Mutated muscle protein causes deafness

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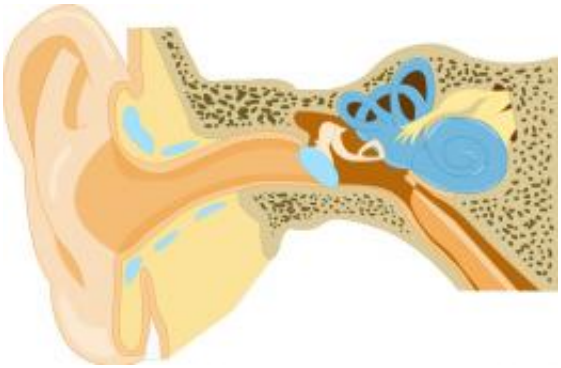

When sound waves reach the snail-shaped structure of the inner ear, sensory cells are activated. If the hair-like cilia of such cells are damaged by a mutation of the SMPX gene, they can no longer respond to acoustic stimuli. Credit: fotolia

(Medical Xpress) -- Excessive noise is not the only thing that causes damage to hearing. In many cases, genetic factors are responsible for the loss of hearing at a young age. Researchers at the Max Planck Institute for Molecular Genetics in Berlin together with colleagues from Nijmegen have discovered a previously unknown genetic cause of progressive hearing impairment: the disease is caused by mutations of the SMPX (small muscle protein) gene, which is located on the X chromosome. It was not previously known that this gene, which is active in the skeletal muscle and heart, also plays a role in hearing. The discovery will make it easier to diagnose progressive hearing impairment and may also provide a starting point for the development of new treatment methods.

Hereditary hearing loss has many causes: researchers have already identified over 50 genes with different functions that could be considered as possible triggers of the disease. However, it is not only the cause of the condition that differs from case to case. The pattern of inheritance is also highly variable. This wide range of possible causes makes it difficult to diagnose the cause of hearing loss and thus poses problems for doctors when counselling patients and their families.

Working in cooperation with colleagues from Nijmegen, scientists at the Max Planck Institute for Molecular Genetics in Berlin have discovered another previously unknown genetic mutation that gradually leads to complete hearing loss. As the researchers discovered, mutations of the SMPX gene can cause deafness.

“In our study, we succeeded in demonstrating for the first time that SMPX is very active in the inner ear,” says Vera Kalscheuer, a scientist at the Max Planck Institute for Molecular Genetics. Up to now, the gene was only known to play an important role in skeletal muscle and in the heart. The researchers were therefore surprised to discover that it is also active in the inner ear. The fact that the mutation only affects the hearing, while the function of the muscles and heart is not impaired, is also astonishing.

The disease-causing mutation involves the substitution of a single base in the genetic material. The mutation in the genetic code causes a premature stop codon. The missing information results in either the premature degradation of the mutated gene transcript or the truncation of the protein, which is unable to function correctly as a result.

Contrary to most X-chromosome disorders, women are also affected by the disease, though usually less severely.

The precise role played by the protein in the hearing process, the

blueprint of which is encoded in the SMPX gene, is presently unknown. The researchers suspect that it is important for the development of the hair cell projections of the cochlea. These fine structures react to sound waves and are responsible for transforming sounds into electrical potential and transmitting them to the auditory centre in the brain. Accordingly, the malfunctioning of these cells, which are known as stereocilia, could be responsible for the hearing impairment.

As part of their study the scientists examined a family that had experienced hereditary hearing impairment across five generations. In order to carry out a targeted search for gene mutations, they concentrated and sequenced all genes of the X chromosome. This led to the discovery of the base substitution in the SMPX gene in all of the family members affected by the hearing impairment. The researchers encountered a second mutation in the course of their analysis which also leads to deafness. During subsequent SMPX mutation search on other families affected by the condition, they discovered a second family with a disease-causing mutation in this gene. This mutation is a deletion of a single base pair which leads to a stop codon and, therefore, the loss of function of the protein.

“Our discovery makes hearing impairment easier to diagnose,” says Vera Kalscheuer. “Up to now, we could only speculate about the function of the SMPX protein.” The next step is to identify the precise role that the protein plays in the hearing process by carrying out functional tests. “When we know the precise mechanism at work here, we can carry out further research and possibly develop new treatment options,” adds the scientist.

More information: Margit Schraders, et al. Next-Generation Sequencing Identifies Mutations of SMPX, which Encodes the Small Muscle Protein, X-Linked, as a Cause of Progressive Hearing Impairment, *The American Journal of Human Genetics* 88, May 13,

2011, pp. 628-34, doi:10.1016/j.ajhg.2011.04.012