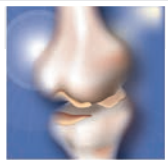
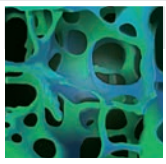




Bulletin Board

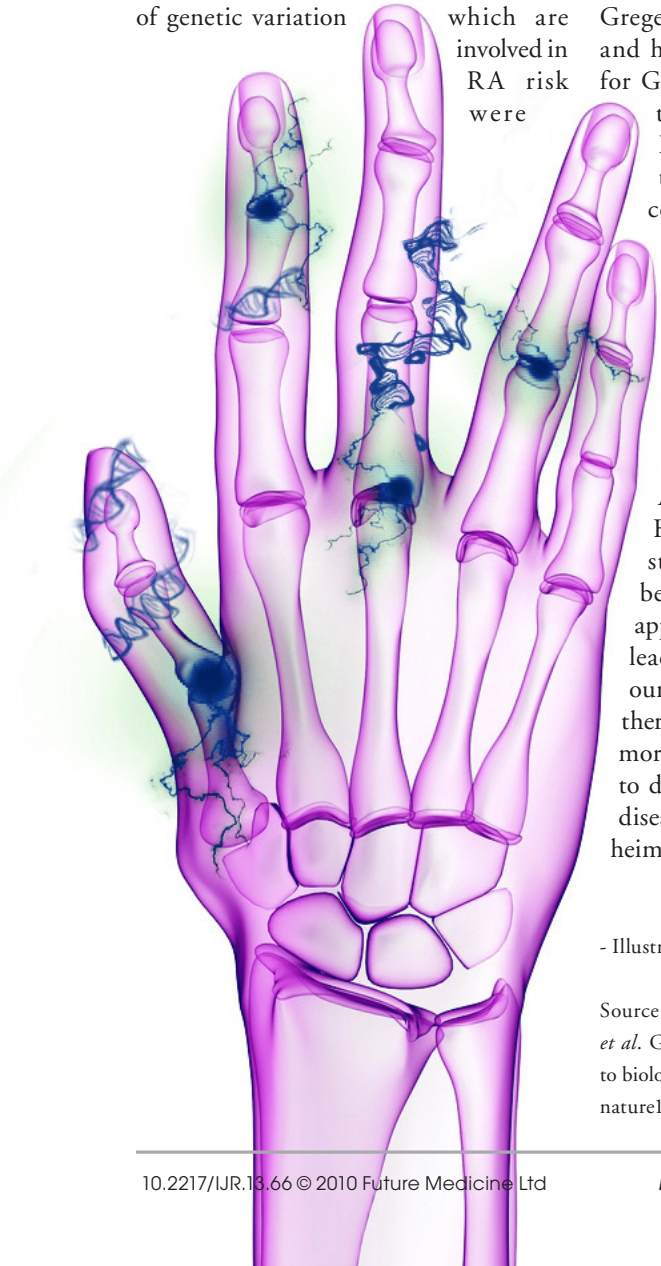
Genetic basis of rheumatoid arthritis further defined

The discovery of new genes, pathways and cell types that are linked with inheriting a susceptibility to develop rheumatoid arthritis (RA) has been made by an international group of researchers. The results are published in *Nature*.

A genome-wide association study meta-analysis of over 100,000 people of European and Asian descent was performed by scientists. A total of 42 new sites of genetic variation which are involved in RA risk were identified. The analysis, which brings the number of confirmed risk variants for RA to over 100 genetic loci, locates genes, DNA sequences or positions on chromosomes. These findings could lead to the development of new treatments.

"This study is the culmination of over a decade of work by an extraordinary group of collaborative scientists from around the world," said Peter K Gregersen, a collaborator on the study, and head of the Robert S Boas Center for Genomics and Human Genetics at the Feinstein Institute for Medical Research (NY, USA). "It provides us with a definitive list of the major common genetic variation involved in this disease, and points the way forward to develop new diagnostic and therapeutic approaches to this illness."

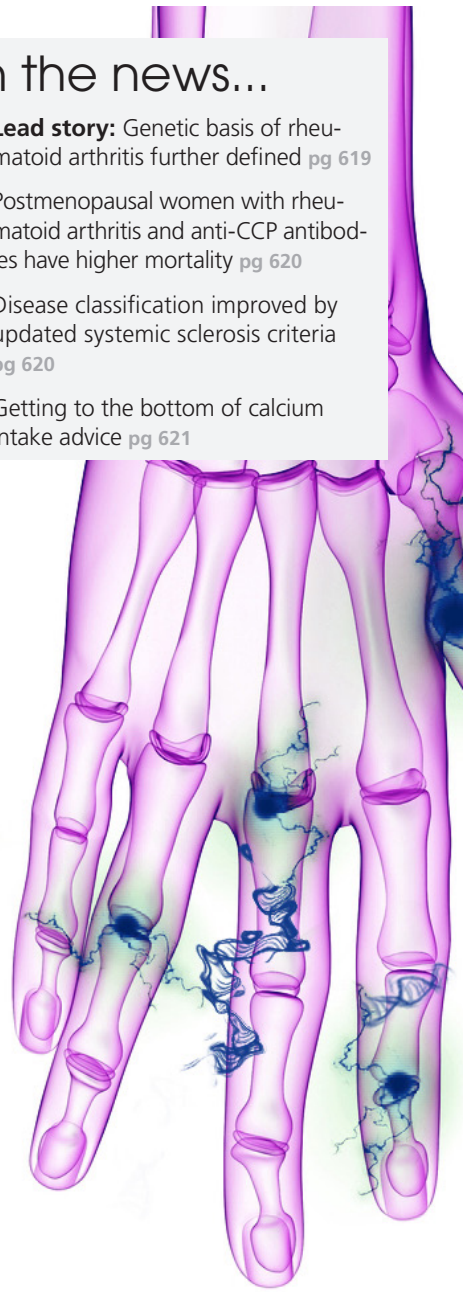
The lead investigator of the study, Robert Plenge, director of Genetics and Genomics, Division of Rheumatology, Immunology and Allergy at Brigham and Women's Hospital (MA, USA) added, "Our study provides a compelling link between human genetics in RA and approved therapies to treat RA. This leads to an intriguing question: can our new genetic discoveries lead to new therapies to treat or cure RA? Furthermore, can a similar approach be used to develop therapies for other complex diseases such as lupus, diabetes and Alzheimer's disease?"



- Illustrated by Hannah Morton

Source: Yukinori Okada, Di Wu, Gosia Trynka *et al*. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature* doi:10.1038/nature12873 (2013) (Epub ahead of print).

in the news...



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Future Medicine part of fsg

Postmenopausal women with rheumatoid arthritis and anti-CCP antibodies have higher mortality

Mortality rates have been found to be two-times higher in postmenopausal women with rheumatoid arthritis (RA) and anti-cyclic citrullinated peptide (CCP) antibodies by a new study. Higher mortality rates were seen to persist after adjusting for age, positive rheumatoid factor, positive antinuclear antibodies and disease modifying antirheumatic drug (DMARD) use. The findings are published in *Arthritis and Rheumatism*.

In the USA, RA affects 11.3 million adults and 75% of these are women, according to the ACR. Mortality rates were reported to be 1.5-fold higher in RA patients than healthy controls by previous studies. It is suggested by medical evidence that this excess mortality is mainly caused by cardiovascular disease and this is seen to be greater in groups with existing RA rather than those who are newly diagnosed. It has been indicated by observational data, however, that methotrexate may reduce cardiovascular disease and mortality.

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In the present study, lead by Lewis Kuller and Larry Moreland (University of Pittsburgh, PA, USA), close to 10,000 women with self-reported RA were assessed for anti-CCP, rheumatoid factor and ANA levels. The mean age of participants was 64 years and 65% were white, 25% black and 10% Hispanic.

The findings indicated that anti-CCP was prevalent in 8.1% of the group; 58% reported DMARD use during follow-up. Of the remaining 9179 women with self-reported RA but negative anti-CCP, only 7.3% were using DMARDs. Over the course of the 10-year study period, 13% of the women died: 14% who self-reported RA at the start of the study and follow-up; 16% who reported RA at baseline; and 11% who reported RA at follow-up.

The main causes of death in women with RA were found by further analysis to be cardiovascular disease, including coronary heart disease and stroke, and cancer. Being positive for anti-CCP conveyed a substantially higher mortality risk that was independent of DMARD use, including methotrexate, and modifiable risk factors (obesity and smoking) associated with mortality.

"Our study is the first large longitudinal study to evaluate anti-CCP, RF, risk factors and mortality," said Dr Kuller. "Further investigation to determine specific causes of excess mortality, particularly among RA patients with positive anti-CCP, are needed."

Source: Kuller LH, Mackey RH, Walitt BT *et al*. Determinants of mortality among postmenopausal women who report rheumatoid arthritis in the Women's Health Initiative. *Arthritis Rheum*. doi:10.1002/art.38268 (2013) (Epub ahead of print).

Dramatic reduction in joint inflammation promised by new compound

An experimental compound that significantly reduces joint inflammation in animal models of rheumatoid arthritis has been synthesized and developed by scientists from The Scripps Research Institute (CA, USA).

The compound, known as SR2211, was found to block the symptoms of virtually all symptoms of rheumatoid arthritis in mice within the first 8–10 days of treatment. Compared with animals that did not receive treatment, the mice also showed significantly reduced bone and cartilage erosion.

A key regulator of TH17 cells, the nuclear receptor RORγ, is targeted by the compound. TH17 cells have been implicated in numerous autoimmune diseases,

including multiple sclerosis, rheumatoid arthritis, inflammatory disease and lupus, since their discovery a decade ago.

"This compound, and its precursors, showed the ability to block the release of specific inflammatory mediators from Th17 cells in culture, so we were confident that SR2211 would demonstrate good efficacy in rodent models of autoimmune disease," said biochemist Patrick R Griffin, chair of the The Scripps Research Institute Department of Molecular Therapeutics. "Our newest study strongly supports the idea that by targeting the RORγ receptor, we can therapeutically repress inflammation and joint destruction associated with rheumatoid arthritis."

It was noted by Griffin that while several treatments are currently available for rheumatoid arthritis, their use is associated with increased risk of infections and pneumonia. A disadvantage of managing opportunistic infections is presented by the fact that these therapies have to be taken by injection meaning they are optimized for long, sustained immunosuppressive action. By contrast, in the case of a potentially life-threatening infection, an oral medication could be taken daily and stopped immediately allowing the drug to leave the body to prevent further complications.

"This study with SR2211 shows that repressing the activity of the RORγ receptor alone works to reduce joint erosion and inflammation," Griffin said. "It's an alternative mechanism of action that can provide doctors with additional treatment options for patients who do not respond well or cannot tolerate current therapies."

"We wanted to develop a compound with the potential to help treat patients suffering from a range of autoimmune diseases, including rheumatoid arthritis," said Staff Scientist Mi Ra Chang, the first author of the study and a member of the Griffin lab. "Compounds such as SR2211 work directly and specifically on at least two immune cell types directly involved in the pathogenesis of autoimmune disease."

Source: Chang MR, Lyda B, Kamenecka TM, Griffin PR. Pharmacological repression of RORγ is therapeutic in the collagen-induced arthritis experimental model. *Arthritis Rheum.* doi:10.1002/art.38272 (2013) (Epub ahead of print).

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Childhood pain, adult chronic pain and fibromyalgia linked

Although few studies have evaluated the characteristics of pain persisting from childhood through to adulthood, there is strong evidence that children who have chronic pain also experience chronic pain as adults. One in six adult pain patients were found by researchers at the University of Michigan (MI, USA) to have had pain as children or adolescents. This pain was widespread and neuropathic with psychological comorbidities and decreased function.

More than 1000 patients who were 18 years or older were included in the study and asked about pain, family history, physical and psychological limitations and treatment history, as well as about childhood pain. Adult patients who reported having pain in childhood, it is hypothesized by the authors, are more likely to experience pain that is neuropathic in nature, and which is of greater severity and meets criteria for a fibromyalgia diagnosis.

A history for chronic pain was found in one in six new adult patients, predominantly young females. In contrast with subjects who denied having childhood pain, the pain of these individuals was found to be more widespread and neuropathic, most likely fibromyalgia. Higher levels of anxiety and worse functional status were also seen in patients who suffered childhood pain.

Source: Links of childhood pain to adult chronic pain, fibromyalgia: www.sciencedaily.com/releases/2013/12/131219162532.htm

– All stories written by Sarah Jones

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology. If you have newsworthy information, please contact: Sarah Jones, Commissioning Editor, *International Journal of Clinical Rheumatology*, Future Medicine Ltd, s.jones@futuremedicine.com