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COMMENTARY

Wnt signalling and the genetics of osteoarthritis

Jon H Tobias

Musculoskeletal Research Unit, University of Bristol School of Clinical Sciences, Avon Orthopaedic Centre, University of Bristol, Bristol, UK.

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Commentary on: Baker-Lepain JC, Lynch JA, Parimi N, McCulloch CE, Nevitt MC, Corr M, Lane NE. Variant alleles of the Wnt antagonist FRZB are determinants of hip shape and modify the relationship between hip shape and osteoarthritis. *Arthritis Rheum* 2012;**64**:1457-1465; Castaño Betancourt MC, Cailotto F, Kerkhof HJ, Cornelis FM, Doherty SA, Hart DJ, Hofman A, Luyten FP, Maciewicz RA, Mangino M, Metrusty S, Muir K, Peters MJ, Rivadeneira F, Wheeler M, Zhang W, Arden N, Spector TD, Uitterlinden AG, Doherty M, Lories RJ, Valdes AM, van Muers JB. Genome-wide association and functional studies identify the *DOT1L* gene to be involved in cartilage thickness and hip osteoarthritis. *Proc Natl Acad Sci USA* 2012;**109**:8218-8223.

Osteoarthritis (OA) is an age-related condition involving the entire joint, including adjacent muscles, underlying subchondral bone, ligaments, synovium and the joint capsule. It is characterised pathologically by loss of hyaline articular cartilage, osteophyte formation and subchondral sclerosis. OA is associated with increased bone mineral density (BMD), suggesting that OA confers a reduced risk of osteoporosis.[1] Nonetheless, as illustrated by the two papers discussed herein, interesting areas of overlap are starting to emerge from the point of view of shared biological pathways and methodology.

Baker-LePain *et al.*[2] recently reported a nested case–control study from the Study of Osteoporotic Fractures, comprising 451 cases with incident radiographic hip OA during follow-up, and 601 controls. Two single-nucleotide polymorphisms (SNPs) in the gene encoding *Frzb*, a Wnt antagonist, were analysed in relation to the hip OA case status as defined radiologically, in an attempt to replicate associations seen in previous studies. Furthermore, relationships were examined with 10 independent modes of hip shape generated by principle components analysis, which were analysed on the basis that alterations in hip shape contribute to the pathogenesis of OA.[3] An SNP within the *FRZB* gene, rs288326, was found to be related to hip shape component two, in which width of the femoral head is narrow relative to width of the femoral neck and shaft. Moreover, an interaction with hip shape was observed, such that the hip shape component two was related only to risk of radiographic hip OA in the presence of the rs288326 variant allele.

Castaño Betancourt *et al.*[4] report findings from a genome-wide association study (GWAS) performed in 6523 individuals from two population-based discovery cohorts from Rotterdam, in relation to radiographically measured joint space width (JSW), a proxy for cartilage thickness and an important intermediate phenotype for hip OA. A strong association was observed in relation to the rs12982744 variant allele, located in the *DOT1L* gene, which was associated with a 5% larger JSW. This finding was subsequently replicated in 4442 individuals from 3 UK cohorts. In further analyses examining associations between this SNP and radiographic hip OA, supplemented with an additional case–control study, the rs12982744 variant allele was also found to be related to a 12% decrease in the risk of hip OA. The gene product of *DOT1L* is a histone methyltransferase, which has previously been identified as an essential and dedicated enzyme for Wnt target gene activation in the intestine. The function of DOT1L in chondrocytes was subsequently explored by knocking down its expression in ATDC5 chondrogenic cell lines; this led to a decrease in chondrogenesis associated with reduced expression of the Wnt target genes.

Taken together, these two reports suggest that Wnt pathways have an important role in joint development, and that the *Wnt* gene SNPs contribute significantly to genetic influences on OA. This may reflect heterogeneous actions of Wnt pathways, including involvement in mechanisms responsible for determining overall joint shape and in forming articular cartilage. Recent reports suggest that the *Wnt* gene SNPs are also important determinants of osteoporosis risk,[5,6] raising a number of interesting questions as to possible functional relationships between OA and osteoporosis. For example, if osteoblasts and chondrocytes are influenced by common Wnt pathways, this may help to explain inverse associations between OA and osteoporosis, whereby a genetic variant favouring chondrogenesis might have reciprocal effects on osteoblasts, leading to reduced BMD. Further research is justified to identify any functional overlap between components of the Wnt pathway implicated in these two conditions.

These two papers also illustrate how methodological approaches to the study of genetic influences on osteoporosis and OA are converging. To date, *GDF5*, *MCF2L* and 7q22 have been identified as being robustly associated with OA risk in a large-scale GWAS study,[7–9] with a further eight loci recently identified in a further GWAS study.[10] This total is substantially less than that identified for osteoporosis; in a recent GWAS,

56 loci were identified as being related to BMD.[11] A potential explanation for this difference is that to date, as well as involving fewer participants, GWAS studies in OA have been based on case–control designs, whereby pooled OA cases have been identified based on radiographic appearances and/or a history of joint replacement. As the epidemiology of OA at different sites is distinct, suggesting that different pathogenic (and therefore genetic) pathways may be involved, heterogeneity of patient groups included in these studies may lead to dilution of effects and reduced power. In addition, case definitions such as presence or absence of joint replacement, or above or below a specific Kellgren–Lawrence radiographic score for OA, are relatively non-specific, with control populations containing substantial numbers of individuals at significant risk of developing OA in the future. Even within the same site, OA is multi-factorial, and so patients meeting OA case definitions may have reached this by a variety of different pathways subject to distinct genetic influences.

The genetic association analysis of quantitative risk factors associated with disease ('endophenotypes') is a powerful alternative strategy through which genetic loci predisposing to disease can be identified, and which has been successfully applied to a number of conditions including osteoporosis based on investigation of genetic influences on BMD and related bone phenotypes. The two studies described above apply this approach to analysis of OA genetics, using intermediary phenotypes, namely JSW and hip shape, as measured in population-based cohorts. It may be that application of this approach to larger cohorts will yield similar numbers of disease-associated loci for OA to those found for osteoporosis. Indeed, it may be possible to use existing phenotypic information from previous osteoporosis genetics study to identify novel genetic markers for OA. Similar hip shape measurements to those analysed by Baker-LePain *et al.*[2] can be derived from hip DXA scans, a measure which formed the basis of previous GWAS studies for osteoporosis, enabling access to considerably larger discovery cohorts than those used to study OA genetics to date.[12]

Conflict of Interest

The author declares no conflict of interest.

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