UC San Diego Health

Genome Study Reveals New Clues Regarding Mystery Childhood Illness

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Physician-Researchers from UC San Diego Medical Center and Rady Children's Hospital Participate in International Kawasaki Disease Study

A study looking at the entire human genome has identified new genes that appear to be involved in making some children more susceptible to Kawasaki disease (KD), a serious illness that often leads to coronary artery disease, according to a new international study published in *PLoS Genetics*. This is the first genetic study of an infectious disease to look at the whole of the genome, rather than just selected genes.

Researchers from UC San Diego School of Medicine Department of Pediatrics joined an international research team, including colleagues from The University of Western Australia, the Genome Institute of Singapore, Emma Children's Hospital, The Netherlands, and Imperial College London, UK. The group studied naturally occurring genetic variation in almost 900 cases of Kawasaki disease from these countries. UC San Diego coordinated the U.S. genetics effort, collecting DNA samples from around the country.

"KD tends to run in families, suggesting that there are genetic components to disease risk," said Jane C. Burns, M.D., professor and Chief, Division of Allergy, Immunology, and Rheumatology, UC San Diego Department of Pediatrics. "We have been trying to understand the step by step development of this disease (pathogenesis) and the chain of events leading to it, using a biological approach but with limited success. This robust, systematic genome wide study is simply letting the genetics tell us what are the key genes in KD pathogenesis. Without this research these newly discovered genes of interest might have continued to remain hidden."

Kawasaki disease is an unusual and serious illness of young children that causes high fever, rash, red eyes and lips, swollen glands, and swollen hands and feet with peeling skin. The disease also causes damage of the coronary arteries in a quarter of untreated children and may increase the risk of atherosclerosis in early adulthood. The cause of Kawasaki disease is unknown, but it seems to be due to an infection in susceptible children. There is no diagnostic test for Kawasaki

disease, and current treatment fails to prevent coronary damage in at least one in 10-20 children and death in one in 1,000 children.

This study found that genes involved in cardiovascular function and inflammation may be particularly important and some seem to function together. The authors consider that these findings will lead to new diagnostics and better treatment and may be informative about adult cardiovascular disease as well.

The findings do not yet prove that the new genes are functionally involved. Other genetic variants may be important, especially in different ethnic groups. The authors are planning detailed studies of the function of these genes and larger collaborative studies including East Asian populations, who are at particular risk of Kawasaki disease, with 1 in 150 Japanese children affected.

"So now it is time to come back to the biology and study the genes and the pathways and their role in KD pathogenesis," explained associate project scientist Chisato Shimizu, M.D., Kawasaki Disease Research Center, UC San Diego School of Medicine. "Most importantly, we will be able to use these data to help us predict which children with Kawasaki disease are at most risk for heart disease from their KD."

"Our laboratory is the focal point where the combination of academic research and clinical investigation lead to better treatment and patient outcome," explained Kawasaki Disease Research Center Assistant Director, Adriana Tremoulet, M.D., assistant adjunct professor, UC San Diego Department of Pediatrics and Rady Children's Hospital. "UC San Diego represents the entire U.S. genetics consortium. Through a grant from the NIH we have been able to support DNA collection in Los Angeles, Hawaii, Chicago, and Boston, as well as Japan and Finland. We coordinate the entire U.S. KD genetics effort and are the conduit for U.S. DNA to join the international effort based in Singapore."

Burns says the next steps include "drilling down" on candidate genes and pathways that were discovered in the genome-wide analysis. This detailed analysis will identify the exact genetic differences that influence disease susceptibility and outcome.

"We can already see a way in which this suggests a new treatment for KD that may be much less expensive than the current treatment with IVIG (intravenous immunoglobulin)," said Burns.

The Kawasaki Disease Research Center at UC San Diego:

The Kawasaki Disease Research Program is a joint collaboration between the Departments of Pediatrics and Sociology at UC San Diego, the Scripps Institute of Oceanography, and Rady Children's Hospital of San Diego.

In San Diego County, 20 to 30 children per 100,000 children less than five years of age are affected each year. More than 50 new patients are treated annually at Rady Children's Hospital, San Diego. The illness is four to five times more common than some more publicly recognized

diseases of children such as tuberculosis or bacterial meningitis. It is also 10 to 20 times more common in Japanese and Japanese American children than in children of European descent.

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