# Genetics and osteoarthritis: implications for the clinic

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After much activity on a large number of common human diseases, it has now been demonstrated beyond doubt that polymorphism in the human genome is a major contributor to disease susceptibility, with the genome-wide association scan methodology proving to be particularly adept at identifying loci harboring common DNA polymorphisms of moderate to high impact on disease risk [1]. As cohort sample sizes increase, more loci of ever-weaker effects will be discovered, with the expectation being that specific pathways fundamental to particular diseases will be uncovered [2]. These will then offer scope for clinical intervention.

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There are still many obstacles to overcome, logistical, technical and theoretical. Logistical obstacles include the collection of ever-larger cohorts with the concurrent need to gather together very detailed medical and environmental measures and to share these resources across different ethical jurisdictions in large collaborative projects. Technical obstacles include the need to develop efficient methods for genotyping complex DNA polymorphisms, such as structural variations [3], and to establish high-throughput strategies for discovering rare variants that may be of greater singular impact on disease susceptibility than common polymorphisms [4,5]. Theoretical obstacles include the fact that, for most common diseases, a much smaller proportion than was expected of the heritability of the diseases is being accounted for by the DNA polymorphisms so far scanned. This has led to some skepticism regarding the overall usefulness of the genome-wide approach, but has also made those actively involved in the field aware that much is still left to discover and to comprehend [6].

So what is the current status of osteoarthritis genetics? A few years ago the genetic analysis of this disease began to emerge from the candidate gene-driven approach, with its inherent bias towards the known, and entered the agnostic approach of genome-wide association scans. Unfortunately, the powerful osteoarthritis scans have not yet published their findings, leaving us currently with the outcomes of the candidate studies as our basis for hypothesizing about the translational potential of genetic discoveries. Although these candidate studies have typically suffered from the quite usual dual shortfalls of testing only a proportion of the variation within the targeted locus in small, underpowered cohorts, several robust hits have nevertheless emerged [7]. The two most compelling are common polymorphisms within the genes *GDF5* and *DIO2*. GDF5, also known as cartilage-derived morphogenetic protein 1 (CDMP1), is a member of the TGF-β superfamily and participates in the development, maintenance and repair of bone, cartilage and other tissues of the synovial joint. A single nucleotide polymorphism (SNP), rs143383 (T/C), located within the 5′ untranslated region of *GDF5* is associated with osteoarthritis in Asian and European populations [8,9]. The associated T-allele demonstrates reduced expression of *GDF5* both *in vitro* and in tissues extracted from the joints of osteoarthritis patients [10,11]. There is also evidence of other functional polymorphism within this gene, and of a *trans*-acting factor, DEAF-1, that differentially interacts with the two rs143383 alleles [12]. *DIO2* codes for iodothyronine-deiodinase enzyme type 2 (D2), a selenoprotein that converts intracellular inactive thyroid hormone to its active form. D2 is a provider of local bioactive thyroid hormone to target tissues, such as the growth plate. A common *DIO2* haplotype, containing the minor allele of rs225014 and the common allele of rs12885300, was, like

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*GDF5* SNP rs143383, associated with OA in Asian and European cohorts [13]. The GDF5 and DIO2 proteins are active during normal skeletal morphogenesis as well as in mature, adult tissues. The associations to polymorphism in *GDF5* and *DIO2* therefore emphasize that we need to consider the role of early developmental events in the osteoarthritis disease process [14,15].

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So what is the likelihood that genetic discoveries in osteoarthritis will have an impact in the clinic? Clearly, speculation is the current order of the day due to our still porous knowledge of the genetic architecture of this common arthritis, although hopefully this situation will be attenuated by the imminent genome scans. The first clinical benefit may be an enhancement of our ability to more accurately phenotype the disease, based less on overt clinical observation, but more on the underlying genetic architecture, such that we may start classifying patients by the major pathways involved in their disease process. This may lead to more refined patient cohorts being selected for the downstream trialing of new treatments. The second benefit may be an enhanced capacity to predict the trajectory of disease progression, based around how genetically loaded a particular individual is. This approach considers the number of susceptibility loci inherited and their cumulative risk [16]. Such predictions sound relatively straightforward but clearly are not, being heavily dependent on the interaction of susceptibility loci with several other factors including other loci (epistasis), with somatic events such as epigenetic changes and with the environment. Large-scale prospective cohort studies, with the concurrent analysis of appropriate tissues for epigenetic evaluations, will be required if we are ever to get a robust handle on how the genome, the epigenome and the environment interact in osteoarthritis initiation and progression [17]. The ultimate clinical benefit will be the development of new treatments. This is not too fanciful, in that if pathways amenable to intervention by small molecules are uncovered, then these can be explored with vigor. Alternatively, genetic discoveries may help guide developments in endogenous and exogenous cell-based treatments.

One very important consideration in all the proposed clinical utilities of the genetic data, and one touched on earlier, is the actual point in an individual's development when the genetic deficit first manifests itself. If this is early, can we realistically expect individuals to embark on potentially prolonged treatments from relatively young ages? For example, it has been reported that the osteoarthritis-associated T allele of the *GDF5* SNP rs143383 is also associated with shorter stature, which is a developmental phenotype [18,19]. The salient question therefore is does this allele initially contribute to osteoarthritis risk during skeletogenesis, and hence long before anyone would present at the clinic with even mild symptoms of the disease? Clearly, many proteins are pleiotropic and it may be that even if this were the case, adult-based interventions could at least attenuate any effect that susceptibility loci are having on disease progression and severity.

In conclusion, from an applied research perspective, osteoarthritis is no different to other common diseases in that by understanding more of the fundamental origins of the disease, it is anticipated that new avenues for clinical intervention will open up. Such interventions may not prevent disease initiation if the initiating factors are laid down early in development, but may slow down or halt progression. There are still a number of extremely difficult challenges ahead, but these may seem less daunting once the data from the genome scans are available. There are also new tools on the horizon, such as whole-genome sequencing, which will overcome some of the technical issues surrounding genetic research in common diseases. There is therefore a long way to go before osteoarthritis genetics translates to the clinic, but appropriate steps are being taken.

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**Financial & competing interests disclosure**

*The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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