



New Genes Provide Additional Targets for Spondylitis Treatment

by Scott P. Edwards | September 30, 2008

The genetics of ankylosing spondylitis (AS) came into clearer focus nearly a year ago, with the discovery of two genes that increase the risk of developing the disease. Scientists now have found what they believe may be the last pieces of the genetic puzzle to this potentially crippling disease.

“When we identified ARTS1 [now called ERAP1, for endoplasmic reticulum aminopeptidase1] and IL23R, we expected to come up with additional genes within the next year to give us all the answers to AS,” says John Reveille, M.D., director of the Division of Rheumatology and Clinical Immunogenetics at the University of Texas Medical School at Houston. “We’re almost there. We’ve identified other genes—some are important, some are not.”

Dr. Reveille, who was one of the scientists to identify ERAP1 and IL23R, recently presented findings at the Sixth International

Congress on Spondyloarthropathies in Ghent, Belgium, that implicate other genes in AS. He calls these findings “equally as big as ERAP1 and IL23R.”

Genetic History

Nearly 38 years ago, scientists identified HLA-B27, a powerful predisposing gene that accounts for approximately 40 percent of the overall cause of AS. HLA-B27 is an inherited gene marker that is associated with several rheumatic diseases, including AS and psoriasis. The gene is found with the highest prevalence—greater than 90 percent—in people with AS. The gene itself does not cause AS, but makes individuals more susceptible to the disease. In fact, not everyone with the HLA-B27 marker will develop AS. If someone with the genetic marker has a child, there is a 50/50 chance they will pass it on to their child; however, there is still only a small risk of the child ever developing AS. The risk of AS increases in a sibling of someone who has the disease and is HLA-B27 positive.

The HLA-B gene, part of the family of genes called the human leukocyte antigen (HLA) complex, provides instructions for making a protein that affects the immune system. This complex helps the body’s immune system distinguish its own proteins from those made by viruses and bacteria that invade the body. There are several different forms of the HLA-B gene, which allow a person’s immune system to react to various foreign invaders. The HLA-B27 version of the gene increases the risk of developing spondylitis.

In October 2007, Dr. Reveille and Matthew Brown, M.D., of Australia’s University of Queensland, identified the ERAP1 and IL23R genes and linked them to spondylitis. The presence of these two genes, as well as HLA-B27 and inflammatory back pain, a hallmark of AS, “will almost make the diagnosis of ankylosing spondylitis complete,” according to Michael Weisman, M.D., a Los Angeles rheumatologist who spoke at a Spondylitis Association of America educational seminar in June about classifying and diagnosing the disease.

Like HLA-B27, the IL23R gene plays a role in the immune response to infection. In this case, it provides instructions for making a receptor present on the surface of certain immune cells. These receptors are involved in triggering chemical signals inside the cell that promote inflammation and coordinate the immune system's response to infection.

"We know that there are different responses from the immune system in inflammatory and rheumatic diseases," says Dr. Reveille. "A key pathway in AS is related to the IL23R gene."

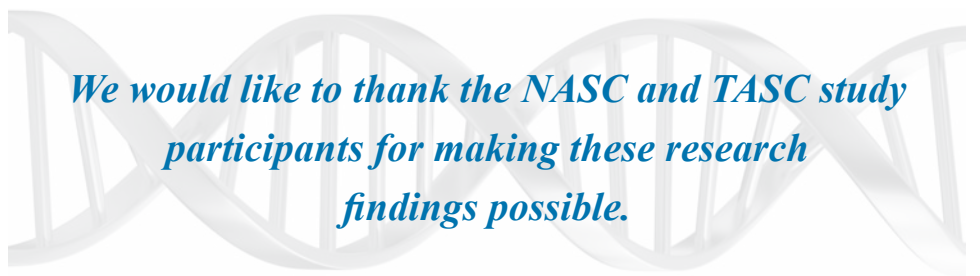
IL23R has been implicated in other diseases, such as inflammatory bowel disease and psoriasis, both of which are related to spondylitis.

ERAP1, on the other hand, says Dr. Reveille, works with HLA-B27 to determine protein levels on the B27 gene that regulate the body's immune response. One of the proteins created by HLA-B27 takes fragments of pathogens (infectious organisms that cause disease) and places them on the outside of immune cells. These fragments activate the immune system so that it fights against the pathogen. ERAP1 breaks the pathogen fragments up into manageable sizes that can attach to the HLA-B27 gene.

"ERAP1 and IL23R show a new pathway of causation [for AS] and could lead to new therapies for this arthritic condition," Dr. Reveille told the SAA soon after the genes' discovery.

New genes provide additional treatment targets

In his presentation at the Ghent conference, Dr. Reveille revealed the results of a genome-wide association study that identified additional AS genes located on the network that contains ERAP1 and IL23R.



We would like to thank the NASC and TASC study participants for making these research findings possible.

As scientists know from previous studies, ERAP1 regulates proteins on the surface of cells that bind to TNF-alpha, or tumor necrosis factor-alpha, a protein that is involved in systemic inflammation and is found in high levels in AS patients. Dr. Reveille's team identified the receptor gene that causes this action.

"This gene interacts with the protein, which then interacts with a whole other set of proteins," he says. "It's like a domino effect."

In addition, he adds, there are other genes in the network that "keep popping up as positive, just like the TNF receptor gene." Another one of these genes regulates how the HLA molecule replicates others.

The identification of these additional genes gives scientists new treatment targets. The primary action of the gene might be downstream (further along the pathway on which the gene's actions occur), says Dr. Reveille, so the goal would be to target that pathway for treatment.

"We can't make a treatment to attack HLA-B27, for example, because that would shut down the body's immune system," he says. "But TNF is downstream [of HLA-B27] and is a good target."

By identifying the genetic networks that are implicated in AS, scientists can look at other, less toxic genes and target them for treatment. If a primary function of the ERAP1 gene is to target cytokines (signaling proteins that play a critical role in the body's immune response), then it might be more effective to attack the cytokines rather than ERAP1.

Findings allow for more effective testing

Dr. Reveille's work, both the Ghent findings and information he presented at the American College of Rheumatology annual meeting, is leading to better testing to determine who has or is more susceptible to developing spondylitis.

Currently, MRI is the gold standard for diagnosis of AS; however, that is changing as the genetic components of the disease are better understood. A simple blood test can now determine an individual's HLA-B27 status. Because this test does not distinguish AS from other inflammatory diseases, however, it has limited diagnostic value. New tests are being developed to gauge ERAP1, IL23R and TNF status, says Dr. Reveille, giving clinicians a better picture of the disease.

"If we know that you have the right allele [an alternative form of a gene pair] of an AS gene, then that's much better than what an MRI tells us. We have a simple gene test right now that costs only \$150 and can tell us about someone's HLA status. New tests are currently being developed to determine status of other genes."

Dr. Reveille's research is part of the Australo-Anglo-American Spondylitis Consortium (TASC), which is involved in ongoing AS genetic research. The SAA serves as the national recruiting center for subjects participating in the TASC study. Last year, Dr. Brown summed up TASC's genetic work, saying, "We can expect really major advances over the next five years in AS research on the back of these genetic studies. These are very exciting times indeed."

Exciting indeed.