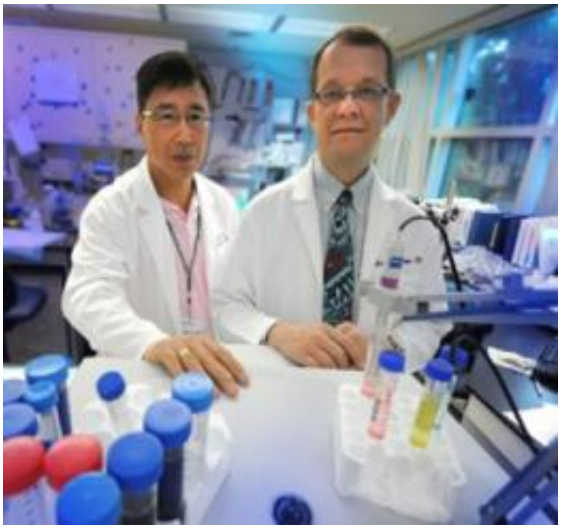
Scientists identify gene linked to facial, skull and cognitive impairment

July 5 2012



A gene whose mutation results in malformed faces and skulls as well as mental retardation has been found by scientists. Credit: Phil Jones

A gene whose mutation results in malformed faces and skulls as well as mental retardation has been found by scientists.

They looked at patients with Potocki-Shaffer syndrome, a rare disorder that can result in significant abnormalities such as a small head and chin and intellectual disability, and found the gene PHF21A was mutated, said Dr. Hyung-Goo Kim, molecular geneticist at the Medical College of Georgia at Georgia Health Sciences University.

The scientists confirmed PHF21A's role by suppressing it in zebrafish, which developed head and brain abnormalities similar to those in patients. "With less PHF21A, brain cells died, so this gene must play a big role in neuron survival," said Kim, lead and corresponding author of the study published in The American Journal of Human Genetics. They reconfirmed the role by giving the gene back to the malformed fish – studied for their adeptness at regeneration – which then became essentially normal. They also documented the gene's presence in the craniofacial area of normal mice.

While giving the normal gene unfortunately can't cure patients as it does zebrafish, the scientists believe the finding will eventually enable genetic screening and possibly early intervention during fetal development, including therapy to increase PHF21A levels, Kim said. It also provides a compass for learning more about face, skull and brain formation.

The scientists zeroed in on the gene by using a distinctive chromosomal break found in patients with Potocki-Shaffer syndrome as a starting point. Chromosomes – packages of DNA and protein – aren't supposed to break, and when they do, it can damage genes in the vicinity.

"We call this breakpoint mapping and the breakpoint is where the trouble is," said Dr. Lawrence C. Layman, study co-author and Chief of the MCG Section of Reproductive Endocrinology, Infertility and Genetics. Damaged genes may no longer function optimally; in PHF21A's case it's about half the norm.

"When you see the chromosome translocation, you don't know which gene is disrupted," Layman said. "You use the break as a focus then use a bunch of molecular techniques to zoom in on the gene." Causes of chromosomal breaks are essentially unknown but likely are environmental and/or genetic, Kim said.

Little was known about PHF21A other than its role in determining how tightly DNA is wound in a package with proteins called histones. How tightly DNA is wound determines whether proteins called transcription factors have the access needed to regulate gene expression, which is important, for example, when a gene needs to be expressed only at a specific time or tissue. PHF21A is believed to primarily work by suppressing other genes, for example, ensuring that genes that should be expressed only in brain cells don't show up in other cell types, Kim said.

Next steps include using PHF21A as a sort of geographic positioning system to identify other "depressor" genes it regulates then screening patients to look for mutations in those genes as well. "We want to find other people with different genes causing the same problem," Layman said, and they suspect the genes PHF21A interacts with or regulates are the most likely suspects. It's too early to know what percentage of Potocki-Shaffer syndrome patients have the PHF21A mutation, Kim noted. "Now that we know the causative gene, we can sequence the gene in more patients and see if they have a mutation," Layman said.

They also want to look at less-severe forms of mental deficiency, including autism, for potentially milder mutations of PHF21A. More than a dozen of the 25,000 human genes are known to cause craniofacial defects and mental retardation, which often occur together, Kim said.

Provided by Georgia Health Sciences University