hands, knees, and hips most frequently affected in descending order.¹ Osteoarthritis of the hip and knee are the main causes of functional limitation, physical disability, and reduced health-related quality of life in adults in developed countries. Furthermore, symptomatic radiographic hip and knee osteoarthritis are associated with excess all-cause mortality, primarily from cardiovascular disease.^{2,3} A strong genetic contribution to osteoarthritis has been recognised for over 60 years since the description of familial aggregation of nodal hand osteoarthritis by Stecher.⁴

High heritability of structural features of hand, hip, and knee osteoarthritis, identified on radiographic imaging and MRI, has been documented in studies of twins in the UK.⁵ However, aside from rare mutations in genes encoding structural proteins in articular cartilage, few common genes have been identified as risk factors for the development of hip or knee osteoarthritis in genome-wide association studies (GWAS).⁶ The three that have demonstrated genome-wide significance in cohorts of Europeans include *GDF5* (growth/differentiation factor 5), *MCF2L* (guanine nucleotide exchange factor DBS), and a locus on chromosome 7q22.^{7–9} We recently confirmed the association of *GDF5* with radiographic knee osteoarthritis in a preliminary analysis of candidate genes in white North Americans using data from the Osteoarthritis Initiative and Johnston County Osteoarthritis Project.¹⁰

In *The Lancet*, Eleftheria Zeggini and colleagues¹¹ now report the identification of eight new susceptibility loci for osteoarthritis of the hip and knee from the arcOGEN study. They included an initial set of people with severe hip and knee osteoarthritis, 80% of whom had undergone total joint replacement, making it the largest GWAS study of osteoarthritis reported so far. As is now the standard for GWAS of complex traits, the investigators used a multistage design, in which they sought to replicate their top hits in the initial set of 7410 cases and 11 009 controls in an independent set of 7473 cases and 42 938 controls, all of European descent. After conventional adjustments for multiple comparisons, five novel loci were detected that surpassed genome-wide levels of significance with an additional three loci approaching this threshold.

The odds ratios of the eight genome-wide significant or near-significant associations were 1.11–1.21, which is sobering but completely in accord with the results of GWAS for other

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complex traits. Although additional osteoarthritis susceptibility loci are expected to be found as sample sizes increase in future GWAS analyses, we can also expect that any new associated loci will have diminishing effect sizes. These associations are thus unlikely to be useful for disease prediction, but their real value might be to provide new biological insights and uncover new pathways. Three of the novel associated loci are strong biological candidate genes (*PTHLH*, *CHST11*, and *FTO*), although the most strongly associated locus, straddling *GLT8D1* and *GNL3* on chromosome 3p21.1, is not. *GLT8D1* encodes the protein glycosyltransferase 8 domain containing 1, a member of the glycosyltransferase family that is of as yet unknown specific function, whereas *GNL3* encodes the guanine nucleotide binding protein-like 3, also known as nucleostemin. The protein resides in the nucleolus and binds p53, regulating differentiation and the cell cycle. In-vitro experiments showed upregulation of nucleostemin in articular chondrocytes from osteoarthritic cartilage, removed at the time of total joint replacement, compared with normal cartilage samples. These data suggest a biological role for this protein in osteoarthritis, although it is uncertain whether this role is in disease development or progression or both. Surprisingly, none of the previous associations for osteoarthritis with *GDF5*, *MCF2L*, and the chromosome 7q22 locus achieved genome-wide levels of significance in the arcOGEN sample.

Most of the genome-wide significant associations were restricted to the hip osteoarthritis phenotype, and one of these was found only in women with total hip replacement. We think this finding supports the results from epidemiological studies that hip osteoarthritis is more likely to arise from local factors related to alterations in bone shape (eg, congenital hip subluxation or femoroacetabular impingement) that might be genetically predisposed, whereas knee osteoarthritis is more likely to arise from environmental factors such as joint injury (eg, anterior cruciate ligament or meniscal tears) and obesity.¹²

The results from the arcoGEN study are consistent with research experience and draw attention to the importance of large sample sizes in the discovery cohort and the need for extensive replication samples from consortia to corroborate initial findings. Furthermore, they draw attention to the heterogeneity of osteoarthritis and the need to undertake these studies in cases with carefully defined disease phenotypes. There were more and stronger signals when the more severe case definition of total joint replacement, which indicates a combination of moderate-to-severe structural damage plus moderate-to-severe pain and functional limitation, was used compared with a less stringent case definition based on only radiographic features. This is a nice illustration of the conundrum in genetic epidemiology of whether it is better to have less misclassification error or a larger sample size. Through this well done and thorough study, we now have some intriguing leads to follow. More genes and single nucleotide polymorphisms will certainly follow through continued GWAS efforts and next-generation sequencing approaches. The challenge will be to connect the biology of these genes to the development and progression of osteoarthritis and to investigate the therapeutic potential of these pathways for disease prevention and treatment.

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