New insights into progressive hearing loss

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In parallel studies in human and mouse, two groups of researchers have come to the same conclusion: that a new kind of gene is associated with progressive hearing loss. The new gene - called a microRNA - is a tiny fragment of RNA that affects the production of hundreds of other molecules within sensory hair cells of the inner ear.

The research provides important new genetic understanding of a condition that is common in humans but remains poorly understood.

One team, led by researchers from the Hospital Ramón y Cajal, Madrid, Spain, followed families who showed hearing loss. The second team, led by researchers from the Wellcome Trust Sanger Institute, Cambridge, UK, examined a new line of mice, called diminuendo, that showed progressive hearing loss from an early age. The two groups shared their emerging data.

"We were able quite quickly to show that if the mice carried one copy of the gene variant they suffered progressive hearing loss, if they carried two variants they were profoundly deaf," explains Professor Karen Steel, principal investigator of the programme at the Wellcome Trust Sanger Institute. "The important questions were could we determine what the variant is and how does it exert its effect on hearing?"

In their studies of families with progressive hearing loss, the Spanish team had proposed that the gene responsible lay on human chromosome 7. Both teams set about sequencing every gene in the equivalent genomic regions in human and mouse identified as implicated in hearing loss; the

sequencing showed that most of the genes in the region could not be responsible for hearing loss.

However, they each found that a mutation in a microRNA gene called miR-96 was associated with the hearing loss.

"We know of a number of genes involved in deafness in humans and mice but, to our great surprise, this was one of a new class of genes called microRNAs," explains Professor Miguel Angel Moreno-Pelayo, senior author on the human study, from Hospital Ramón y Cajal and Centro de Investigación Biomédica en Red de Enfermedades Raras, Madrid, Spain.

MicroRNAs are tiny snippets of genetic information that, it is increasingly clear, can have dramatic consequences. Only five years ago, their role in human biology and disease was unknown. Today, it is becoming clear that these little molecules can control the activity of many genes. MicroRNAs can bind to the messengers involved in protein production in cells, disrupting this process.

"No one has seen a disease-causing mutation in the mature sequence of a microRNA," says Dr Moreno-Pelayo. "This is the first microRNA gene associated with hearing impairment and, remarkably, it is the first to be associated with an inherited disorder."

In the mouse, the precise role of the mutation can be examined. Mutation of the miR-96 gene seemed to disrupt development of intricate sensory hair cells in the mutant mice. Mice with two copies of the mutant gene had malformed hair cells from birth and the cells degenerated from an early age. In mice with one copy of the mutant gene, the effects were less severe, but became worse with age.

"The mutation - a change of a single letter of genetic code from A to T -

in this tiny stretch of sequence is enough to lead to dramatic loss of hearing in these mice," explains Dr Morag Lewis, a Sanger Institute scientist, who found this mutation. "We wondered if this single change was preventing the miR-96 from binding to the sites it would normally target to influence gene activity, and looked at ways to determine if this was the case."

The scientists looked at many thousands of messengers to determine which of them seemed altered in the mice with the miR-96 mutation. Significantly, a handful of these seemed to play vital roles in the working of the ear.

"Finding that these targets are affected by the mutation in miR-96 was a real landmark in our studies," says Karen Steel. "Any one of the strongest candidates could have explained the hearing loss effects on its own. It was a really remarkable result.

"We had gone from one amazing result - that this variant microRNA was causing these dramatic effects - to another - that miR-96 does affect genes important for normal hearing and a clear path was laid."

In the human studies, two families showed mutations in miR-96 - but they each carried the mutation at different locations in the miR-96 gene. Intriguingly, neither mutation in humans is the same letter as in the mouse, but all three are close to one another in the miR-96 sequence.

"The mutation in the second family is just one letter away from the mutation in the first and just one away from the mutation in the mouse gene. All three sit in a vital region of seven letters in the mature sequence of miR96" says Dr Angeles Mencía, the Spanish team member who found the human mutations.

Remarkably, then, cases of deafness in two different organisms are both

tied to equivalent microRNAs and to the equivalent region within the microRNA - just seven letters that are known to be important for interacting with the messenger targets.

"The human variants of miR-96 identified in the affected families were found to alter activity of other genes in experiments in test tubes," explains Dr Moreno-Pelayo.

The team also looked to see whether the mutations altered the production or stability of miR-96 and to see whether they affected the normal workings of miR-96. Both the genesis and function of miR-96 were impaired by these human mutations in the lab studies.

Researchers are using models of hearing in the mouse to understand human hearing deficits: by the age of ten, one in 500 children has suffered significant hearing impairment and the majority of over-70s are affected. The same genes have often been shown to be involved in deafness in both the mouse and humans.

The research was part funded by the UK's medical charity for deaf people, Deafness Research UK. The charity's Chief Executive, Vivienne Michael says "Hearing is an exquisitely complex process, involving the intricate interaction of genes and our environment. These exciting studies have opened new avenues to explore to understand better the processes that lead to deafness, with the hope that we will develop new tests and new treatments."

The research team expect that understanding the mechanism by which miR-96 leads to progressive hearing loss will give us clues to help develop therapies to ameliorate the effects of progressive deafness, whatever the trigger.

More information:

The Human Study
Mencía A et al. (2009) Mutations in the seed region of human miR-96 are responsible for non-syndromic progressive hearing loss. *Nature Genetics*
Published online
doi: dx.doi.org/10.1038/ng. 355

The Mouse Study
Lewis M et al. (2009) An ENU-induced mutation of miR-96 associated with progressive hearing loss in mice. *Nature Genetics*
Published online
doi: dx.doi.org/10.1038/ng. 369

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