New research identifies key mechanism behind some deafness

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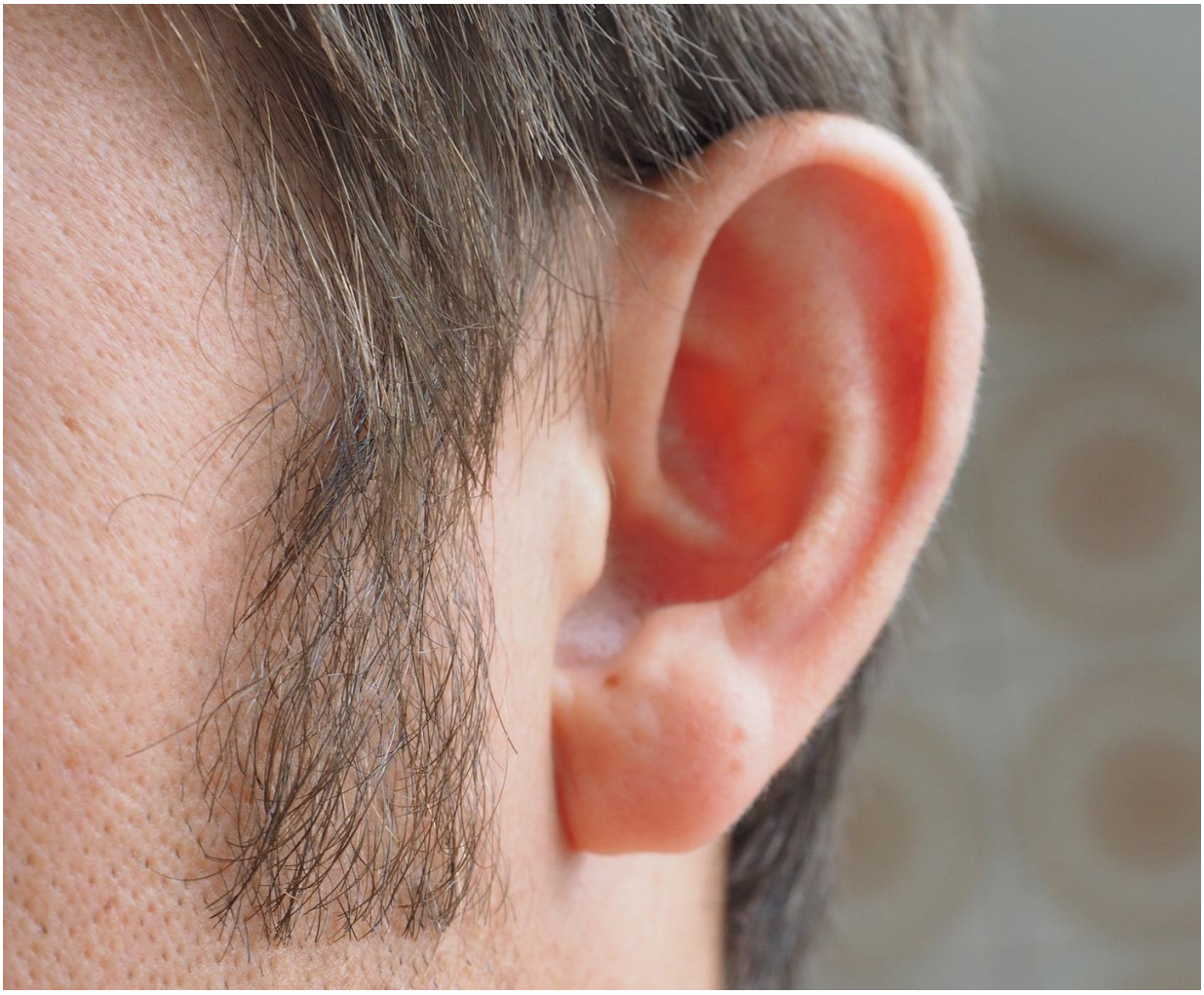

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Although the basic outlines of human hearing have been known for years - sensory cells in the inner ear turn sound waves into the electrical signals that the brain understands as sound - the molecular details have remained elusive.

Now, new research from the University of Maryland School of Medicine (UM SOM), has identified a crucial protein in this translation process.

The findings were published today in the latest issue of *Nature Communications*. The study is the first to illuminate in detail how a particular protein, which is known as CIB2, allows hearing to work.

"We are very excited by these results," said the senior author of the study, Zubair Ahmed, professor in the Department of Otorhinolaryngology-Head and Neck Surgery at UM SOM. "This tells us something new about the fundamental biology of how hearing works on a molecular level."

CIB2, which is short for calcium and integrin-binding protein 2, is essential for the structure of stereocilia, the structures at the top of the sensory hair cells in the inner ear. Stereocilia are extremely small, less than a half a micrometer in diameter, which is about the wavelength of a visible light. Each ear contains 18,000 hair cells that do not divide or regenerate.

Dr. Ahmed and his colleague Saima Riazuddin, professor in the Department of Otorhinolaryngology-Head and Neck Surgery at UM SOM, along with their collaborators, discovered five years ago that CIB2 was involved in hearing. Since then, they have studied this protein in flies, mice, zebrafish and humans. The new study is the first to explain the mechanism behind CIB2 in hearing.

In this study, they genetically engineered mice without CIB2, as well as

mice in which a human CIB2 gene mutation had been inserted. The researchers found that the human mutation affects the ability of the CIB2 protein to interact with two other proteins, TMC1 and TMC2, which are crucial in the process of converting sound to electrical signals. This process is known as mechanotransduction.

People with this mutation cannot turn soundwaves into signals that the brain can interpret, and so are deaf. When the researchers inserted the human CIB2 mutation into the mouse, they found that the mice were deaf.

"This is a big step in determining the identity of key components of the molecular machinery that converts sound waves into electrical signals in the inner ear," said the study's co-senior author, Gregory Frolenkov, of the Department of Physiology at the University of Kentucky.

Dr. Ahmed and his colleagues are now looking for other molecules beyond CIB2 that play a key role in the process. In addition, they are exploring potential therapies for CIB2-related hearing problems. In mice, they are using the gene editing tool CRISPR to modify dysfunctional CIB2 genes. They suspect that if this modification occurs in the first few weeks after birth, these mice, which are born deaf, will be able to hear. The scientists are also experimenting with gene therapy, using a harmless virus to deliver a normal copy of the normal CIB2 gene to baby mice that have the mutated version. Dr. Ahmed says the early results of these experiments are intriguing.

Nearly 40 million Americans suffer from some level of hearing loss. This includes around 74,000 children with profound, early-onset deafness. At least 50 percent of these deafness cases are due to genetic causes.

It is not clear how common CIB2 mutations are in the US population, or

how large a role these mutations play in deafness in humans worldwide. In his research on a group of families in Pakistan that have a higher risk of deafness, Dr. Ahmed has found that about 8 to 9 percent seem to have mutations in CIB2. Overall, he says, the gene could play a role in tens of thousands of cases of deafness, and perhaps many more than that. He is also studying CIB2 among the general population. It may be that some versions of the gene also play a role in deafness caused by environmental conditions, creating a predisposition to hearing loss.

Provided by University of Maryland School of Medicine