SOUTHWESTERN NEWS

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SCIENTISTS FIND FOUR GENES THAT COULD PREVENT LUPUS

DALLAS-August 31, 1999-The recent discovery of four genes that can halt lupus, an incurable and potentially fatal autoimmune disease that affects about 1.5 million Americans, could lead to the development of preventive drugs.

By studying mice biologically altered to have the disease, a team of scientists, spearheaded by the director of the UT Southwestern Medical Center at Dallas Center for Immunology, found the location of four genes that prevent susceptibility to lupus. The findings were published this week in the current issue of *Immunity*.

Systemic lupus erythematosus causes inflammation of the joints, lungs and kidneys, and can cause neurological disorders. Lupus is most severe and potentially fatal when it develops into severe kidney disease, resulting in kidney failure. The mice studied had this form of the disease.

UT Southwestern's Dr. Ward Wakeland, senior author of the paper, said the finding is important because the chromosomal regions associated with lupus are the same in both humans and mice, suggesting that the genetic causes are quite similar.

In a previous paper, published last month in *The Journal of Clinical Investigation,* Wakeland and his colleagues showed that genes in three biological pathways lead to development of lupus. Using that knowledge they were able to show that disease does not develop if a susceptibility gene is in the same pathway with its corresponding suppressor gene.

"By using mice that have the full-blown disease, we found not only the genes that suppress lupus-susceptibility genes, but we elucidated that there are several distinct pathways involved in this disease process," said Wakeland, who holds the Edwin L. Cox Distinguished Chair in Immunology and Genetics. "We also determined that at least two susceptibility genes in different pathways must interact for lupus to develop."

The suppressor genes, *Sles1* (*systemic lupus erythematosus suppressor gene 1*), *Sles2*, *Sles3* and *Sles4*, still must be identified and their structure determined. Currently no curative

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or preventive therapy is available for lupus, though the symptomatic inflammation and skin lesions can be treated.

"Once we identify the genes, we will have specific targets to block a particular biological pathway that contributes to lupus, and we can stop the disease," Wakeland said.

The investigators already have determined that at least one of the suppressor genes is near the beginning of one of the biological pathways. Wakeland said that if scientists can turn that gene on at will, the disease will not develop.

In lupus, as in other autoimmune diseases, the body loses the ability to differentiate between foreign substances, or antigens, and its own cells. Antibodies made by the immune system begin attacking the body to rid itself of these supposed invaders. This causes inflammation that can affect multiple systems or organs in the body.

Lupus can occur at any age in either sex, although 90 percent of sufferers are female. About 10 percent of people with the illness have a close relative who also is affected.

It is hard to diagnose lupus because the organs and tissues involved vary between patients, even in identical twins. Chance and environmental factors such as infections, antibiotics, ultraviolet light, extreme stress and certain drugs influence the manifestations of the disease.

"Because there are several susceptibility and suppressor genes involved, it will be challenging to use genetic diagnosis to determine who is predisposed to lupus," Wakeland said.

Other researchers involved in the study were Xiang-Hong Tian, at UT Southwestern, and scientists at the University of Florida College of Medicine.

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