MedicalXpress

Fast-track gene-ID method speeds rare disease search

September 16 2010

A University of Michigan-led research team has identified a gene responsible in some families for a devastating inherited kidney disorder, thanks to a new, faster method of genetic analysis not available even two years ago. The success offers hope that scientists can speed the painstaking search for the genes responsible for many rare diseases and test drugs to treat them.

The U-M scientists report their success with exome capture, a groundbreaking genetic analysis technique, in the September issue of Nature Genetics.

The U-M- led international research team collaborated with two companies to test the emerging technology's ability to isolate the culprit gene in families with inherited single-gene kidney diseases. Many rare diseases that strike children and young adults result when a single gene malfunctions.

"We are one of the first research teams to take this technology and move it forward to identify single genes," says senior author Friedhelm Hildebrandt, M.D., a Howard Hughes Medical Institute Investigator, a Doris Duke Distinguished Clinical

Scientist and Frederick G. L. Huetwell Professor for the Cure and Prevention of Birth Defects at U-M.

"For us, it's a big leap in what genetics can do," Hildebrandt says. "In

five years, families may be asked, 'Do you want to look at the cause of your rare disease?' In the not-too-distant future, we may be able to enroll them in a drug study."

Hildebrandt is an internationally known expert on the genetic basis of several severe kidney diseases that cause early renal failure in infants and children. He is also a professor in the U-M departments of human genetics and pediatrics and communicable diseases.

Hildebrandt and colleagues combined exome capture with a method of ultra-fast data analysis called massively parallel processing to identify a new gene involved in a family of congenital cystic kidney diseases known as nephronophthisis-related ciliopathies, or NPHP-RC. Taken together, these ciliopathy disorders are the most frequent genetically caused kidney disease in the first three decades of life.

The study results mean that Hildebrandt's team and other researchers now have an efficient way to identify yet-undiscovered genes involved in NPHP-RC disorders.

Hildebrandt's goal is to identify the genes responsible for these ciliopathies and find therapies to prevent or reverse their effects.

Research details

Hildebrandt used a combination of strategies of genetic analysis to expedite the search for the faulty gene in 10 NPHP-RC families. To screen candidate genes, the team collaborated with two companies, Roche NimbleGen, Inc., and Agilent, to apply the exome capture technique.

In the cell nucleus, exons, known collectively as the exome, are chains of nucleotides, or basic compounds that make up DNA, which leave the

nucleus and produce proteins vital to body processes. Messenger RNA carries exons outside the nucleus, whereas other genetic material called introns remains behind. Capturing and analyzing only the exons speeded the search.

Context

People with NPHP-RC have abnormal development or degeneration of the kidneys, retina and cerebellum. Dialysis and kidney transplant are the only treatment options available.

The search for the genetic basis of these disorders, and other rare diseases as well, has turned out to be much more complicated than researchers hoped decades ago. Scientists have found that different single genes are responsible for disease in different subgroups of affected families. Discovering a culprit gene may yield insights for screening and future treatment, but only for a limited portion of all those affected.

Collaborating with scientists worldwide, Hildebrandt's lab has discovered more than 10 gene mutations that contribute to NPHP-RC diseases. But in an estimated 70 percent of cases, the gene involved is unknown.

What's next

"Once exome capture is used on a large scale, there will be databases that will reveal regions where mutations are known to cause disease," Hildebrandt says.

Future databases for rare diseases may take five to 10 years to develop. Testing of potential drug treatments can be expected to move forward at the same time. In zebrafish, Hildebrandt's lab has started to screen two

drug compounds to see if either can restore the protein levels that the newly identified gene would produce if it functioned normally.

More information: *Nature Genetics*, September 2010
doi:10.1038/ng.662