Scientists identify genetic cause for type of deafness

September 3 2009

A team led by scientists from The Scripps Research Institute has discovered a genetic cause of progressive hearing loss. The findings will help scientists better understand the nature of age-related decline in hearing and may lead to new therapies to prevent or treat the condition.

The findings were published the September 3, 2009, in an advance, online issue of the American Journal of Human Genetics, a publication of Cell Press.

"It is thought that mutations in several hundred genes can lead to deafness," said team leader Ulrich Mueller, a professor in the Department of Cell Biology and member of the Skaggs Institute for Chemical Biology at Scripps Research. "However, for many forms of deafness, we don't know what effects the genes have. In this new research, we have linked a previously uncharacterized gene to deafness, first in mice and then in humans."

The team found that the gene responsible for the hearing loss—called Loxhd1—is necessary for maintaining proper functioning hair cells in the inner ear. Mutations in Loxhd1 lead to degradation of the hair cells and a disruption of the process that enables hearing.

Tracking Down a New Gene

In the new study, members of the Mueller lab used a technique called forward genetics in their quest to better understand the genetic basis of

hearing and hearing loss.

In forward genetics, scientists make mutations at random in germ cells, screen the resulting models for physical characteristics of interest (in this case hearing impairment), then amplify these traits through the breeding of several generations. The gene responsible for the trait is then identified through positional cloning.

In this case, the scientists were able to generate a new mouse line with hearing impairment that they called samba and then clone the gene responsible, Loxhd1, which had never before been associated with deficits in hearing. When the mice inherited two copies of the mutated gene, they were profoundly deaf shortly after birth.

The scientists' next task was to determine why.

Normally, "hair cells" or stereocilia in the inner ear respond to fluid motion or fluid pressure changes caused by sound waves that enter the outer ear, travel down the ear canal into the middle ear, then strike the eardrum, which vibrates and moves a set of delicate bones that communicate with the inner ear. There, the movement of the stereocilia transmits signals to sensory neurons, sending signals to the brain and eventually resulting in hearing.

The scientists found that mutations in the Loxhd1 gene did not appear to affect the initial development of the stereocilia. However, these mutations did impair the function and maintenance of these essential structures, eventually leading to their degradation and to hearing loss.

But one essential question remained—was there a parallel gene in humans that also caused hearing impairment?

To find out, the Mueller lab reached out to Professor Richard J. H.

Smith, the Sterba Hearing Research Professor at Carver College of Medicine, Iowa State University. Smith had been spearheading an effort to collect DNA samples from deaf families for years, and had hundreds of groups of samples in which to search for Loxhd1. Indeed, when the analysis was completed, the team found that mutations in the Loxhd1 gene were present in some of these families with hearing loss.

Clues to Age-Related Deafness

This is the third hearing-related gene that the Mueller lab has discovered, and one he is particularly excited about.

"In humans, the prevailing difficulty is progressive hearing loss," he said. "As you age, you lose your hearing slowly. Since this mutation can lead to progressive hearing loss, it provides us with more information on the genetic underpinnings of this condition and gives us clues as to how it might be corrected."

Mueller's lab is currently investigating the possibility that a therapeutic drug could be effective in reversing the molecular problems that result from the defective gene.

More information: The first authors of the paper, "Mutations in LOXHD1, an evolutionarily conserved stereociliary protein, disrupt hair cell function in mice and cause progressive hearing loss in humans," are Nicolas Grillet and Martin Schwander of Scripps Research.

Source: The Scripps Research Institute (news : web)