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With just 3 affected individuals, researchers find gene behind rare form of epilepsy

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Researchers have found a gene responsible for a particularly debilitating form of epilepsy that also leads to kidney failure, according to a report published online on February 28th and also in the March 7th print issue of the *American Journal of Human Genetics*, a publication of Cell Press. What's more, the new findings, which begin to "crack open the cell biology of the problem," were made with the help of just three affected individuals.

"Many people will not have heard of this extraordinarily rare disease," said Samuel Berkovic of the University of Melbourne in Australia. "Nonetheless, the findings speak to the power of genetics to solve even quite rare problems."

Epilepsy is overall a common condition, affecting some two percent of people. The genetics behind the seizure disorder are often complex. However, progressive myoclonus epilepsies, which Berkovic said can be quite disabling and tend to get worse over time, usually have a simpler, Mendelian pattern of inheritance caused by a variety of single genes.

Action myoclonus-renal failure (AMRF) syndrome is a lethal inherited form of progressive myoclonus epilepsy associated with kidney failure. Symptoms usually arise when people reach the age of 15–25 with signs of kidney trouble or neurological symptoms including tremors, seizures, and later other movement disorders. Upon close inspection, the kidneys of those with AMRF show scarring, and their brains show an unusual buildup of storage material.

“The recessive gene defect underlying AMRF was unknown and the lack of large pedigrees and lethality of the disorder precluded a conventional mapping strategy,” Berkovic said. So, his team came up with a new one.

The researchers first identified three unrelated families, each with a member having AMRF. They then used a modified version of “homozygosity mapping” to narrow the candidate regions of the genome down to places where both copies of a gene were identical in one inbred family, and they used affected and unaffected family members to narrow the hunt further. That exercise suggested that the gene involved could be found in a region on chromosome 4.

Then, they took another “quick shortcut” to finding the culprit, Berkovic said. Using microarray analysis, which measures gene expression, they identified genes within the implicated region that were turned down in those with AMRF.

That led them to SCARB2/Limp2as the likely candidate. Indeed, they showed, all of the families under study carried a mutation in the SCARB2/Limp2gene, which the researchers confirmed in two other unrelated AMRF families.

SCARB2/Limp2is active in a wide range of tissues, earlier studies had shown, where it is found on the surface of cellular components called lysosomes. Lysosomes play an important role inside of cells in breaking down spent parts, a process known as autophagy.

As luck would have it, mice lacking the gene had already been developed. Upon examination of those animals, the investigators found inclusions in the animals’ brains and subtle abnormalities in their kidneys, reminiscent of people with AMRF.

Although further study is needed to work out exactly what happens in

the brain and kidneys of people lacking this lysosomal gene, Berkovic said they do have some ideas.

“SCARB2/Limp2 might have a role in physiological autophagy and its deficiency could thus lead to accumulation of normally recycled proteins or organelles manifesting as inclusions [in the brain],” the researchers said.

On top of the insights into AMRF, the team’s newly developed method might unlock other rare disorders.

“The whole trick is to exploit the particular family structure of affected and unaffected individuals,” Berkovic said. “This strategy may be more widely applicable to the still many rare, Mendelian disorders yet to be solved.”

Source: Cell Press