Study finds genetic clues to major cause of kidney disease worldwide

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(PhysOrg.com) -- For the first time, researchers have found five regions in the human genome that increase susceptibility to immunoglobulin A (IgA) nephropathy, a major cause of kidney failure worldwide — systematically identifying those that point to a tendency for IgA nephropathy, or a protection against it.

"The study is unique in identifying the biological pathways that mediate IgA nephropathy, mapping the way for further study that may reveal practical targets for diagnosis and treatment," said Dr. Ali Gharavi, Division of Nephrology at Columbia University in New York City, the principal investigator.

"The cause and development of IgA nephropathy is poorly understood. Many biological pathways have been suggested, but none has been conclusive until now," he said.

The ongoing genome-wide association study is funded by the National Institutes of Health's Office of the Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Center for Research Resources, under an NIH Challenge Grant. The project is a part of the $10.4 billion provided to NIH through the Recovery Act. Results were published in the April issue of *Nature Genetics*.

Researchers looked at the genes of 3,144 people of Chinese and European ancestry, all of whom have IgA nephropathy. The disease

occurs when abnormal IgA antibodies deposit on the delicate filtering portion of the kidney and form tangles. The immune system tries to get rid of the tangles, but the kidneys are caught in the crossfire, further destroying the delicate filters.

Worldwide prevalence of IgA nephropathy appears highest in Asia and southern Europe, and is responsible for most cases of kidney failure in those populations. The U.S. prevalence is much lower — up to 10 percent, although Native Americans from New Mexico have reported rates as high as 38 percent.

"IgA nephropathy is most common in Asia, intermediate in prevalence in Europeans and rare in Africans. We found that the frequency of genetic risk variants was similarly highest in Chinese people, intermediate in Europeans and lowest in Africans. This suggests that their higher frequency in Asians may in part account for increased prevalence in this population," said Gharavi.

"Genetics are helpful if they tell you a story about the biology of disease. Here, we're seeing a story unfold about the precise immune basis of IgA nephropathy, which also appears to be genetically associated with other rare kidney diseases — connections that were previously unsuspected," said Dr. Rebekah Rasooly, an NIDDK scientist. "The beauty is that nobody had been looking in this direction, and now they are."

Some of the genes implicated in the study are especially interesting because they play a role in other (not kidney-related) immune disorders. For example, the complement factor H region, called a locus, has been associated with macular degeneration, a progressive eye disease that can result in blindness; and susceptibility to meningococcal infection, the bacteria that causes meningitis.

Rasooly noted that since the genes identified in the Asian population were also found in North American and Mediterranean European populations, this suggests the genetic basis for the disease is similar in these populations. "It's possible that this research might be relevant to all populations," she said. "The study is also a great opportunity to conduct meaningful research with Recovery Act funding. Thanks to an NIH Challenge Grant, we now have a small but growing portfolio in this area, whereas we had nothing on it just a few years ago."

IgA nephropathy appears to be a benign disease in some people, causing only occasional blood in the urine, while others need a kidney transplant, according to Dr. Marva Moxey-Mims, a pediatric kidney specialist at NIDDK.

"What's the difference between these groups of people? This study begins to answer that question," she said. "Although these gene locations by themselves do not unequivocally predict individual risk for disease or severity of it, now we can do more specific, prospective clinical studies to determine if they have predictive power about clinical outcomes in IgA nephropathy."

Moxey-Mims added that the study also may one day point the way to a more accurate, less invasive way of diagnosing IgA nephropathy. Current diagnostic methods require a kidney biopsy, an invasive procedure that must be performed in a hospital.

The findings resulted from long-term collaborations among investigators in the United States, Italy and China. "This worldwide collaboration was critical to achieve sufficient momentum for the study and make progress in the field," said Gharavi. He and study co-principal investigator, Dr. Richard Lifton at Yale University in New Haven, Conn., will recruit another 5,000 patients worldwide.

More information: For additional information on IgA Nephropathy, please visit kidney.niddk.nih.gov/kudisease … ephropathy/index.htm

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