



THE TASC GENETIC STUDY UNCOVERS TWO NEW GENES IMPLICATED IN ANKYLOSING SPONDYLITIS

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The good news is in. We are delighted to tell you that due, in large part, to your continued commitment to AS genetic research since 1996, a critical milestone has been achieved with the discovery of two new genes implicated in AS. The new genes have been identified as ARTS1* and IL-23R*. This new finding means that researchers now have uncovered roughly 70% of the genetic contribution toward susceptibility toward AS.

What does this mean for patients?

This new information resulting from the work coming out of the TASC genetic study, headed by Drs. John D. Reveille and Matthew Brown, provides two more critical pieces of the puzzle with regard to unraveling the mystery of how AS develops. Further, the discovery of IL-23R could very likely lead to new biological medicines in the treatment of AS with new clinical trials beginning as early as within two years. The reason for this likelihood is that IL-23R has already been implicated in Crohn's Disease and as a result research has already begun to develop a class of drugs specific to this gene target. What is more, researchers are suggesting that eventually these findings very likely will lead to a faster diagnosis for people who show early symptoms of AS.

Who conducted the study?

Work done in part by the Australo-Anglo-American Spondylitis Consortium (TASC), which includes the SAA, led to the discovery of the two genes. The findings, which will be announced in the November issue of *Nature, Genetics*, resulted from the largest and most comprehensive genome-wide association scan ever conducted to date. Several other unrelated diseases were included in this scan. These included breast cancer and multiple sclerosis, but according to the AS researchers, it is encouraging to note that most significant findings were in AS.

How did genetic studies start?

In 1944, three researchers at Rockefeller University published a paper that laid a foundation for the modern revolution called molecular biology. By discovering that DNA is the material that is involved in transmitting genetic information, the good and the not-so-good, from one generation to the next, Avery, MacLeod and McCarty paved the way for the work later picked up by Crick, Watson and Wilkins in the early 1950s, which eventually led to a Nobel Prize award for elucidating DNA's structure.

What many people do not realize is that the original pivotal work actually was driven by the quest to understand a specific disease; pneumonia. During that epoch—in the early decades of the 20th century, pneumonia was the leading cause of death in America. It was responsible for the premature death of more people than cancer or heart disease.

Without the investigation of how certain types of pneumonia “transformed” into others, the discovery that DNA carried genetic information would most likely not have been uncovered as early as it was.

Fast forward to the 1970s. Humans have roughly between 20,000 and 25,000 genes, but according to researchers, fewer than a dozen most likely play any significant role in AS. The first of these genes, HLA-B27, was discovered in the 1970s. At that time this was a spectacular and important discovery to aid diagnosis in some patients, and also led to a better understanding of the worldwide distribution of the disease in different populations, since it was recognized early on that the rate of HLA-B27 in population largely determined the likely prevalence of AS.

It is thought that HLA-B27 accounts for approximately 40 percent of the overall cause of AS, and now with this new discovery, according to Drs. Reveille and Brown, together with B27, the identified genetic susceptibility toward AS now stands at roughly 70 percent of the overall cause.

How is AS triggered in a person?

Many AS researchers think that AS occurs because people carrying particular combinations of genes are exposed to some common environmental trigger, most likely some bacteria that we carry in the gut. This suggests that it is likely that nearly everyone is exposed to the trigger, but only those with particular combinations of genes develop the disease.

What is DNA?

DNA, or deoxyribonucleic acid, is the hereditary material in humans and most other organisms. Most DNA is located in the cell nucleus (where it is called nuclear DNA), but a small amount of DNA can also be found in the mitochondria, where it is called mitochondrial DNA or mtDNA.

The information in DNA is stored as a code made up of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). Human DNA consists of about 3 billion bases, and more than 99 percent of those bases are the same in all people. The order, or sequence, of these bases determines the information available for building and maintaining an organism, similar to the way in which letters of the alphabet appear in a certain order to form words and sentences.

DNA bases pair up with each other, A with T and C with G, to form units called base pairs. Each base is also attached to a sugar molecule and a phosphate molecule. Together, a base, sugar, and phosphate are called a nucleotide. Nucleotides are arranged in two long strands that form a spiral called a double helix. The structure of the double helix is somewhat like a ladder, with the base pairs forming the ladder's rungs and the sugar and phosphate molecules forming the vertical sidepieces of the ladder.

An important property of DNA is that it can replicate, or make copies of itself. Each strand of DNA in the double helix can serve as a pattern for duplicating the sequence of bases. This is critical when cells divide because each new cell needs to have an exact copy of the DNA present in the old cell.

What does the future hold?

Research typically advances in micro-steps that are barely perceptible even within the scientific community itself. However, this discovery is much more significant with far reaching potential. Indeed, the researchers tell us that the identification of these new genes will become part of the AS permanent record upon which new and important future advances will be made.

In an interview with Spondylitis Plus from Brisbane, Australia, Dr. Matthew Brown stated that the scan that identified these two genes looked at around 15% of the genetic diversity between individuals, and that going forward the Australo-Anglo-American Spondyloarthritis Consortium study (TASC) will survey 80-85% of that diversity, and so is likely to find still more genes. He concluded, “We can expect really major advances then over the next 5 years in AS research on the back of these genetic studies - these are very exciting times indeed.”

The SAA acknowledges with deep gratitude the work of Drs. Reveille and Brown and the TASC team, in addition to the researchers at the Wellcome Trust in Oxford, UK, who have made this discovery possible.

Reference: NIH.gov

Glossary: The unabbreviated name for the IL23R gene is “interleukin 23 receptor”

The unabbreviated name for the ARTS1 gene is “type 1 tumor necrosis factor receptor shedding aminopeptidase regulator”