In-depth scan of the human genome has resulted in the identification of two genes linked with a common rheumatological disease

Genetic breakthrough for ankylosing spondylitis

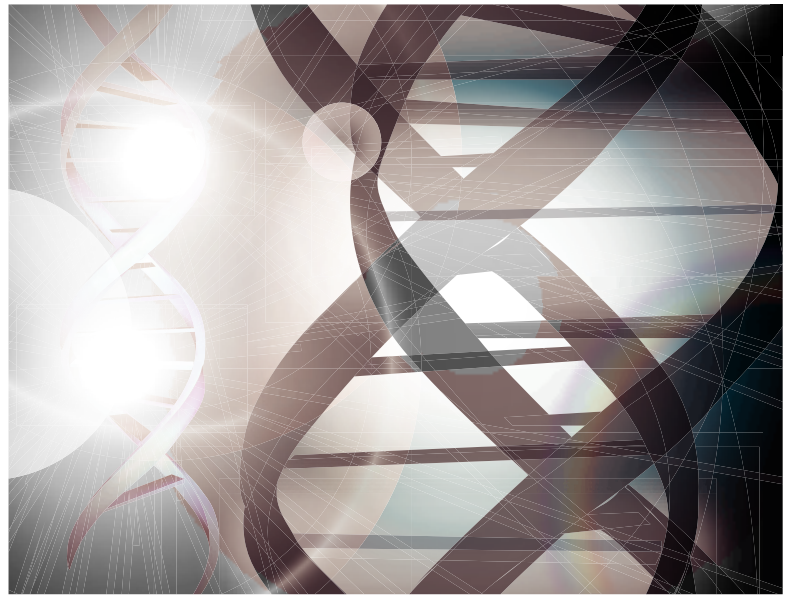
Ankylosing spondylitis (AS) is a chronic form of arthritis that attacks the spine, causing the vertebrae to fuse, resulting in loss of normal curvature, as well as affecting other joints and organs. New findings concerning the genetic basis of the disease could lead to novel therapies for the condition, which is thought to affect around one in 200 men and one in 500 women, usually developing during adolescence and young adulthood.

The discovery of the genes, *ARTS1* and *IL23R*, represent a considerable advance in our knowledge of the genetic basis of AS; until now only one gene (*HLA-B27*) has been known to be influential in the condition. Professor John Reveille, Director of Rheumatology and Clinical Immunogenetics at the University of Texas Medical School (TX, USA) and one of the lead researchers on the project, explains. "Now we have found two new genes. Together with *HLA-B27*, these genes account for roughly 70% of the overall cause. This means we've almost nailed this disease."

The discovery of both genes is the result of a comprehensive scan of the human genome, using a method known as genome-wide association scanning, to compare the DNA of thousands of sufferers with healthy controls to find what genetic differences there are between the two groups. Reveille is convinced that further discoveries concerning the genetics that underlie AS are soon to be made; "Within the next year, I predict we will have identified all the genes that play a role in this insidious disease. There is more exciting news to come."

Scientists believe that AS is triggered in susceptible individuals by common gut bacteria, although the exact mechanism behind this is unclear at present.

"This looks very promising as a potential treatment for ankylosing spondylitis."



The researchers hope to next study the genes' functions in model organisms in order to elucidate the precise pathogenetic mechanisms that lead to AS, with a view to improving diagnostics and drug discovery.

IL23R has previously been linked to Crohn's disease (an inflammatory bowel disease) and psoriasis (a skin disease). The implication of the gene in AS goes some way to accounting for the frequent, and hitherto unexplained, co-occurance of these conditions. Furthermore, this suggests that drugs used to treat Crohn's disease and psoriasis may be useful in treating AS, and *vice-versa.*

Professor Matthew Brown of the Wellcome Trust Centre for Human Genetics at the University of Oxford, who worked on the project, reveals, "A treatment for Crohn's disease that inhibits the activity of this gene is already undergoing human trials. This looks very promising as a potential treatment for ankylosing spondylitis."

The discovery comes during a remarkable period of productivity for the Wellcome Trust Case Control Consortium. The group has discovered more genes linked to common diseases in the last year than have been made in the entire history of the field. This study in particular also identified two genes linked to Grave's disease, an autoimmune condition that affects the thyroid gland, as well as genetic contributions to breast cancer and multiple sclerosis. However, the most significant discoveries are those linked to AS.

The work, a result of collaboration between the Australo–Anglo–American Spondylitis Consortium and the Wellcome Trust Case Control Consortium, can be read in full in the online, October 21st issue, of *Nature Genetics*.

Source: Wellcome Trust Case Control Consortium. Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. *Nature Genetics*, (2007) (Epub ahead of print).

Priority Paper Alerts

The cost–effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis.

Vergel YB, Hawkins NS, Claxton K *et al.*: *Rheumatology* 46(11), 1729–1735 (2007).

A probabilistic decision analytic model was constructed that analyzes the cost–effectiveness of two TNF antagonists (etanercept and infliximab) and palliative care. The success of each treatment was judged using quality-adjusted life years (QALYs) derived from the Health Assessment Questionnaire. The model was extrapolated beyond the trial period to a 10-year and lifetime horizon using the available evidence and expert-opinion-based assumptions. At a 10-year time horizon the incremental cost–effectiveness ratio was found to be between £26,361 and £30,628 per QALY for etanercept compared with palliative care, and between £165,363 and £205,345 for infliximab compared with etanercept. Only the results for etanercept fall within cost-effectiveness estimates for the UK National Health Service, as defined by the National Institute for Health and Clinical Excellence. This is due to the higher acquisition and administration costs of infliximab, despite little superior effectiveness compared with etanercept. Further research into short-term effectiveness, utility parameters and the assumptions of the model is called for.

EULAR evidence based recommendations for the management of fibromyalgia syndrome.

Carville SF, Arendt-Nielsen S, Bliddal H *et al.*: *Ann. Rheum. Dis.* DOI: 10.1136/ard.2007.071522 (2007).

A systematic review of clinical trials of treatments for fibromylagia syndrome (FMS) was conducted in order to determine a consensus set of evidence-based guidelines for treatment. A multidisciplinary group was formed to appraise the trials using predesignated criteria for search stategy, participants, outcome measures and methods of data collection and analysis. A literature review was conducted using the keywords 'fibromyalgia', 'treatment or management' and 'trial'. Studies that did not use ACR classification, were not clinical trials, or included patients with chronic fatigue syndrome or myalgic encephalomyelitis were not included. Outcome was assessed by changes in pain assessed by visual analogue scale, and fibromyalgia impact questionnaire. Only high-quality studies were used, after being judged randomly, blinded and having allocation concealed. This gave 98 eligible studies, although in many the sample size was small and the quality of the study was insufficient for strong recommendations to be made. Treatment options were categorized as antidepressents, analgesics, 'other pharmogalogical', exercise, cognitive behavioral therapy, education, dietary interventions and 'other nonpharmocalogical' treatments. Finally a consensus of nine recommendations emerged for the management of FMS.

Reduced response to painkillers in fibromyalgia sufferers explained

New findings by researchers from the University of Michigan Health System (MI, USA) helps to explain why some fibromyalgia sufferers respond poorly to pain relief medication.

Fibromyalgia is characterized by specific or diffuse pain in the muscles, joints and bones, fatigue and a wide range of other symptoms. Sufferers often claim that opioid painkillers aimed at relieving pain, such as morphine and codeine, have little effect.

Research published recently in *The Journal of Neuroscience* appears to explain this anecdotal observation. It has been found that the receptors in the brain that bind opioid painkillers have reduced binding activity in fibromyalgia patients, resulting in reduced effectiveness of pain relief medication.

> "The finding is significant because it has been difficult to determine the cause of pain in patients with fibromyalgia"

Positron emission tomography (PET) scans of the brains of fibromyalgia sufferers reveal that the μ-opioid receptors (which are targeted by opioid painkillers) of patients have a reduced availability when compared with those of healthy individuals. This reduced binding activity was found to be localized mainly in the nucleus accumbens, the anterior cingulate and the amygdala, all of which are involved in processing and dampening pain signals. Because the painkillers cannot bind the receptors they are unable to effectively alleviate the patient's pain.

The findings have important implications in the diagnosis and treatment of the condition, as explained by Dr Richard Harris, researcher in the Division of Rheumatology within the Department of Internal Medicine, and lead author of the paper. "The finding is significant because it has been difficult to determine the cause of pain in patients with fibromyalgia, to the point that acceptance of the condition by medical practitioners has been slow."

The PET scans also revealed a link to depression. It was shown that fibromyalgia patients with more depressive symptoms were especially deficient in μ-opioid receptors in the amygdala, a region of the brain thought to modulate mood and the emotional dimension of pain.

Source: Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK. Decreased central mu-opioid receptor availability in fibromyalgia. *J. Neurosci.* 27(37), 10,000–10,006 (2007).

Potential new treatment for systemic lupus erythematosus

Researchers in Indiana, USA, have developed a new technique that may offer a way to treat the autoimmune disease systemic lupus erythematosus (SLE). Current treatment relies on high doses of steroids and other medication that often have serious side-effects, making the development of a safe alternative an important breakthrough in the field.

SLE is an autoimmune disease in which the body's immune system attacks healthy cells, leading to damage of muscles, joints, kidneys and other organs. Using a treatment known as folate-hapten-targeted immunotherapy Dr Philip Low and colleagues of Purdue Univeristy (IN, USA) were able to target abnormal immune cells for destruction while leaving healthy cells alone.

This approach resulted in a large reduction in damage to kidneys and other tissues, as well as a 10-month extended lifespan in treated mice when compared with untreated mice.

The report, published in the September/October issue of ACS *Molecular Pharmaceutics*, concludes that: "this therapy warrants further evaluation as a possible approach for treatment of SLE in humans."

Source: Varghese B, Haase N, Low PS: Depletion of folate-receptor-positive macrophages leads to alleviation of symptoms and prolonged survival in two murine models of systemic lupus erythematosus. *Mol. Pharm.* 4(5), 679–685 (2007).

Gold-standard arthritis therapy

Scientists at the Duke University Medical Center (NC, USA) have uncovered the mechanism by which gold salts, traditionally used to treat inflammation, reduce swelling, raising the possibility of new gold-based treatments. David Pisetsky, chief of the division of rheumatology and immunology at Duke and co-author of the paper, explains, "Scientists have never really understood why gold works. Now that we have a better handle on its action, we may be able to use that mechanism to create new and better gold-like drugs to treat arthritis."

Gold has been used as a remedy for joint pain since the early 1900s; however, the treatment has a number of side effects including rashes, mouth sores, kidney damage and, occasionally, interruption of the production of new blood cells. As a result, gold salts have fallen out of favor as treatment options, replaced instead by treatments such as methotrexate and biologically engineered drugs. But recent research may lead to new, gold-based pharmaceuticals.

'…the discovery concerning HMBG1 is of special importance in arthritic disease…'

Pisetsky and colleagues from the University of Pittsburgh (PA, USA) and the Karolinska Institute, Sweden, have uncovered the molecular basis of gold's effect. It appears that gold salts block the release of HMGB1 from the nucleus. HMGB1 plays an important role in transcription inside the cell. When released, however, it stimulates the immune system and causes inflammation. Pisetsky explains that the discovery concerning HMBG1 is of special importance in arthritic disease as "there is an unusually high amount of it in the synovial tissue and fluid around the joints – where arthritis occurs."

By interfering with interferon-b and nitric oxide, molecules which aid the release of HGMB1 from the cell, gold salts are able to reduce the amount of extracellular HGMB1.

It is hoped that this discovery will lead to new arthritis therapies, although further studies are required to confirm that the same mechanism is active *in vivo* and not just under laboratory conditions.

Source: www.dukehealth.org/HealthLibrary/News/10159?from=RSS

Potential new mechanism for synovial inflammation in degenerative arthritis

Researchers from the University of Leeds and Cardiff University have uncovered what may be a novel source of inflammation in sufferers of osteoarthritis (OA).

Synovitis has been shown to occur in early OA patients, when the articular cartilage appears to remain intact. This anomaly, along with recent findings that implicate the enthesis in spinal joint inflammation, prompted Professors Michael Benjamin, of Cardiff University (UK), and Dennis McGonagle, of the University of Leeds (UK), to turn their attention to the enthesis, the site of attachment of the ligament or tendon to the bone, as a possible source of inflammation.

They specifically focused on what they call the 'synovial–entheseal complex' (SEC), a functional unit comprising the enthesis and adjacent synovium. The authors hypothesized that fibrocartilage may draw nourishment from the synovium, meaning that if the enthesis is damaged then the fibrocartilage may break down, aggravating the associated synovium, thereby causing inflammation.

Testing this hypothesis, 49 entheses were taken from cadavers and preserved for examination. Many SECs were located close to the articular cartilage, however were also found at 47% of locations examined away from the articular cartilage. At many attachment sites, changes in the entheses mirrored those typically found in articular cartilage. "Such changes at certain entheses could be directly relevant to older subjects with joint symptoms due to degenerative disease and some of the symptoms could be emanating from the SEC," McGonagle concluded.

Source: Benjamin M, McGonagle D: Histopathologic changes at synovio-entheseal complexes suggesting a novel mechanism for synovitis in osteoarthritis and spondylarthritis. *Arthritis & Rheumatism* DOI: 10.1002/art.23078 (2007) (Epub ahead of print).