

Gene for devastating kidney disease discovered

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(PhysOrg.com) -- Researchers from Children's Hospital Boston and Brigham and Women's Hospital have identified an important genetic cause of a devastating kidney disease that is the second leading cause of kidney failure in children, according to The NephCure Foundation.

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The study, published online December 20 by [Nature Genetics](#), may provide clues to developing treatments for the disease, focal segmental glomerulosclerosis (FSGS), which currently forces children and young adults onto dialysis and often requires a kidney transplant. No effective treatments are known, and years of research have failed to uncover the underlying disease mechanism.

FSGS attacks the kidney's filtering system, causing proteins to be lost into the urine and reducing the kidney's ability to filter wastes from the blood. According to NephCure, which helped fund the study, 26 million Americans suffer from [chronic kidney disease](#), of which FSGS is one of the most common forms.

Patients with FSGS are often treated with steroids, which are only partially effective and have very harsh side effects. In addition, they often face several trips a week to the hospital for dialysis, and many require a [kidney transplant](#), along with lifelong treatment with powerful

immunosuppressants to prevent [organ rejection](#).

The research team, led by Elizabeth Brown, MD, of Children's Division of Nephrology, working in the laboratory of Martin Pollak, MD, of the Renal Division at Brigham and Women's Hospital, identified the gene by performing a genetic linkage analysis in two large families with FSGS. Linkage analysis is a gene-finding technique that compares affected with unaffected family members, looking for a piece of DNA whose location is already known, and that is inherited only by affected members. Using that piece of DNA as a "signpost," researchers can then look nearby to find the disease gene.

Using this technique, Brown and colleagues homed in on a region of chromosome 14q. By sequencing multiple genes in this region, they detected nine different mutations, all of them in a gene called INF2. They then sequenced INF2 in 91 additional families. In all, they found INF2 mutations in 11 of 93 families.

There have been a few descriptions of other genes that result in FSGS, but Brown and colleagues think INF2 is an important find. Mutations on this gene seem to affect larger numbers of families than those on previously discovered genes, and may be more relevant in understanding how the disease originates physiologically.

"The discovery that multiple families have mutations in INF2 is exciting and not only furthers our understanding of FSGS, but also tells us that INF2 and the pathways in which it is involved are important for normal kidney function," says Brown. "FSGS is a frustrating disease for clinicians, as we have little understanding of the biology and poor treatment options. We hope that further scientific work on INF2 will lead to better options."

INF2 encodes a protein that regulates actin, a protein vital to creating and maintaining the architecture of the cell. Both actin and INF2 are

abundant in podocytes, the kidney cells that are crucial to filtering toxins. These cells are structurally complex, with extensions that interlock with those of other cells. Based on their findings, the researchers believe that disruption of INF2 in podocytes compromises their structure and, hence, their function.

In 2007 alone, 1,117 kidney transplants were performed on FSGS patients, according to NephCure. "To make matters worse, many patients have recurrence of the disease soon after transplant," says William Harmon, MD, chief of Children's Division of Nephrology. "First it ruins your native kidney, then it can return instantly in the transplant and ruin that also."

"It truly is heart-breaking to have to look a child in the eye and know there's currently little that can be done to cure them of this disease," says Henry Brehm, executive director of The NephCure Foundation, which has dedicated over \$6 million towards research of FSGS and Nephrotic Syndrome in recent years. "This study shows that the answers are there to be found."

More information: The study abstract can be accessed [online](#).

Provided by Children's Hospital Boston

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