

Study reveals 2 genes linked to disabling arthritis

An international team of researchers led by a Fred Hutchinson Cancer Research Center geneticist has discovered two genes linked to a disabling form of arthritis called ankylosing spondylitis, a painful and progressive disease in which some or all of the spine's vertebrae fuse together. The researchers also validated the association of two genes implicated in Graves' disease, an autoimmune condition that causes overactivity of the thyroid gland.

Principal investigator and corresponding author Lon Cardon, Ph.D., and colleagues in the U.K.-based Wellcome Trust Case Control Consortium and The Australo-Anglo-American Spondylitis Consortium reported their findings online Oct. 21 in *Nature Genetics*.

The study revealed two genes linked to ankylosing spondylitis: ARTS1 and IL23R, both of which influence immune function. Together with the previously known gene HLA-B27, the new findings increase to three the number of genes known to be involved in the disease. A person who carries all three genetic variants would be expected to have a one-in-four chance of developing the disease.

The discovery of both genes, as well as the validation of two prime genetic suspects in Graves' disease – genes known as TSHR and FCRL3 – arose from a comprehensive scan of the human genome in which dozens of researchers used genotyping technology to analyze DNA samples from thousands of patients suffering from a variety of common diseases and compared them to DNA from a similar number of healthy control subjects.

In addition to Graves' disease and ankylosing spondylitis, the study mined for common genetic variations associated with multiple sclerosis and breast cancer. The most significant findings, however, were in ankylosing spondylitis, a type of arthritis that not only affects the spine but also can attack other joints and organs, including the heart, lungs and eyes. The condition afflicts an estimated one in 200 males and one in 500 females and typically strikes during adolescence and young adulthood.

Previous research also has linked IL23R with inflammatory-bowel disease (Crohn's disease) and psoriasis. "Clinically these diseases tend to occur together – people with inflammatory-bowel disease also tend to have a higher probability of having ankylosing spondylitis and psoriasis. The IL23R gene provides a genetic link that sheds new light on their co-occurrence," said Cardon, a member of the Hutchinson Center's Human Biology Division.

With these new clues in hand, researchers next will study the genes in model organisms to work out the pathways by which they cause disease. The ultimate goal is improved diagnostics and drug discovery. For example, knowing that genetic variation in IL23R is a risk factor for both Crohn's disease and ankylosing spondylitis suggests that drugs being tested for one also may be effective against the other.

"We already knew that IL23R is involved in inflammation, but no one had ever thought it was involved in ankylosing spondylitis," said Matthew Brown, M.D., a clinical researcher from the Wellcome Trust Centre for Human Genetics at the University of Oxford, who co-led the study with Cardon. A treatment for Crohn's disease that inhibits the activity of this gene already is undergoing human trials, Brown said, and the drug also looks very promising as a potential treatment for ankylosing spondylitis.

"This is an exciting time for genetics. The Wellcome Trust Case Consortium has yielded more genetic discoveries for common diseases in 2007 than have been made in the entire history of the field," said Cardon, a statistical methodologist who last year came to the Hutchinson Center's Human Biology Division

from the University of Oxford, where he conducted the research and retains an academic post.

“Seattle is very, very strong in epidemiology and genetics and has a worldwide reputation in biostatistics – that’s what brought me here,” said Cardon, also a professor of biostatistics at the University of Washington.

Source: Fred Hutchinson Cancer Research Center

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