Osteoarthritis linkage scan

Osteoarthritis linkage scan: more loci for the geneticists to investigate

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Chromosomal loci potentially harbour osteoarthritis susceptibility genes, as shown by a genomewide linkage scan

Those investigating the molecular genetic basis of osteoarthritis must believe that all the hard work is beginning to reap rewards, as yet another linkage scan shows several interesting chromosomal loci potentially harbouring osteoarthritis susceptibility. In the September issue of the Annals of Rheumatic Diseases, Greig et al. reported the results of a comprehensive genomewide linkage scan performed on 202 families that contain individuals with nodal osteoarthritis, recruited from Nottinghamshire, UK. By using both a qualitative analysis (presence or absence of nodal osteoarthritis) and a quantitative analysis (severity of the disease), major hits were reported for chromosomes 3, 4, 8, 11 and 16. Intriguingly, the chromosome 3 and 16 hits overlap with osteoarthritis loci reported by other groups, implying that at least these two linkages are likely to be genuine.

CURRENT STATUS OF GENETIC SUSCEPTIBILITY OF OSTEOARTHRITIS

So how does this latest linkage data fit in with what we currently know about the molecular genetic basis of osteoarthritis susceptibility? The Greig et al. report is the fifth genomewide osteoarthritis linkage scan so far published, the others being conducted on affected relative pairs collected in the UK, Finland, Iceland and the USA. The UK scan was performed on patients who had osteoarthritis of the hip or knee; other scans performed on patients with osteoarthritis of the hand were ascertained using a global hand osteoarthritis score or by focusing on particular joints of the hand. There have also been two gene-based association scans, the first performed on Japanese patients who had osteoarthritis of the hip or knee, and the second on UK Caucasian patients who had osteoarthritis of the knee. The linkage and association scans uncovered several important loci, which have subsequently yielded several susceptibility genes. The most compelling findings are the secreted frizzled-related protein 3 gene FRZB on chromosome 2q, the interleukin-1 gene cluster on chromosome 2q, the asporin gene ASPN on chromosome 9q, the metalloprotease gene ADAM12 on chromosome 10q, the leucine-rich repeats and calponin homology domain containing protein 1 gene LRCH1 on chromosome 13q, and the calmodulin-1 gene CALM1 on chromosome 14q.

What makes a finding compelling? Two things—(1) the significance of the result obtained and (2) the independent confirmation by another group of an original finding. The most compelling data regarding significance come from the ASPN study, with p values <0.001 for the association with osteoarthritis of a functional repeat polymorphism in the coding region of the gene. The most compelling finding with regard to independent confirmation is the FRZB association, which was originally reported in UK Caucasians and which has now been confirmed in studies carried out in The Netherlands, Belgium and the USA. Sometimes strong significance and independent confirmation do not go together. For example, the compelling ASPN and CALM1 associations were identified in Japanese patients but have not been replicated in Europeans. This implies the existence, at different frequencies between Asians and Europeans, of other polymorphic loci that act epistatically with ASPN and CALM1 to influence the osteoarthritis risk mediated by these two genes. Furthermore, non-genetic (environmental) differences between the two populations may also affect the penetrance of the ASPN-encoded and CALM1-encoded osteoarthritis susceptibility. We should therefore not necessarily expect to replicate a positive finding in all ethnic groups.

THE LATEST LINKAGE REPORT

The Greig et al. study is one step away from the above association analyses in that it has defined new chromosomal regions, each of which contains tens if not hundreds of genes. Therefore, there is still work for the geneticists to do in characterising the osteoarthritis susceptibility at each locus. Do any of the five loci detected by Greig et al. overlap with any of the genes listed above? No. The chromosome 16 linkage does, however, overlap with a linkage reported in an Icelandic family with early-onset osteoarthritis. This region was also linked to disease in the UK large-joint scan, with the investigators subsequently reporting an association with single-nucleotide polymorphisms in the interleukin 4 receptor gene IL4R.

Analysis of IL4R by Greig et al. is therefore called for, although it needs to be borne in mind that another gene within the interval could also encode osteoarthritis susceptibility, as the original IL4R association has not yet been independently replicated.

The quantitative analysis conducted by Greig et al. focused on three specific osteoarthritis traits: distal interphalangeal nodes, joint space narrowing and osteophytes. A very important observation from this quantitative analysis was the limited overlap seen in the loci detected by the three traits. For example, the chromosome 16 linkage was restricted to the joint space narrowing trait, whereas the chromosome 8 linkage was principally accounted for by the distal interphalangeal node trait. This implies a very specific effect of each susceptibility locus, with their cohesiveness in an individual tipping the balance towards overt, clinical disease. This aspect of the study by Greig et al. merits further epidemiological investigation by them and by others.

SUMMARY

The findings by Greig et al. provide us with new loci to investigate and also stimulate our thoughts relating to the overall nature of genetic susceptibility of osteoarthritis. Clearly, osteoarthritis is a complex disease both clinically and genetically. It is also clear that genetic studies are providing us with new insights into the fundamental causes of this disease. The recent advances in human molecular genetics exemplified by the sequencing of the human genome project, the delineation of the human HapMap and the development of high-throughput genotyping platforms now provide us with an opportunity to comprehensively search the genome for osteoarthritis risk alleles. The Greig et al. study represents another step towards this goal.

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