

OCTOBER 31, 2000

## Common Kidney Disease Has a Genetic Basis

Researchers have located a gene that causes immunoglobulin A nephropathy (IgAN), one of the most common kidney diseases. IgAN, which was not previously recognized to be an inherited disorder, affects up to one percent of the population worldwide and 100,000 people in the United States. In discovering that the development of IgAN is influenced by a gene on chromosome 6, the scientists have opened the way to better understanding of the cause of IgAN and the possibility that treatment aimed at the molecular cause of IgAN may one day prevent kidney failure in patients with the disorder.

In a research article published in the November 2000 issue of *Nature Genetics*, Howard Hughes Medical Institute investigator Richard P. Lifton and his colleagues report that genetic analyses of 30 families in the United States and Italy indicate that IgAN is caused by a gene located on chromosome 6. "Prior to this finding, IgA nephropathy was recognized as the most common form of glomerulonephritis worldwide, but its causes were unknown and were believed to be diverse," said Lifton, who is at the Yale University School of Medicine.

---

"Until now, there was little suspicion that this disease would have a strong contribution from a single gene."

— **Richard P. Lifton**

---

Signs of the disease are commonly revealed by presence of blood in the urine following an upper respiratory infection or cold, said Lifton. As the disease progresses, deposits of the immune-related antibody IgA, or immunoglobulin A, lead to scarring of the kidneys. Ultimately, a substantial fraction of patients develop kidney failure, and must rely on dialysis treatment or renal transplantation for survival.

"Until now, there was little suspicion that this disease would have a strong contribution from a single gene. It was recognized, however, that the disease shows wide variation in incidence in different parts of the world. For example, the disease is uncommon in some ethnic groups, such as African-Americans, whereas it is very common in among people from

Southeast Asia. This ethnic variation, as well as studies demonstrating that the disease sometimes recurs within families, suggested that there was a genetic contribution to the disease," Lifton said.

Lifton and Ali Gharavi at Yale and Mount Sinai Medical Schools, teamed with clinical investigators who had studied families with IgAN, including Francesco Scolari from Brescia, Italy; Paolo Schena from Bari, Italy, Bruce Julian from University of Alabama at Birmingham, and Robert Wyatt from University of Tennessee. In their search for a genetic cause of IgAN, they studied 24 families in Italy and six in the United States that had multiple members with the disease. Because IgA deposits are obvious signs of the disease, the researchers first screened for abnormalities in genes that govern the synthesis, modification or clearance of IgA from the kidneys. They found no evidence for abnormalities in those genes.

"So, we went on to take a less biased approach, and simply looked to see whether there were any chromosomal sites in the human genome that were inherited together with the disease more often than expected by chance," said Lifton. "And, we found very strong evidence that a single gene on chromosome 6 influences the disease in about 60 percent of families we studied.

"Our analyses indicate an odds ratio of 400,000 to one in favor of a linkage of this locus with the disease in the affected families. This is surprisingly strong evidence for linkage," Lifton said. So far, the scientists have shown that a single area of the chromosome, a region called 6q22-23, is linked to the disease.

"We presume that this genetic finding will reflect the effects of a single gene on chromosome 6," he said. "We don't know what that gene is, but this finding tells us where to look and that the gene we find is likely to have a large role in the development of IgA nephropathy," he said. The researchers are now trying to identify the gene involved and are recruiting patients from different ethnic groups with IgAN. "It will be of particular interest to determine whether the wide variation in disease occurrence is due to different frequencies of the mutant gene in different populations," Lifton said.

Discovery of the gene might yield clues to whether particular environmental influences trigger the disease, said Lifton. Even though there were no signs that known IgA-related genes were involved in the disease, Lifton speculates that the culprit gene could still turn out to influence IgA metabolism. The involvement of a key immune-related protein, for example, might explain why the disease appears to be triggered by an infection. "This interaction between a gene and an environmental factor might explain why not everyone who inherits this gene ends up getting the disease," he said.

Lifton believes that discovering the gene and tracing its physiological effects will have an important impact on treatment. "Right now there are no effective treatments for IgA nephropathy," he said. "We hope that finding this gene will tell us what metabolic pathways are involved, and give us some idea of how to intercede to try to prevent affected patients from developing severe

kidney damage."