

# Research links genetic mutations to lupus

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A gene discovered by scientists at Wake Forest University School of Medicine has been linked to lupus and related autoimmune diseases. The finding, reported in the current issue of *Nature Genetics*, is the latest in a series of revelations that shed new light on what goes wrong in human cells to cause the diseases.

“This research is a huge leap toward understanding the cause of lupus and related autoimmune diseases,” said Fred Perrino, Ph.D., a co-author on the paper and a professor of biochemistry at Wake Forest. “There had been few clues before now.”

Perrino, who discovered the gene in 1998, said he suspected it was involved in human disease, but it took a group of researchers from around the world collaborating to put the puzzle together.

“We’ve known that lupus was a complex disease, but now we have a specific protein and a particular cellular process that appears to be one of the causes,” said Perrino. “We’re connecting the dots to understand the biology of what’s going on with the disease.”

In *Nature Genetics*, lead author Min Ae Lee-Kirsch, M.D., from the Technische Universität Dresden in Dresden, Germany, and colleagues report finding variations of the TREX1 gene discovered by Perrino in patients with systemic lupus erythematosus. The study involved 417 lupus patients from the United Kingdom and Germany. Mutations were found in nine patients with lupus and were absent in 1,712 people without lupus.

"Our data identify a stronger risk for developing lupus in patients that carry variants of the gene," said Lee-Kirsch.

In recent years, the gene was also linked to Aicardi-Goutieres syndrome, a rare neurological disease that causes death in infants, and to chilblain lupus, an inherited disease associated with painful bluish-red skin lesions that occur during cold weather and usually improve in summer. The current research also links it to Sjogren's syndrome, a form of lupus.

The diseases are all autoimmune diseases, which means that the body makes antibodies against itself. In lupus, these antibodies cause pain and inflammation in various parts of the body, including the skin, joints, heart, lungs, blood, kidneys and brain. The disease is characterized by pain, heat, redness, swelling and loss of function.

Perrino began studying the protein made by the gene more than 14 years ago.

"We basically cracked open cells to locate the protein and find the gene," said Perrino. "In the 14 years since, we've learned a lot about the protein and how it functions."

The gene manufactures a protein, also known as TREX1, whose function is to "disassemble" or "unravel" DNA, the strand of genetic material that controls processes within cells. The "unraveling" occurs during the natural process of cells dying and being replaced by new cells. If a cell's DNA isn't degraded or unraveled during cell death, the body develops antibodies against it.

"If the TREX1 protein isn't working to disassemble the DNA, you make antibodies to your own DNA and can end up with a disease like lupus," said Perrino.

Perrino and colleagues at Wake Forest have been studying the gene and its protein since 1993. Thomas Hollis, Ph.D., an assistant professor of biochemistry at Wake Forest, is credited with solving the structure of both TREX1 and a similar protein, TREX2. Perrino has also developed a way to measure the function of the proteins.

In a study reported in April in the Journal of Biological Chemistry, Hollis and Perrino found that three variations of the gene reduced the activity of the protein by four- to 35,000-fold.

“Now that we have the structure, we can understand how it disassembles DNA and how mutations in the gene may affect that process,” said Hollis.

The researchers hope that understanding more about the gene’s mutations and the structure of the protein may lead to drug treatments to help ensure that mutant copies of the gene are inactive.

Source: Wake Forest University Baptist Medical Center

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