Study points to increased risk for lupus in men

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Lupus Research Institute-funded researcher Betty Tsao, PhD, at the University of California Los Angeles has discovered that humans -- males in particular -- with a variant form of the immune receptor gene "Toll Like Receptor 7 (TLR7)" are at increased risk of developing the autoimmune disease systemic lupus erythematosus (lupus). This breakthrough finding offers renewed hope for developing more targeted treatments.

The powerful finding recently published in the Proceedings of the National Academy of Sciences (*PNAS*) represents additional strong evidence from human cells—as opposed to mice or other animal cells- that alterations in the TLR7 gene can promote lupus.

Scientists had long been looking for an association between TLR7 gene function and lupus in humans after LRI-funded researcher Silvia Bolland, PhD, reported the discovery in the mouse in 2006.

Validating the Lupus Research Institute's (LRI's) "Human Lupus Biology" initiative to translate mouse findings to human disease, Dr. Tsao has now made the discovery and provided the first evidence that alterations in the TLR7 gene promote lupus in people.

"This is an extremely important scientific and medical advance," said Mark Shlomchik, MD, PhD, professor of laboratory medicine and immunobiology at Yale University. "Before this work, it was known that Toll like receptors 7 and 9 were important in mouse models of lupus, but

there was no good, but there was no good evidence for this in people. We only had some evidence that other genes that may work with TLRs were linked to lupus."

"Dr. Tsao's finding that an overactive TLR7 is associated with lupus risk directly implicates the TLR7 gene itself in lupus," Dr. Shlomchik said. "This confirms the mouse data using genetic deficiency and hyperactivity and most importantly identifies TLR7 inhibition as a potential therapy for lupus."

Lupus is a disease of no known cause or cure, although many scientists suspect that a combination of genes and environmental triggers is likely to blame. Approximately 1.5 million Americans and millions more worldwide suffer from the destructive disease that can attack the heart, kidneys, skin, and other vital organs and tissues.

Major Finding on the Development of Male Lupus

Dr. Tsao's discovery that the lupus link to TLR7 is stronger in males supports the idea that there are different genetic pathways to lupus between males and females. Only 10 percent of people with lupus are male, but the disease tends to be particularly severe in this population.

In her novel study, Dr. Tsao and colleagues noted that men with an extra X (female) chromosome have a higher risk for lupus, and predicted that genes located on the X chromosome would be critical in male lupus. So they narrowed their search among the approximately 2,000 genes on the X chromosome to genes already implicated in lupus.

After genotyping DNA of blood samples from over 4,000 people with lupus from East Asia, the team discovered a variant form of the TLR7 gene associated with lupus. The link was stronger in men of Chinese and Japanese ethnicity—89% of men with lupus had the risk allele,

compared with only 77% of healthy male subjects.

"Now that we know the sex-specific genetic contributions to lupus, we can proceed to find more targeted therapies than currently exist," said Dr. Tsao.

Lupus Research Institute Successfully Pioneers Discovery

It was nearly a decade ago that the LRI supported a bold and innovative hypothesis that Dr. Tsao subsequently built upon—that a strain of mice prone to lupus carry an extra copy of the TLR7 gene located on the Y-chromosome. Silvia Bolland, PhD, made this major discovery soon after she joined the NIH to form her own group.

The LRI subsequently supported Dr. Tsao's innovative proposal to translate Dr. Bolland's discovery in mice to a discovery in humans.

"Dr. Tsao's findings demonstrate the power of genetic studies in mouse lupus models to guide the hunt for susceptibility genes in the more complex human disease," said Michel Nussenzweig, MD, PhD, the Sherman Fairchild Professor and a senior physician at Rockefeller University.

Validation of TLR7 in Human Lupus Increases Potential for New Therapies

The search for new therapeutics acting on TLR7 is already underway with candidate drugs in development at several companies.

"This finding strongly confirms the selection of TLR7 as a target for drug therapy, and bolsters the ongoing efforts to develop TLR7

antagonists as future therapeutics for lupus, and further lends credence to the LRI's support of novel research to help find therapies and cures for lupus," said Benjamin Schwartz, MD, PhD, a professor of clinical medicine at the Washington University School of Medicine in St. Louis.

More information: The research appears in the Aug. 23 online edition of the journal *Proceedings of the National Academy of Sciences (PNAS)*.

Provided by Lupus Research Institute