Cellular channels vital for hearing identified

18 July 2013

Ending a 30-year search by scientists, researchers at Boston Children's Hospital have identified two proteins in the inner ear that are critical for hearing, which, when damaged by genetic mutations, cause a form of delayed, progressive hearing loss. Findings were published online July 18 by the journal *Neuron*.

The mutations, affecting genes known as TMC1 and TMC2, were reported in 2011 by the laboratory of Jeffrey Holt, PhD, in the Department of Otolaryngology at Boston Children's. Until now, however, it wasn't clear what the genes do. In the new study, Holt and colleagues at the National Institute on Deafness and Other Communication Disorders (NIDCD) show that the proteins encoded by the genes form channels that turn mechanical sound waves into electrical signals that talk to the brain. A tiny point mutation—a change in one base or "letter" in the genetic sequence—is enough to cause deafness.

Corresponding channels for each of the other senses were identified years ago, but the sensory transduction channel for both hearing and the sense of balance had remained a mystery, says Holt.

The study involved so-called Beethoven mice that carry mutations on TMC1 and become deaf by their second month of life. Each mutation has a human counterpart that causes a prominent form of genetic deafness, causing children to become completely deaf by the age of 10 to 15 years.

Studies of sensory hair cells from the cochleas of the mice, which sense sound vibrations and signal the brain, showed that the TMC1 and TMC2 proteins are necessary to get calcium into the cells. The researchers showed that when TMC1 was mutated, the calcium influx was reduced and the resulting electrical current was weaker in response to sound. "This is the smoking gun we've been looking for," says Holt.

The study also provided evidence that:

- The TMC1 and TMC2 proteins act as backups for each other, explaining why hearing loss is gradual and not immediate. "TMC2 can compensate for loss of function of TMC1, but not completely," Holt says.
- The two proteins can create channel structures either singly or combined in groups, suggesting they may help make different hair cells sensitive to different pitch ranges. "There are gradients of expression of these two proteins, which we think are involved in tuning of the sensory cell," says Holt.

Based on the initial genetic discovery in 2011, a gene therapy study is now underway in mice to see whether reintroducing TMC1 and/or TMC2 genes to the inner ear could restore hearing. The team is looking for electrical signals in the 8th cranial nerve—indicating that the brain is being signaled—and more importantly whether the animals respond to sound.

Provided by Children's Hospital Boston