Breakthrough developments in rheumatoid arthritis reported

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Peter K. Gregersen, MD, stares at x-rays of hands, searching out the telltale signs of inflamed joints and wrists from his research subjects with rheumatoid arthritis. With these clinical features at his side, he turns to the basic building blocks of life – the human genome – to figure out what makes these people susceptible to the disabling inflammatory condition.

Dr. Gregersen has finally closed the circle between key genes identified in his laboratory at the Robert S. Boas Center for Genomics and Human Genetics at The Feinstein Institute for Medical Research in Manhasset, NY and more than a 1,000 patients with rheumatoid arthritis. The genes will help tell the story of how the immune system works to create specific antibodies that in turn increase a person's risk for this crippling disease.

On Monday at the Federation of Clinical Immunology Services' (FOCIS) meetings in San Diego, CA, Dr. Gregersen and his colleagues will be presenting the lab's latest genetic findings. The group conducted genome-wide scans to identify polymorphisms, or genetic variants, that are associated with the inflammatory condition and can be used to understand the triggers of the disease. This will provide key insights into the pathways underlying rheumatoid arthritis and other autoimmune diseases. It may ultimately provide tests to predict who will respond to the available new treatments. Franak Batliwalla, PhD, also of The Feinstein Institute, will be presenting related studies on biomarkers and genetic influences on drug response at the same meeting.

Identifying Immune System Mediators

About one percent of the US population will develop rheumatoid arthritis, an autoimmune disease that leads to painful joint swelling. Scientists are cracking the genetic code that makes the immune system wage an attack on a person's joints. Over the last decade, Dr. Gregersen and his colleagues have been amassing a genetic database complete with siblings with rheumatoid arthritis (and some family members without it) in an attempt to single out those genes that are involved in the autoimmune process. In fact, in 2004, they identified a gene called PTPN2 that confers a two-fold risk for rheumatoid arthritis and a number of other autoimmune diseases. The Feinstein now holds the largest collection from rheumatoid arthritis patients in the world.

Following the cellular pathway, it has been shown that PTPN22 influences the "trigger point" for activation of T-cells, immune cells that are normally called on to wage battle against infection. In autoimmune diseases like rheumatoid arthritis, PTPN22 appears to put people at higher risk of a wayward T-cell response.

The group has since gone on to use modern genetic methods to search for single nucleotide polymorphisms, or SNPs, to identify players that have fallen under the radar of older methods. The group has discovered another signaling molecule that seems to increase a person's risk for rheumatoid arthritis by 30 percent. (The paper reporting the gene is in press.)

In collaborations with other scientists worldwide, Dr. Gregersen has also been able to show that certain markers are strongly linked to certain ethnic groups and others are not. "This will help us in figuring out what exactly is going on in this illness," he said. "It's pretty exciting."

Early on in the rheumatoid arthritis research game, when HLA popped out as a major genetic player in the condition in the 1980s, Dr. Gregersen discovered that there was a shared bit of DNA that traveled in the disease. What took two years to identify in the laboratory – shared bands of genetic material – would take two days today. And that speed is what excites Dr. Gregersen. “We have the tools to get at these genes rather quickly now,” he said. “The more patients and controls that we have, the more power we will have to pull out new genes and make associations.”

In another major breakthrough, scientists have discovered the importance of a substance called citrulline as a target for immune attack in rheumatoid arthritis (RA). This immune system antibody associated with rheumatoid arthritis recognizes citrulline, which seems to be a key player in the condition. Indeed, the HLA associations with RA have now been shown by Dr. Gregersen and others to directly regulate the immune response to proteins containing citrulline. Citrulline is formed when a specific enzyme comes in contact with arginine, one of 20 common amino acids in proteins. When one of the enzymes is present, nitrogen is removed from the chemical structure of arginine and it converts into citrulline.

Laboratories have developed a test to measure for anti-cyclic citrullinated peptide antibody, or anti-CCP. It is now being used as a diagnostic for rheumatoid arthritis. Scientists are now finding that patients have CCP antibodies months or years prior to the illness, suggesting a way to identify the disease before it starts and perhaps offer treatments to stave off the symptoms. It turns out that those with these antibodies who also have a particular variety of HLA, a complex of genes that regulate immune function, have a 30 times higher risk of developing rheumatoid arthritis than those without these genetic risk factors.

Scientists at the University of Colorado are now analyzing the genes from 2,500 first degree relatives of rheumatoid arthritis patients and testing CCP levels to see whether there is a way to predict, based on these measurements, who will go on to develop rheumatoid arthritis.

Ultimately, understanding how the genes work to confer illness will help in the development of new treatments.

Normal Control Genetic Database

In addition, The Feinstein Institute is participating in a groundbreaking effort to release large amounts of genetic data on normal subjects for use by the scientific community. A key barrier to progress for many geneticists is the costs of obtaining genetic data from normal control populations to use for comparison to the genetic variation seen in people with disease.

In collaboration with the Children's Hospital of Philadelphia, The Feinstein will release genetics data on approximately 6,000 normal volunteers. A company that designs new genetic testing technology, Illumina, Inc. will maintain the database and make it available to scientists. The data will not include personal identifiers but scientists will have information on age and ethnicity to best match their groups to study.

Source: North Shore-Long Island Jewish (LIJ) Health System