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Gene therapy involving antibiotics may help patients with Usher syndrome

Barcelona, Spain: A new approach to treating vision loss caused by Type 1 Usher syndrome (USH1), the most common condition affecting both sight and hearing, will be unveiled by a scientist at the annual conference of the European Society of Human Genetics today (Tuesday 3 June). Ms Annie Rebibo Sabbah, from the Genetics Department of the Rappaport Faculty of Medicine, Technion, Haifa, Isreal, will tell the conference that preliminary results using a class of drugs called aminoglycosides, commonly used as antibiotics, had had promising effects *in vitro* and in cell culture.

Usher syndrome is a recessively- inherited disease; in order to have it, the child must receive a mutated form of the Usher gene from each parent. Approximately 3 to 6 percent of all children who are deaf and another 3 to 6 percent of children who are hard-of-hearing have it. In developed countries, about four babies in every 100,000 births have Usher syndrome. Children born with USH1 begin to develop visual problems in early childhood, and these develop quickly into an eye disorder called retinitis pigmentosa, which leads to complete blindness.

“There are several types of genetic mutations involved in Usher syndrome, including nonsense mutations. In this type of mutations the protein in the cell is totally absent, or abnormally short”, says Ms Rebibo Sabbah. “We knew that aminoglycosides are able to suppress nonsense mutations to the extent that, instead of having no protein at all, or a truncated protein, the cell receives a partial amount of full-length protein that may even be functional.”

As a model, the team took several nonsense mutations of the *PCDH15* gene, which is responsible for Usher syndrome. They were able to produce partial suppression of the mutations *in vitro* using commercial aminoglycosides. The same result was achieved *ex vivo*, in cultured cells. /more

“Despite these promising results, the most serious problem with aminoglycosides is their toxicity to the kidney and to the inner ear, which causes limitation in their use”, says Ms Rebibo Sabbah. “We worked with Professor Baasov, from the Chemistry Faculty at Technion, to try to develop a new compound based on aminoglycosides which will have reduced toxicity.”

The scientists tested more than forty new compounds for ones which had the same efficacy as aminoglycosides, but with significantly reduced toxicity. “We found a very promising new compound, called NB30”, says Ms Rebibo Sabbah. “After testing its toxicity in cells, we tried it in mice. In both models the toxicity was significantly reduced compared to the current commercially available aminoglycosides, and we could also see the suppressive activity of NB30 in the cultured cells.”

This is the first time that this therapeutic strategy has been tried in Usher syndrome, the scientists say. Their next step will be to look at another USH1- related gene (*CDH23*) and its nonsense mutations in both humans and mice. “Our final aim is to prove that a nonsense mutation underlying Usher syndrome is capable of being suppressed in vivo in a mouse model by commercial aminoglycosides, and also by NB30, and that this will have a positive effect on retinal function”, says Ms Rebibo Sabbah. “We will also continue to look for new compounds with improved characteristics.”

The researchers hope that their work will lead to therapy to delay the progression and, indeed, the onset, of vision loss in patients with USH1. “Because it is recessively inherited, this is a particularly invidious disease”, says Ms Rebibo Sabbah. “In most cases, parents have normal hearing and vision and are not aware that they are carriers of Usher syndrome. But if they have a child with another carrier, they will have a one in four chance of having a child with the condition at each birth. We need urgently to find an effective treatment.”

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