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Kidney disease linked to defects in cells' ability to repair damaged DNA

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(Medical Xpress) -- Howard Hughes Medical Institute investigator Friedhelm Hildebrandt has discovered that genetic mutations that impair cells' ability to repair damaged DNA can cause chronic kidney disease.

Although chronic kidney disease is a major health burden in the United States, it has no cure. "Very little is known about how kidneys fail," Hildebrandt says, and no one understands why the incidence of the disease has been increasing over the past 20 years. Now, Hildebrandt and his colleagues have linked mutations in four different DNA damage repair genes to chronic kidney disease.

Because such mutations increase cells' sensitivity to genetic damage, Hildebrandt says the findings suggest that environmental toxins may be contributing to the increased prevalence of kidney disease. Their findings on the first of those genes, FAN1, are described in the August, 2012, issue of the journal *Nature Genetics*. Their work on the other three genes, MRE11, ZNF423, and CEP164, was reported in Cell on August 3, 2012.

Attempting to answer lingering questions about what causes kidney disease, Hildebrandt has, over the past fifteen years, collected genetic information from more than 5,000 families with childhood kidney disorders. By analyzing that data, his team has discovered that some types of kidney disorders can be caused by mutations in a single gene. Still, most cases of chronic kidney disease remain unexplained.

Four years ago, Hildebrandt's lab at the University of Michigan Medical School began to use a new strategy to search for rare mutations associated with chronic kidney disease. Their approach combined two technologies. The first, whole exome sequencing, examines only the part of the genetic sequence that codes for proteins, where most disease-causing mutations occur. By focusing on this area, known as the exome, scientists find mutated genes while avoiding the cost and time of sequencing the remaining 99 percent of the genome.

Many harmless variations exist between the DNA sequences of individuals, so to find the mutations most likely to be causing kidney failure, Hildebrandt followed the sequencing process with a technique called homozygosity mapping. For diseases that are inherited recessively -- meaning they occur only when a mutated copy of the gene is inherited from each parent -- homozygosity mapping identifies disease-causing mutations in populations where genetic diversity is low. Hildebrandt used the mapping data to reduce the number of variations resulting from the exome sequencing data to identify the single gene that causes kidney failure in each individual examined.

It took eight members of Hildebrandt's lab more than a year to sift through the genetic sequences of the fifty families in their study. The lab found four mutations—in the genes FAN1, MRE11, ZNF423, and CEP164—that were associated with kidney degeneration.

The first mutation that the team investigated, FAN1, appeared in the sequences of two siblings with karyomegalic interstitial nephritis, a disorder featuring early onset kidney failure alongside other cellular abnormalities. To find out if other patients with karyomegalic interstitial nephritis carried the same mutation, Hildebrandt contacted scientists researching the disorder and requested blood samples from affected individuals. After a year of persistent emailing, he was able to screen patients' DNA for the FAN1 mutation. "In nine out of ten patients," he

says, “we saw that there were mutations in FAN1.”

The FAN1 gene was discovered in 2010 by HHMI investigator Steve Elledge’s lab at Brigham and Women’s Hospital, and found to be involved in repairing damaged DNA.

Using a similar procedure, the team also linked mutations in the CEP164, ZNF423, and MRE11 genes to chronic kidney disease. Surprisingly, Hildebrandt says, all four normally control DNA damage repair. When they tested the function of FAN1, CEP164, and ZNF423 in zebrafish and rats, they found that mutations in any of the four genes impaired cells’ ability to repair damaged DNA, and also led to kidney degeneration. To further study DNA repair mechanisms they collaborated with Bruce Hamilton at the University of California-San Diego, Rachel Giles at the University of Utrecht and Agata Smogorszewska at Rockefeller University.

The DNA-repair system fixes slipups in the genetic code made during replication or caused by genotoxins—environmental factors inflicting damage on genetic material. When the process fails, mutations remain and cells cannot function normally. Defects in DNA damage repair had not previously been associated with chronic kidney disease.

The connection between DNA repair and kidney failure is not yet clear, Hildebrandt says. “It can take decades to draw a line from the primary defect to what the disease does to the organism or the human.” But he suspects DNA damage that accumulates in the absence of DNA repair leads to cell degeneration. This model may explain chronic organ failure in general, he says, not just in the kidneys. However, the kidneys could be particularly susceptible to DNA degeneration caused by genotoxins, since they process and eliminate many toxins from the body. It could be, Hildebrandt says, that increased exposure to environmental genotoxins has contributed to an increasing incidence of end-stage kidney failure.

Hildebrandt also points out that different mutations of the same DNA-repair gene could cause drastically different conditions. Individuals with mutations that prevent function of the encoded protein entirely would accumulate significant, often fatal damage early in development. Those with less severe mutations, in contrast, would acquire DNA damage more slowly, causing degenerative changes over time.

Hildebrandt says the discovery of this disease mechanism will help in diagnosing kidney failure, which is widespread and often lacks an identified cause. Further, it gives researchers working to develop treatments for chronic kidney disease new clues about where to begin. “That’s the hope,” says Hildebrandt. “That now we might be able to look for drugs that mitigate those effects and or to avoid the genotoxic substances.”

Provided by Howard Hughes Medical Institute

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