UT SOUTHWESTERN MEDICAL CENTER NEWS

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Gene linked to lupus might explain gender difference in disease risk, UT Southwestern researchers report

DALLAS – March 30, 2009 – In an international human genetic study, researchers at UT Southwestern Medical Center have identified a gene linked to the autoimmune disease lupus, and its location on the X chromosome might help explain why females are 10 times more susceptible to the disease than males.

Identifying this gene, *IRAK1,* as a disease gene may also have therapeutic implications, said Dr. Chandra Mohan, professor of internal medicine and senior author of the study. "Our work also shows that blocking *IRAK1* action shuts down lupus in an animal model. Though many genes may be involved in lupus, we only have very limited information on them," he said.

The study appears online this week in the *Proceedings of the National Academy of Sciences.*

Locating *IRAK1* on the X chromosome also represents a breakthrough in explaining why lupus seems to be sex-linked, Dr. Mohan said. For decades, researchers have focused on hormonal differences between males and females as a cause of the gender difference, he pointed out.

"This first demonstration of an X chromosome gene as a disease susceptibility factor in human lupus raises the possibility that the gender difference in rates may in part be attributed to sex chromosome genes," Dr. Mohan said.

Systemic lupus erythematosus, or lupus for short, causes a wide range of symptoms such as rashes, fever or fatigue that make it difficult to diagnose.

The multicenter study involved 759 people who developed lupus as children, 5,337 patients who developed it as adults, and 5,317 healthy controls. Each group comprised four ethnicities: European-Americans, African-Americans, Asian-Americans and Hispanic-Americans.

In previous genetic studies, the researchers had found an association but not a definite link between lupus and *IRAK1*.

For the current study, the researchers studied five variations of the *IRAK1* gene in the subjects, and found that three of the five variants were common in people with either childhood-onset or adult-onset lupus.

To further test the link, the researchers then took mice of a strain that normally is prone to developing lupus and engineered them to lack the *IRAK1* gene. In the absence of *IRAK1,* the animals

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lacked symptoms associated with lupus, including kidney malfunction, production of autoimmune antibodies and activation of white blood cells.

"The extensive involvement of *IRAK1* in the regulation of the immune response renders its association with lupus a prime candidate for careful genetic and functional analysis," Dr. Mohan said.

Future research will investigate the role that X-linked genes, versus hormonal differences, play in the gender susceptibility rates of lupus.

Other UT Southwestern researchers involved in the study were Dr. Jiankun Zhu, assistant instructor in medicine; Mei Yan, research associate; Jie Han, research assistant; Dr. Joseph Zhou, professor of pathology; and Dr. James Thomas, associate professor of pediatrics.

Investigators from the University of Southern California; the University of California, Riverside; Children's Hospital of Los Angeles; Texas Children's Hospital and Baylor College of Medicine in Houston; Oklahoma Medical Research Foundation; Children's Memorial Hospital and Northwestern University in Chicago; University of California, Los Angeles; LaRabida Hospital and University of Chicago; Wake Forest University; and Medical University of South Carolina also participated, as did international researchers from the Hospital for Sick Children in Toronto; the University of Puerto Rico; Hanyang University in the Republic of Korea; and Imperial College London.

The study was funded by the National Institutes of Health, the Alliance for Lupus Research and the Republic of Korea Ministry for Health.

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