

Genomewide Search for OA Risk Is Largest Ever

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A genomewide association study of osteoarthritis susceptibility has begun in the United Kingdom with 8,000 patients and 6,000 controls, the largest study of its kind ever undertaken.

Dr. John Loughlin, principal investigator of the study and a geneticist at the Nuffield Department for Orthopaedic Surgery at the University of Oxford (England), said the study's massive size would provide it with "unprecedented power."

The results will be made freely available to the public upon the study's completion.

In an interview, Dr. Loughlin explained that the study, known as arcOGEN ("arc" stands for Arthritis Research Campaign, who is funding the study; the "O" for osteoarthritis; and the "GEN" for genetics), will genotype only U.K. citizens of white



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DR. ALTMAN

British ancestry. He said his group already has 4,000 cases and is collecting another 4,000. "The controls are those genotyped as part of other studies," he said.

The inclusion criterion for cases is a diagnosis of severe primary osteoarthritis (OA). "The vast majority of our cases [more than 75%] will have undergone arthroplasty of a hip or of a knee," he said. There will be no inclusions or exclusions related to past or present drug treatment.

Dr. Loughlin hopes to have the first 4,000 cases genotyped by the summer of 2008 and the second 4,000 genotyped by the summer of 2009, with analyses performed by the autumn of 2009.

Dr. Roy Altman, visiting professor in the division of rheumatology at the University of California, Los Angeles, said "it's a little bit early to say what the clinical relevance [of this study] is going to be. ... Unless you put in formulas for, for example, ... whether the cases play soccer or not," it will be difficult to tell how great is the effect of environmental factors like trauma on genetically predisposed OA candidates.

In addition, Dr. Altman, who is not affiliated with the study, pointed out the study will be limited by the fact that it will look only at white British subjects. However, regarding Dr. Loughlin's suitability to undertake such research, he added: "You can't get anybody better than [Dr. Loughlin]. He is the best of the osteoarthritis geneticists, and I know he will do a very credible job."

Several genes have already been found to be associated with susceptibility to OA. "The most compelling so far are FRZB, GDF5, and ASPN," said Dr. Loughlin. "Intriguingly, all encode proteins that are involved in cell-signaling pathways in the tissues of the articulating joint, implying that OA susceptibility may partly be accounted

for by aberrant cell signals. This is exciting, as these are potentially modifiable." He added, however, that although several studies have been published on OA genetic susceptibility, few have been replicated.

Dr. Loughlin and his associates hope to find 10-20 of the genes that confer a strong to moderate risk for OA.

Large, genomewide studies like arcOGEN (versus smaller, linkage region-focused studies) will likely become more common as the cost of these studies con-

tinues to drop, Dr. Loughlin said. "Focusing on particular candidates will happen when a [genomewide association study] has highlighted a particular genomic region as likely to harbor susceptibility genes."

Dr. Altman said, "The technology of identifying genes has advanced so much that now we can do these kind of genomewide studies in bulk, with 8,000 patients, that we couldn't have done 3 years ago. ... I'm not quite sure how it's going to apply [to clinical practice], but it's certainly something

that's important. If you find genetic predispositions and you have a way of altering those genes, then it may be relevant."

The £2.2 million grant from the Arthritis Research Campaign funding this study is the biggest ever given by the group, which says it is the fourth-largest medical research charity in the United Kingdom.

The arcOGEN study will be undertaken across eight centers in the United Kingdom. Dr. Loughlin reported no conflicts of interest for himself or his associates. ■



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