Osteoarthritis has a strong genetic component and family based studies have indicated that heritability of the disease ranges between 40% and 80% depending on the site affected and the characteristics of the population being studied. Although genetic factors clearly contribute to the pathogenesis of osteoarthritis, we are still a long way from understanding how genes and environment interact to cause this common and disabling disease.

So far, two main approaches have been used to try and identify the genetic variants that predispose to osteoarthritis; genome wide linkage analysis in families and candidate gene association studies in unrelated individuals. Family based linkage studies have identified several candidate loci that potentially harbour genes which predispose to osteoarthritis, but with some exceptions the regions so far identified by these studies have failed to reach the logarithm of the odds score thresholds required for genome wide significance. Nonetheless, analysis of candidate genes from some of these loci has resulted in the identification of variants that appear to predispose to osteoarthritis.

One example is MATN3 which is a candidate gene that lies within a locus on chromosome 2 that was linked to hand osteoarthritis in the Icelandic population. The MATN3 gene encodes matrilin-3, a component of extracellular matrix, and mutation screening of this gene identified a protein coding polymorphism which was found to segregate with hand osteoarthritis in Icelandic families. Subsequently, the same polymorphism was reported to be associated with osteoarthritis in other populations, supporting the hypothesis that MATN3 is a true susceptibility gene for osteoarthritis. Further proof of the importance of MATN3 in the pathogenesis of osteoarthritis came from the recent observation that targeted inactivation of MATN3 causes premature osteoarthritis in mice and a generalised increase in bone density. This phenotype is of special interest since increases in bone density are well known to be associated with osteoarthritis in humans, thereby raising the possibility that some genetic variants which predispose to osteoarthritis might protect against osteoporosis and vice versa.

Another example is the FRZB gene which maps to within a weak candidate locus for hip osteoarthritis that was originally identified on chromosome 2q23 by linkage analysis. The FRZB gene encodes frizzled related protein 3, an antagonist of wnt signalling and mutation screening of this gene identified a coding polymorphism at position 324 resulting in an arginine to glycine substitution (R324G) which was associated with osteoarthritis in the families originally used to identify linkage as well as additional families and a case control study of unrelated subjects. Functional studies suggest that the osteoarthritis associated glycine variant has diminished ability to antagonise wnt signalling thereby raising the possibility that activation of wnt signalling could play a role in the pathogenesis of osteoarthritis.

Candidate gene association studies have resulted in the identification of several variants that could potentially predispose to osteoarthritis including the oestrogen receptor alpha (ESR1) gene, and the Calmodulin-1 gene. There is evidence that genetic variants within the interleukin-1 cluster both predispose to osteoarthritis and are involved in disease progression. Although some of these associations have been replicated in different populations, others have not, even with adequately powered studies. It is unclear to what extent failure to replicate association studies in different populations represent true differences in alleles that predispose to osteoarthritis across ethnic groups; population-specific differences in environmental factors that interact with these variants; or false positive results. There is considerable controversy over whether or not ethnic differences in genetic effects for complex disease truly exist and it could be that some instances of failure to confirm associations are due to unrealistically high estimates of the genetic risk in the initial “positive” study. It is certainly clear that few of the genetic associations which have been described in osteoarthritis have been validated by really large scale studies, such as those that have started to emerge in other areas of musculoskeletal genetics. Indeed, most of the genetic studies performed so far in the osteoarthritis field have been underpowered to detect the modest effects expected for polygenic influences on this complex disease.

In the current issue of Osteoarthritis and Cartilage, Kraus and colleagues describe the characteristics of a large family based study (the Genetics of Generalised Osteoarthritis or “GOGO” study) involving 2706 subjects from 707 kindreds who were selected on the basis that two or more relatives had clinical evidence of hand osteoarthritis. Although osteoarthritis of the hand has less of an impact on morbidity than osteoarthritis of the hip or knee, many affected subjects in GOGO also had radiological osteoarthritis at other sites including the spine, the knee, and the hip. In view of this, it is probable that GOGO will provide a resource for mapping genes that predispose not only to hand osteoarthritis, but also to osteoarthritis of other joints.

The GOGO population is the largest family based cohort study of osteoarthritis assembled so far and represents an
important resource with which to identify susceptibility genes for the disease. But is the study big enough to identify novel genes that regulate susceptibility to osteoarthritis? Power calculations performed by the authors indicate that GOGO has good power to detect linkage to a locus that doubles the risk of hand osteoarthritis assuming that a single locus is involved in at least 20% of the study population. Whilst the genetic architecture of osteoarthritis is poorly understood, the studies that have so far been performed indicate that the susceptibility genes act in a site specific and gender specific manner and with modern genetic mapping techniques such as using family based cohorts that have selected for involvement of major joints such as the knee and hip and with modern genetic mapping techniques such as using dense single nucleotide polymorphism maps for linkage and genome wide association, the power may actually be better than originally estimated.

The clinical importance of identifying genetic determinants of susceptibility to osteoarthritis is to improve understanding of pathophysiology; to develop new markers for progressive disease and perhaps most importantly, to identify signalling pathways that can act as a target for the development of new treatments. The GOGO cohort will be of value in furthering some of these aims and this was undoubtedly an important motivation for GlaxoSmithKline — the pharmaceutical company that funded collection of the GOGO cohort. The pharmaceutical industry has also become involved in funding the collection of other cohorts with osteoarthritis in collaboration with publicly funded bodies. In the USA for example, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) has joined forces with several pharmaceutical companies to collect longitudinal information on clinical, radiological and biomarker based determinants of progression of knee osteoarthritis in over 5000 subjects within the osteoarthritis initiative (OAI) (http://www.nih.gov/news/pr/aug2006/niams-01.htm). The OAI project will provide a very valuable resource to investigate the genetic epidemiology of knee osteoarthritis and would help to answer the question as to whether or not the genetic variants that predispose to osteoarthritis overlap with those that mediate disease progression. It is to be hoped that the NIAMS initiative, coupled with the lead provided by GOGO will also provide an impetus for funding bodies in Europe and elsewhere, to assemble large intensively phenotyped cohorts of patients with osteoarthritis so that we can continue to make progress in understanding the pathogenesis of this common disabling disease.

References