



Bulletin Board

Third gene linked to osteoarthritis discovered in genome-wide association scan

Uk researchers identify a new gene, *MCF2L*, thought to be involved in the development of osteoarthritis, providing a new focus for future research.

Researchers from the Wellcome Trust Sanger Institute (UK) have discovered a new gene associated with osteoarthritis, making it only the third gene to be identified for this common disease. The newly identified disease-associated variant forms part of the *MCF2L* gene and was identified using information from the 1000 Genomes Project to increase the power of the researchers genome-wide association scan. This initial study compared the genomes of 3177 individuals with osteoarthritis with 4894 people from the general population and evaluated a total of 600,000 variants.

By imputing the information from the 1000 Genomes Project, a total of 7.2 million variants were scanned in the new study and revealed the connection of *MCF2L* with osteoarthritis without needing any new sequencing to be carried out. "By using the 1000 Genomes Project information to add value to our original genome-wide association scan for osteoarthritis, we have uncovered a disease-associated gene that had previously remained hidden. We were able to analyze our results in greater detail and zoom in on variants that we hadn't been able to identify before. We hope that this approach and our findings will help to improve our biological understanding of this very painful disease," explained Eleftheria Zeggini, senior author of the study from the Sanger Institute.

To date, genes linked to osteoarthritis have remained illusive due to the complicated nature of the disease. Only two loci have been discovered so far in European populations: *GDF5* and a signal from a region on chromosome 7. *MCF2L* is located on chromosome 13 and is responsible for regulating a NGF. It has been reported that when patients with

osteoarthritis in the knee are treated with a humanized monoclonal antibody against NGF, they experience reduced pain and show improvement in their movement. These observations suggest a role of *MCF2L* in the development of osteoarthritis and it is hoped that this will provide a new focus for investigations in the future. "The discovery of this *MCF2L* variant suggests a possible genetic link to the finding that regulating NGF is important in knee osteoarthritis, and is supported by the fact that the variant is more strongly linked with knee osteoarthritis than hip osteoarthritis in the investigation. We hope the identification of this variant will lead to further insights into the biological processes at work and offer potential treatment targets," enthused Aaron Day-Williams, first author of the study from the Sanger Institute.

"Osteoarthritis is a complicated disease with many genetic causes. However, it has proved very difficult to discover the genes involved and help us to identify potential areas of treatment. We are delighted that investigators at the Sanger Institute have been able to identify a new gene connected with this painful condition and offer new lines of research for possible treatments. We are also excited that employing the technique of using the 1000 Genomes Project data to investigate genetic associations in far greater depth could reveal even greater insights into this debilitating disease," concluded Alan Silman, Medical Director of Arthritis Research UK.

Source: Day-Williams AG, Southam L, Panoutsopoulou K *et al.* A variant in *MCF2L* is associated with osteoarthritis. *Am. J. Hum. Genet.* doi: 10.1016/j.ajhg.2011.08.001 (2011) (Epub ahead of print).

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New study shows pegloticase helps treat patients with severe, chronic gout

In a report published in the 17 August issue of *JAMA*, researchers from the Duke University Medical Center (Durham, NC, USA) demonstrated that pegloticase was superior to placebo for lowering uric acid levels in two identical, placebo-controlled trials. Patients additionally experienced better levels of quality of life, physical function and less intense pain.

The two trials, named Trial C0405 and Trial C0406 enrolled a total of 109 and 106 patients, respectively. Patients were randomly assigned to receive either biweekly infusions of pegloticase (biweekly treatment), biweekly infusions with alternating pegloticase and placebo (monthly treatment) or biweekly placebo. The patients' uric acid levels were measured at 3 and 6 months, with the primary end point of the study defined as plasma uric acid levels of less than 6.0 mg/dl.

In the biweekly treatment group, the investigators found that 47 and 38% of patients met the two trials' primary outcome, compared with 20 and 49% of patients in the monthly treatment group. In addition, 40 and 21% of patients in the biweekly and

monthly treatment groups, respectively, also experienced a complete response for one or more tophus by the final follow-up visit, compared with 7% in the placebo group.

Pegloticase also demonstrated a good safety profile, with a significant reduction in tender joint count compared with placebo. Adverse events were common in the treatment groups, with one or more occurring in more than 90% of patients receiving active treatment. Serious adverse events were more common in the biweekly treatment groups and the monthly groups, compared with the placebo groups (24 and 23 vs 12%, respectively).

It should be noted that the investigators of the trial emphasized the importance of stabilizing cardiovascular (CV) comorbidities prior to initiating treatment, as a result of a relatively small number of serious CV adverse events that occurred during these studies. In total, there were two deaths attributed to CV adverse events in the biweekly treatment group, and one nonfatal myocardial infarction that occurred in a patient receiving monthly treatment. "Despite the fourfold greater number

of patients receiving pegloticase versus placebo, the elevated CV risk profile of this population and the absence of a compelling mechanism connecting pegloticase with CV AEs, the observed numerical imbalance in these events underlines the need for care in selecting patients for pegloticase treatment," explained the investigators of the study.

"These parallel, 6-month, placebo-controlled trials of pegloticase treatment have documented sustained UA reductions and significant clinical improvements in a substantial proportion of patients with chronic gout and refractoriness to, or intolerance of, conventional urate-lowering therapy. The significant disease-modifying benefits of pegloticase given every 2 weeks were demonstrable within 6 months, a time frame unique in randomized controlled trials of urate-lowering agents," concluded the investigators.

Source: Sundy J, Baraf H, Yood R *et al.* Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment – two randomized controlled trials. *JAMA* 306(7), 711–720 (2011).

New research indicates physical activity goals can be of benefit to the lives of rheumatoid arthritis patients

In a new study now available in *Arthritis Care and Research*, researchers from The Netherlands have demonstrated that patients with rheumatoid arthritis (RA) who have higher levels of self-efficacy for physical activity are more likely to achieve their physical activity goals. According to the study, the achievement of physical activity goals is associated with lower self-reported arthritis pain and increased health-related quality of life.

The study evaluated a total of 106 patients with RA and assessed physical activity, motivation and self-efficacy for

physical activity, level of arthritis pain and quality of life. Participants in the study were instructed to indicate the extent to which they achieved their baseline physical activity goal after 6 months.

Previous research had shown that self-efficacy, defined as one's belief in his or her's own capability to perform a specific behavior, is associated with physical activity participation among RA sufferers.

Results of the study demonstrated that 75% of participants rated their physical goal achievement at 50% or more. The

likelihood that patients would achieve their physical activity goals was also increased by higher levels of self-efficacy for physical activity. In addition, goal achievement had a direct positive effect upon quality of life outcomes.

Researchers found that patients who achieved their physical activity goal reported less arthritis pain and greater quality of life. No differences were found between men and women who completed the surveys, or between patients newly diagnosed versus those with RA for 10 years or more.

“Our results suggest that an increased focus on self-efficacy enhancement, realistic goal-setting, and techniques that increase the likelihood of goal achievement will assist clinicians and researchers

develop interventions that have a positive impact on pain reduction and quality of life outcomes for RA patients.” concluded Keegan Knittle, Leiden University and investigator of the study.

Source: Knittle K, De Gucht V, Hurkmans E *et al.* Self-efficacy and physical activity goal achievement predict arthritis pain and quality of life among patients with rheumatoid arthritis. *Arthritis Care Res.* doi: 10.1002/acr.20587 (2011) (Epub ahead of print).

Advanced MRI technique can detect early osteoarthritis

In a study published in the July issue of the *Journal of the American Academy of Orthopaedics*, researchers from NYU Lagone Medical Center’s Department of Orthopaedic surgery and radiology (NY, USA) have identified an advanced MRI technique that can be utilized to detect subtle changes in joint cartilage microstructure and provide physicians with a diagnostic tool for identifying key markers of early osteoarthritis. It is believed that the use of this new imaging technique during patient examinations will help clinicians to identify osteoarthritis earlier and lead to a shift in clinician management of the disease, from eventual joint reconstruction to long-term preservation.

“Imaging technology is now sensitive and powerful enough to enable detection of subtle changes in the intricate balance

of water, chondrocytes and the collagen fibers and protein molecules that make up our joint cartilage which we now know can point to future osteoarthritis,” explained Laith Jazrawi, Associate Professor of Orthopaedic Surgery and lead author of the paper. “With an active and aging baby boomer population beginning to experience joint pain associated with age, we think there is great potential for bringing these imaging techniques from the lab to the benefit of patients.”

“It is believed that the use of this new imaging technique during patient examinations will help clinicians to identify osteoarthritis earlier...”

The standard clinical practice is to use conventional MRI to assess the quality

of cartilage in patients with joint pain, or known arthritis, which focuses on the morphological integrity of the cartilage.

“The development and optimization of these innovative MR techniques has opened up a new window into the understanding and possible treatment of arthritis before irreversible structural and morphological changes has occurred,” enthused Michael P Recht, Louise Marx Professor of Radiology and Chairman of the Department of Radiology.

Sources: Jazrawi LM, Alaia MJ, Chang G *et al.* Advances in magnetic resonance imaging of articular cartilage. *J. Am. Acad. Orthop. Surg.* 19, 420–429 (2011); New York University Langone Medical Center. News release: <http://communications.med.nyu.edu/media-relations/news/nyu-langone-experts-find-mri-techniques-can-detect-early-osteoarthritis>

in brief...

Symptomatic effect of chondroitin sulfate 4&6 in hand osteoarthritis the finger osteoarthritis chondroitin treatment study (FACTS). Gabay C, Medinger-Sadowski C, Gascon D *et al.* *Arthritis Rheum.* doi: 10.1002/art.30574 (2011) (Epub ahead of print).

A new study suggests that chondroitin 4&6 sulfate (CS) may be effective for relieving the symptoms of hand osteoarthritis (OA). The single-center, placebo-controlled Finger osteoArthritis Chondroitin Treatment Study (FACTS) evaluated the symptomatic effect of highly purified CS in patients with OA. A total of 162 patients with radiographic hand OA who met predefined inclusion criteria were included in the trial. Patients in the CS group exhibited a significant decrease in global hand pain compared with the placebo group (8.7 decrease in Visual analog scale (VAS)) as well as significant improvement in hand function (two point decrease on the Functional Index for Hand OA (FIHOA)). CS also demonstrated a strong safety profile. Chondrosulf®, the chondroitin sulfate agent used in this study, is licensed as a drug in Europe whereas in the USA CS is sold as a supplement and often paired with glucosamine.

Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Mariette X, Matucci-Cerinic M, Pavelka K *et al.* *Ann. Rheum. Dis.* doi: 10.1136/ard.2010.149419 (2011) (Epub ahead of print).

Biological agents used for the treatment of rheumatoid arthritis may be associated with an increased risk of skin cancer according to recently published research. These findings are based on 21 studies and eight conference abstracts that met strict inclusion criteria of the systematic review. Information was provided for more than 40,000 patients and almost 150,000 cumulative years of exposure to these drugs. From a pooled risk of seven studies, the research demonstrated a negligible or no increased risk for the development of cancer. Furthermore, two of the studies indicated that there was no evidence that patients taking TNF inhibitors over the long term were at increased risk of cancer either. However, it was shown that in four of the studies, patients treated with these drugs were 45% more likely to develop skin cancer other than melanoma, with two studies indicating that patients taking TNF inhibitors were 79% more likely to develop a melanoma than patients not taking these drugs.

5-year study suggests that arthritis patients are at an increased risk of death due to cardiovascular events

A new study in over 400 people suggests an increased cardiovascular risk in patients with highly active rheumatoid arthritis

A recently published prospective study has produced data suggesting that highly active rheumatoid arthritis (RA) may increase the risk of new cardiovascular (CV) events. In their article published in *Arthritis Research & Therapy*, the authors of the study, from several hospitals across Sweden, highlight that many studies already examining CV event risk in RA patients are retrospective or cross-sectional, while their study examined both conventional and RA-related CV disease risk factors at RA onset and in the 5 years following the diagnosis of RA. The study also examined the potential of using these risk factors for predicting CV events, as well as the effect of RA treatment on the risk factors and CV events.

From December 1995, all patients receiving a new RA diagnosis in the four most northern counties in Sweden were recruited into the study, with information being gathered on CV morbidity. A total of 700 patients were recruited into the study, with 442 patients reaching 5-year follow-up.

At the 5-year evaluation point, 48 of the patients recruited had experienced a new CV event, with 12 proving fatal. Throughout the entire follow-up period of the study, 23 patients died. The list of risk factors that the researchers identified which increased the risk of CV events included a shorter period of treatment with

disease-modifying antirheumatic drugs and the use of COX-2 inhibitors.

The study's authors highlighted the advantages of their study of previous works investigating CV risk in RA. In the discussion of their article the authors noted the benefits of the study and its design, "First, the patient group comprises a large regional cohort and the prospective design involves few physicians at each rheumatology centre. In Sweden, essentially all patients with newly diagnosed RA are referred to a specialist. Thus, the results for the present cohort can be regarded to be general and, therefore, applicable to all patients with early RA. Furthermore, since only patients with very early disease were included, left censorship was avoided. Furthermore, repeated measurement of the parameters associated with inflammation made it possible to take variability in disease activity into account."

The authors concluded that the results of the study confirm the cardioprotective role of disease-modifying antirheumatic drugs and they stress the importance of reducing disease activity as well as the efficient treatment and prevention of CV risk factors in RA patients.

Source: Innala L, Möller B, Ljung L *et al.* Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: a five year prospective study. *Arthritis Res. Ther.* 13(4), R131 (2011).