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By Renee Twombly

DEAFNESS CAUSE PINPOINTED BY GENETIC DISCOVERY

Researchers at The Scripps Research Institute have discovered a new gene they say is essential for both hearing and balance in mice and humans. They found that a mutation in this gene causes a form of deafness that has nothing to do with structural proteins in the inner ear—commonly altered in hereditary deafness. On the contrary, the mutation affects an enzyme with a known catalytic function, which gives hints as to how the problem might be preventable with novel drug therapy.

The study appears in this week's Early Edition of the Proceedings of the National Academy of Sciences (PNAS).

The new gene, which the scientists labeled COMT2, is a sister to the well-known COMT (catechol-O-methyl transferase) gene. Both of these genes encode proteins that degrade catecholamines, key neurotransmitters such as dopamine and norepinephrine, to keep them from accumulating and harming cells that have receptors for them. Defects in the COMT gene within the brain have already been linked to development of schizophrenia.

The study began when it was observed that certain mice carried a mutation that caused deafness and balance problems. The team of scientists used a technique known as "positional cloning" to find the defective gene, which is highly expressed in the hair cells of the inner ear of mice. The study was then carried forward to reveal that some deaf people have mutations affecting the equivalent human gene.

"We think it is possible that when COMT2 is defective, catecholamines accumulate around the hair cells, which are specialized to interpret sound energy and generate signals to be processed by the brain," says Bruce Beutler, chair of the Scripps Research Dept. of Genetics, who led the study with Ulrich Mueller, professor in the Scripps Research Dept. of Cell Biology. "The catecholamines may then overexcite and damage or kill the hair cells. This is a wholly unexpected finding. Previously, we only knew that structural defects of the hair cells could cause deafness. We were surprised to find that an enzyme for catecholamine inactivation is also required for hair cells to survive."

He adds that while the researchers suspect that defects in COMT2 cause only a small percentage of human deafness—mutations in the gene were only found in only about two percent of 192 deaf patients in the study—Beutler says that this

discovery may lead to new understanding about the role that catecholamines play in other forms of deafness and perhaps in other disorders.

The researchers made their discoveries using forward genetics, a field the Beutler group has pioneered, especially in its search for genes involved in immune function. Using this technique, the scientists induce genetic mutations at random with chemicals and look for phenotypic (observable physical or behavioral) changes. In this case, the mice became hyperactive and ran in circles, which is typical of loss of hearing, Beutler says. The scientists then bred the offspring and followed the phenotype across generations in order to map the mutation causing the behavior.

The gene the scientists eventually found encoded a protein that was 35% identical in amino acid structure to COMT, which performed the same function of degrading dopamine, the researchers say.

"In forward genetics, you let the organism tell you what is wrong," Beutler says, "and we are seeing things none of us would have imagined before."

He adds that because COMT mutations probably do not directly cause structural problems within the inner ear, it may one day be possible to treat related deafness with specific therapy that restores catecholamine degradation or prevents catecholamine signaling in the inner ear.

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The first authors of the study are Xin Du and Martin Schwander, both from Scripps Research. In addition to Beutler, Mueller, Du, and Schwander, other authors include: Eva Moresco, Pia Viviani, Claudia Haller, Amanda Roberts, George Koob, and Heather Richardson of Scripps Research; Michael S. Hildebrand and Richard J.H. Smith of the Univ. of Iowa; Kwang Pak and Allen F. Ryan of Univ. of California, San Diego School of Medicine; Lisa Tarantino of the Genomics Institute of the Novartis Research Foundation; and Hossein Najmabadi of the Genetic Research Center (Tehran, Iran).

SOURCE: The Scripps Research Institute