Study identifies molecular process behind form of non-syndromic deafness

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Researchers identify an underlying molecular process that causes a genetic form of non-syndromic deafness in a new study that also suggests affected families may be at risk of damage to other organs.

A multi-national research team led by scientists at Cincinnati Children's Hospital Medical Center report their findings in a study posted online Aug. 27 by the *Journal of Clinical Investigation*. The research opens the door to finding possible treatments for the condition (called DFNB49 non-syndromic hearing loss) and points to possible cellular damage in other organs like the heart, thyroid and salivary glands.

"Understanding the function of a deafness-causing mutation and the mechanism of disease progression is an important first step towards finding a therapeutic solution," said Saima Riazuddin, PhD, senior investigator and a scientist in the Division of Otolaryngology/Head and Neck Surgery at Cincinnati Children's. "But our study on mice also suggests we should clinically evaluate affected individuals more thoroughly, as they may have some other and not very obvious clinical problems involving multiple organs."

DFNB49 non-syndromic deafness is an inherited condition caused by mutations in the gene TRIC. Its "non-syndromic" designation means the hearing loss has not previously been linked to any other medical conditions.

To conduct their study, the researchers developed a first-ever "knock-in" mouse model of DFNB49 deafness by inserting mutations in the corresponding mouse version of the TRIC gene, known as Tric. This led to the loss of a critical protein called tricellulin in the mice.

Researchers report that loss of tricellulin disrupted the structure of what are called tight junctions in the epithelial cells of the cochlea in the inner ear. The authors suggest this affected the permeability of inner ear epithelia tissue, creating a possible channel that caused an imbalance in the quantity of ions and macromolecules. Researchers theorize this resulted in a detrimental environment and loss of cochlear hair cells, leading to hearing loss in the mice.

But the researchers also observed other unexpected characteristics in their newly generated Tric-mutated mice – potentially harmful alterations in the cellular structures of salivary glands, thyroid glands and in heart cells. The animals also had enlarged hearts, livers, spleens and kidneys.

In particular, the scientists pointed to enlarged nuclei in the cardiomyocyte cells of mice, suggesting the possibility that the gene mutation in mice is linked to myocardial hypertrophy in the animals – a dangerous thickening of the heart muscle.

The researchers stressed the need for additional research into their findings but cautioned against the immediate interpretation of data involving mouse models for treatment of human patients. Still, they suggest consideration of their findings is advisable in clinical follow-up of people with DFNB49.

"In previous studies, affected members of DFNB49 families did not reveal any other obvious conditions besides hearing loss, but the human families were not assessed to the same extent as the evaluation we conducted on the tricellulin mutant mice," said Riazuddin. "In light of our current findings, we are beginning to understand the broader function of tricellulin, and this study will guide us for further follow-up clinical evaluations of affected families to help us understand their complete medical spectrum."

Provided by Cincinnati Children's Hospital Medical

Center