Scientists have determined the presence of three genes that may be associated with the development of rheumatoid arthritis. The study, performed on sets of twins, also demonstrates that these genes occur randomly and may appear in one sibling, but not in the other.

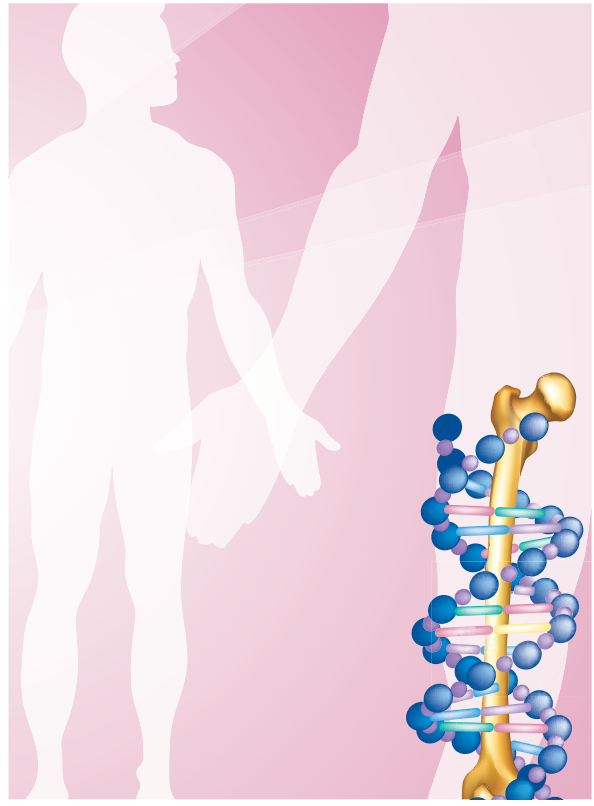
Genes linked to rheumatoid arthritis discovered from twin study

Results generated from a new study carried out on (human) twin subjects suggest that although the development of rheumatoid arthritis (RA) may be linked to the presence of three specific genes, their occurrence in siblings is random.

"Our findings provide the first evidence that laeverin is abundantly expressed in synovial tissue."

B-lymphocytes have, in previous studies, been heavily associated with the progression of RA. Using this information, a team of researchers led by Joseph Holoshitz, University of Michigan in Ann Arbor, MI, USA, carried out genetic microarray analyses on lymphoblastoid B cell lines (LCLs) on 11 pairs of twins, with one twin suffering from RA and one without the affliction. Microarray analysis allows the expression of thousands of genes to be observed at once. Complementary DNA from the cells of each subject were labelled with fluorescent dye to separate and distinguish those from RA subjects with non-RA individuals. After hybridization, immunohistochemistry and real-time polymerase chain reaction were completed, the scientists established the expression of the most significantly over-expressed genes in synovial tissues. Their results are published in the July issue of the journal, *Arthritis & Rheumatism*.

Differences were observed between the sets of twins analyzed. In particular, three genes were found to be notably over-expressed in the cells of RA patients and not in their siblings. The gene *FLJ90650* encodes the enzyme laeverin and was found to have the highest level of expression. *HSD11B2* – a steroid pathway enzyme linked to inflammation and bone erosion – and *CYR61* – which has a key role in the formation of new blood vessels and in inflammatory conditions – were found to be the second and third most over-expressed genes, respectively.



The authors explain the significance of the study and their subsequent results; "We report herein a novel approach for identification or potential disease-relevant genes in RA, using LCLs from disease-discordant MZ twins. The representation of many established pannus-associated genes in this analysis suggests that this approach could provide mechanistic insights into the pathogenesis of RA and could help identify novel candidate targets for therapeutic intervention."

"The occurrence of the disease among genetically susceptible individuals seems to be random."

Holoshitz goes on to describe the consequences of identifying the three genes linked to RA; "Our findings provide the first evidence that laeverin is abundantly expressed in synovial tissue. *11ß-HSD2* and *Cyr61* have not previously been directly implicated in RA."

Despite the identification of these genes in RA and the prior suggestion of inherited susceptibility of the condition, the results also clearly show discord of the disease between the tested siblings. "The occurrence of the disease among genetically susceptible individuals seems to be random, as evidenced by the high disease discordance rate among monozygotic twins," the researchers explain.

The team hope that, as well as using their results, further genetic analysis will provide more insight into RA, and may even be used to establish individuals that would benefit the most from related therapies.

Priority Paper Alerts

Anti-tumor necrosis factor-alpha-induced psoriasis.

Sari I, Akar S, Birlik M, Sis B, Onen F, Akkoc N. *J. Rheumatol*. 33(7), 1411–1414 (2006).

The authors of this study present a patient who developed psoriasis after treatment with etanercept, a drug commonly used to treat rheumatoid arthritis. Discontinuation of the drug resulted in the psoriatic lesions healing, yet they began to appear again after treatment restarted. The researchers found that changing the medication to infliximab resulted in no such skin reactions occurring. A Medline search found several studies concerning 32 patients that had demonstrated similar symptoms after being treated with tumor necrosis factor inhibitors.

Inflammatory suppression rapidly attenuates microvascular dysfunction in rheumatoid arthritis.

Datta D, Ferrell WR, Sturrock RD, Jadhav ST, Sattar N. *Atherosclerosis* Epub ahead of print (2006).

The inflammatory part of rheumatoid arthritis (RA) is associated with an increased risk of cardiovascular morbidity and mortality, and endothelial dysfunction – linked to atherosclerosis – has been found in larger vessels of RA. The authors examined whether skin microvascular function was inhibited in eight patients with RA and their reaction to anti-inflammatory treatment using laser Doppler imaging with iontophoresis of the vasodilators acetylcholine (ACh, endothelium dependent) and sodium nitroprusside (SNP, endothelium independent). When compared with a control group, patients with RA were found to have a notable decrease in vascular function.

Dietary caffeine intake does not affect methotrexate efficacy in patients with rheumatoid arthritis.

Benito-Garcia E, Heller JE, Chibnik LB *et al*.: *Rheumatol*. 33(7), 1275–1281 (2006).

This investigation aimed to determine whether patients with rheumatoid arthritis (RA) and taking methotrexate (MTX) responded poorly when on a high caffeine diet compared with those on a lower diet. Subjects taking MTX were defined as either being low, moderate or high caffeine consumers. It was found that in three multivariate models, no significant difference in the efficiency of MTX activity between the patients with high and low caffeine intakes was seen. Moreover, the consumption of varying amounts of caffeine did not affect the long-term activity of MTX in patients taking high doses of this drug.

Chilli peppers take the heat away from arthritic pain

An unorthodox new treatment may soon be used to arthritic inflammation and its painful symptoms – chilli peppers.

A research team led by Susan Brain, Kings College, London, UK, have been studying how capsaicin – which gives chilli peppers their distinctive heat – can be used to treat inflammation seen in arthritis.

The scientists found that capsaicin triggered the activation of TRPV1, a mechanism found on pain sensitive nerves that is believed to be involved in arthritic conditions. However, as Brain describes, "Little is known of mechanisms that link the inflammatory and pain sensitive components." As a result of this lack of information, Brain explains the aims of the study performed by her team; "The project is designed to learn more precisely how capsaicin works to combat the effects if one of the best-known inflammatory substances, TNF-alpha, and in turn work towards the possibility that agents without the burning side effects of chilli peppers may be useful in the treatment of arthritis."

Capsaicin is already used in creams to treat aches and pains, and drug companies have already shown an interest in the findings observed by Brain and colleagues. Similarly, the Arthritis Research Campaign, UK has been quick to praise the results of the study; "We welcome any new initiatives to help reduce the pain of arthritis, as existing drugs are far from perfect, and the only effective alternative for severe osteoarthritis is joint replacement."

The researchers hope that their findings will allow the development of new and efficacious anti-inflammatory drugs that do not have the side effects associated with current drug therapies.

Transitional care hope for juvenile idiopathic arthritis

Scientists from the University of Birmingham, UK, have demonstrated the benefits of using a structured program of transitional care (PTC) for teenagers suffering from juvenile idiopathic arthritis (JIA).

The team, led by Janet McDonagh, studied 308 teenagers with JIA and 303 parents to examine the affects of using PTC. Different stages of adolescent development was observed by selecting patients who were 11 (n = 103), 14 (n = 128), or 17 (n = 77) years of age. The findings are published in the journal *Rheumatology*.

The PTC for each patient was comprised of age and developmentally appropriate informational resources for the teenagers and the use of a transition plan for each individual, aimed to reflect the different stages of adolescence. The team found that adolescent and parent-proxy ratings of health-related quality of life were notably improved compared with baseline values measured by scores given on the Juvenile Arthritis Quality of Life Questionnaire. The awareness of the condition and the satisfaction felt over treatment also significantly improved in both patient and parent groups.

The team also found that starting PTC early in adolescents may be beneficial, as the subjects aged 11 or 14 years appeared to benefit more from the program compared with those aged 17 years.

The team expect these results to have an advantageous impact on the treatment of sufferers of JIA and their families.

Fetal DNA levels during pregnancy affects rheumatoid arthritis symptoms

It is often observed in women with rheumatoid arthritis (RA) that during pregnancy, their condition improves or they may even undergo remission. Now, scientists from the Fred Hutchinson Cancer Research Center in Seattle, WA, USA, have begun to identify why this is the case.

> "If the changes reflect immune modulation, further studies could generate new therapeutic strategies for RA."

Zhen Yan and colleagues measured the levels of fetal DNA in 25 pregnant women aged between 23 and 43 years and who had RA. In total, 17 women were classified as having adult-onset RA and 6 women had juvenile idiopathic arthritis (JIA). Peripheral venous blood was taken at least three times during pregnancy and within 3 months after birth. The subjects did not take any medication that would alter or modify their disease. Cell-free fetal DNA was calculated using real-time quantitative polymerase chain reaction, which targeted genetic markers that were specific to the fetus. All the pregnancies resulted in one single live birth.

In total, 21 women (79% of adult-onset and 100% of JIA sufferers) experienced an improvement in their condition. Of these subjects, 62% demonstrated an improvement in their first trimester and maintained this observation throughout their gestation period. The levels of serum fetal DNA ranged from 24 gE/ml in the first trimester, to 199 gE/ml in the third trimester. It was also observed that as the serum fetal levels doubled, the improvement in the disease also increased by 1.2-fold. However, by the third or fourth month after birth, 90% of the subjects saw their disease recur and was associated with a drop in serum fetal DNA to low or undetectable levels. In four of the test subjects, very little or no increase in fetal DNA was observed. Correlating with the results previously seen, these women did not experience any improvement in their disease.

The team said of their findings; "The serum fetal DNA concentration increased throughout gestation and was effectively cleared after delivery, with an inverse correlation observed between changes in fetal DNA levels and arthritis activity."

However, they also describe that there are limitations to their study and explain that further investigations are required; "Whether the dynamic changes in fetal DNA reflect the potential for immune modulation of maternal arthritis, are a result of disease activity changes, or are not causally related cannot be determined from these studies. If the changes reflect immune modulation, further studies could generate new therapeutic strategies for RA."

New methods assess damage in Sjögren's syndrome

Delegates at the Annual European Congress of Rheumatology (EULAR) have heard how newly developed systems can measure the extent of disease damage and activity observed in sufferers of Sjögren's syndrome (SjS). The collaborative study was presented by Claudio Vitali, Villamara Hospital, Piombino, Italy, on behalf of the Study Group for SjS of the Italian Society of Rheumatology, and may resolve the problems seen because of the lack of criteria available for SjS.

SjS is an autoimmune disease that causes dry eyes and mouth. Is affects predominantly women and, in a secondary form, is often associated with rheumatic diseases. This study analyzed 206 patients with the primary form of SjS from 12 different Italian centers. Using the results generated, the scientists aimed to identify possible systems that would allow the international and uniform analysis of SjS.

The study included mainly women (97.6%) who were aged between 19-85 years and had a mean duration of disease of 8.9 years. At the start of the study, the clinical and serological data and variables of the subjects were recorded and divided into 16 sections. Both uni- and multivariate analyses were used to select these variables and to generate the SjS disease assessment score (SjSDAM). The classification of these sections was noted in a glossary and standard forms were used to assess and measure the damage caused by SjS, the results of which were processed into a database for further examination. After 3 months, 121 patients were deemed to have active SjS. As a result, the reversible clinical and serological variables were measured for change in disease from the start of the study.

The SjS disease damage index (SjSDDI) was created by using an observer judgement given after each clinical observation. To create both the SjSDDI and SjSDAM scoring systems, variables were weighted depending on their beta correlation coefficient and these weights and their selected variables were used to build up the scoring system. The scores generated correlated with the observer judgements and their scores for SjSDDI and SjSDAM.

Vitali recognizes the need for debate over the use of this system to measure disease damage and assessment of SJS internationally, and hopes the use of larger patient numbers in multicenter studies will fuel these discussions.