Genetic testing in epilepsy -- it takes more than one gene

June 23 2011

Imagine two flat screen televisions tuned to the same channel and sitting side-by-side. From a distance, their pictures are virtually the same, however up close, you can see subtle variations in the pixels – one blurred here, another dropped out there.

Suppose some of these 'bad pixels' are known to produce periodic black-out spells on the screen. Would a sharper image revealing all of the defects help identify which of the screens works perfectly, and which one needs repair?

Seven years ago, Dr. Jeffrey Noebels, professor of neurology, neuroscience and molecular and human genetics at Baylor College of Medicine, and Dr. Richard Gibbs, director of the Baylor Human Genome Sequencing Center, began the first large-scale sequencing project to survey nearly all the genes encoding ion channels, the electrical 'pixels' of the brain.

These channels are the tiny pores that allow molecules of sodium, calcium, potassium, and chloride to move in and out of the cell, creating the electrical impulses that drive signaling within brain networks. A disruption of the signaling pattern leads to epilepsy, a common severe neurological disorder.

Because the causes of most epilepsies remain mysterious, they hoped to identify specific "pixels" that might predict who will have seizures. Hundreds of subjects and terabytes of data later, Noebels, Gibbs and

their colleagues at BCM found dozens of individually rare variants in the epilepsy-related ion channel genes in people who had epilepsy, and intriguingly, nearly just as many in those who did not. Why are some individuals more fortunate?

Analyzing those personal variations and how they contribute to a large picture is part of the next step in understanding unexplained epilepsy – and many other disorders linked to ion channel diseases throughout the body – including the brain, eye, ear, heart, muscle, kidney and pancreas. Typically, when a known disease gene is uncovered, a patient is told he or she is at risk for the condition. However, a better answer may lie in the patterns of all the defective channels rather than any single one of them.

"We are all born with a few erratic pixels, but luckily they do not always add up to disease. It takes a village," said Noebels, who is also director of the Blue Bird Circle Developmental Neurogenetics Laboratory at BCM and a pioneer in genetic epilepsy research. A report on the work appears in the current issue of the journal *Cell*.

"We began looking at ion channels because they are the largest class of genes that contribute to seizures. In some families, even a single defective one is a master switch for epilepsy," said Noebels. "But we soon realized that small defects in other channels could aggravate the problem in some individuals, or mask it in others. Instead of looking at one incriminating gene at a time and pronouncing it guilty, as is often done in single gene testing, we wanted to step back and examine them all."

Baylor neurologists were able to recruit many people with and without epilepsy to participate in the DNA study, and together with the Human Genome Sequencing Center, a leader in mammoth sequencing projects, developed an 'ion channel pipeline' to analyze the DNA.

They sequenced the exomes or coding regions of 237 ion channel genes in 152 people with epilepsy and 139 individuals without epilepsy and compared the personal variation profiles they found in the ion channel genes.

"We found there were perfectly healthy people walking around with single gene mutations that are known to cause epilepsy and yet they don't have the disease," said Dr. Tara Klassen, a postdoctoral researcher in Noebels' laboratory and lead author of the study. "Why not?"

The answer could rest with the way ion channels work, she said.

"Many genes in a cell have very distinct functions, and the more mutated genes you have, the worse off you are."

Ion channels work differently. They are a family of genes that all tune the firing patterns of brain cells in small overlapping ways. They open and close at different rates and in different combinations, but together share control of the overall excitability in networks of nerves. When certain networks become overexcited, a seizure may result.

"We conclude that epilepsy may arise from a complex mixture of altered channels, and may be prevented by other channels working in the background," said Noebels. "If one works poorly, another can compensate by working better. The combination can mask the individual defect."

"Looking at a full profile rather than jumping to a conclusion after a single result completely changes our way of thinking about how to counsel those who might test positive for a single genetic variant," he said.

"We now know the profile of these channel variations is more important

than the presence of any single ion channel defect, and that understanding the meaning of the profile and applying it to patients will require the skills not only of neurologists, but also bioinformatics specialists and experts in devising computational models of disease," said Noebels. "The next step is to take the ion gene profile and figure out what it means for the individual."

This understanding could also lead to better therapy. Nearly one-third of people with epilepsy do not respond to current drugs used to treat the disorder. Many of those drugs target individual ion channel genes implicated in epilepsy.

"We also found that it was quite common for a person with epilepsy to have more than one genetic cause for it," he said. "What if an individual has epilepsy arising from five or more defective ion channels? One drug won't cover them all."

This finding is a wonderful example of how we can bring personalized genomic analysis closer to everyday health care, said Gibbs. "We now know how important the pattern of rare variants found in each individual really can be."

More information: http://www.cell.com/

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