

The Genetic Basis of Hearing Loss in the Elderly

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Hearing loss is the most prevalent sensory deficiency in humans (Morton and Nance, 2006; Quaranta et al., 2014). Hearing impairment can be genetic and hereditary or acquired by environmental factors. It can be manifested by different severities and ages and may be isolated or as part of a syndrome. It is estimated that about a half of deafness cases are genetic (Nance, 2003). Life with deafness has considerable social and psychological difficulties. In adults, in particular in the elderly, hearing impairment causes communication difficulties, which, in turn, can lead to social isolation (Palmer et al., 2016). Disabling hearing loss is highly prevalent in the elderly population, with about 25% between ages 65-74 and 50% of those aged 75 and above. Epidemiological and clinical studies have demonstrated that hearing loss is associated with cognitive decline in older adults (Lin and Albert, 2014). Given the predicted increase in Alzheimer's Disease in the near future, this association is particularly disturbing, given that there are no optimal solutions for hearing loss in the elderly today.

Genetic treatment for hearing loss is crucial, since the benefit from general solutions for deafness, such as hearing aids, is often low (Almeida et al., 2015; Pisoni et al., 1999). Today about 350,000 patients have been treated with cochlear implants worldwide, but about a third do not benefit from this form of intervention. The number of cochlear implant users is expected to rise and reach one million by the year 2020. Cochlear implants assist in the conversion of sound waves into electrical stimulation of the auditory nerve (Macherey and Carlyon, 2014), but it does not aid changes further along the hearing pathway (Roche and Hansen, 2015; Willaredt et al., 2014). The synchronized and complex route from external air vibrations to perceived sound in the auditory cortex depends on a series of conditions affected by timely and spatially precise gene expression (Dror and Avraham, 2010; Nothwang, 2016). Finally, while some elderly patients use cochlear implants, it still provides better benefit at younger ages (Lin et al, 2012).

My project focuses on the genetic basis for deafness repair using two independent but complementary approaches. The first is "Bedside to bench", encompassing the study of

ATOH1, a bHLH transcription factor crucial for inner ear hair cells (IHC) development (Chen et al., 2002). The inner ear hair cells are the functional sensory cells required for hearing, a fact that makes Atoh1 robustly studied and considered a candidate for hearing repair (Shibata and Raphael, 2010). A clinical study for the safety of CGF166, a recombinant adenovirus 5 vector containing Atoh1 cDNA, is being conducted by Novartis (ClinicalTrials.gov identifier (NCT number) NCT02132130). A mutation of a single base-pair deletion in the ATOH1 gene was discovered in our laboratory, the first reported case of a viable mutation in ATOH1 in humans. The resulting protein is seven amino acids longer and lacks the last four serines (S), two of which are phosphorylated (pS). Our hypothesis predicts that the variant found in ATOH1 changes phosphorylation and as a result increases protein stability. Utilizing a CRISPR-Cas9 generated mutant mouse model, functional tests are being performed and further molecular characteristics, such as altered protein association and stability, are being examined in the animal model and *in vitro*.

The second part of my project is “Bench to bedside”, since although more than 100 mutations are currently implicated in deafness, the majority of the cases remain unsolved. The inner ear and the brainstem are central anchors of the hearing pathway and based on previous work, are suggested to have a shared genetic program (Duncan and Fritzsche, 2012; Willaredt et al., 2014). We suggest that by mapping the common transcriptional program of these components, we will gain a better understanding of hearing development and pathology. mRNA and microRNA (miRNA) for time points during hearing development will be sequenced from both inner ear sensory epithelium and the superior olivary complex (SOC). This will be followed by bioinformatics analysis to elucidate differentially expressed transcripts. Finally, functional analysis will be carried out for common pathways.

I envision that the convergence of these two different approaches will provide a more wholesome understanding of the formation of the normally functioning hearing organ and provide a comprehensive, variant dependent approach, for the personalized treatment of hearing impairment, along with the possibility of hearing regeneration. The work will have relevant implications for the elderly, given the prevalence of this sensory defect in the aging population.

Bibliography

- Almeida, RP de, Matas, CG, Couto, MIV, Carvalho, ACM de. 2015. Quality of life evaluation in children with cochlear implants. *Codas* 27: 29–36.
- Chen, P, Johnson, JE, Zoghbi, HY, Segil, N. 2002. The role of Math1 in inner ear development: Uncoupling the establishment of the sensory primordium from hair cell fate determination. *Development* 129: 2495–2505.
- Dror, AA, Avraham, KB. 2010. Hearing impairment: a panoply of genes and functions. *Neuron* 68: 293–308.
- Duncan, JS, Fritsch, B. 2012. Transforming the vestibular system one molecule at a time: the molecular and developmental basis of vertebrate auditory evolution. *Adv. Exp. Med. Biol.* 739: 173–186.
- Lin, FR, Albert, M. 2014. Hearing loss and dementia – who’s listening? *Aging Ment. Health* 18: 671-673.
- Lin, FR, Chien, WW, Li, L, Niparko, JK, Francis, HW. 2012. Cochlear implantation in older adults. *Medicine (Baltimore)*. 91: 229-241.
- Macherey, O, Carlyon, RP. 2014. Cochlear implants. *Curr. Biol.* 24: R878–R884.
- Morton, CC, Nance, WE. 2006. Newborn hearing screening--a silent revolution. *N. Engl. J. Med.* 354: 2151–2164.
- Nance, WE. 2003. The genetics of deafness. *Ment Retard Dev Disabil Res Rev* 9: 109–119.
- Nothwang, HG. 2016. Evolution of mammalian sound localization circuits: A developmental perspective. *Prog. Neurobiol.* 141: 1–24.
- Palmer, AD, Newsom, JT, Rook, KS. 2016. How does difficulty communicating affect the social relationships of older adults? An exploration using data from a national survey. *J Commun Disord* 62: 131–146.
- Pisoni, DB, Cleary, M, Geers, AE, Tobey, EA. 1999. Individual differences in effectiveness of cochlear implants in children who are prelingually deaf: new process measures of performance. *Volta Rev* 101: 111–164.

Quaranta, N, Coppola, F, Casulli, M, Barulli, MR, Panza, F, Tortelli, R, Capozzo, R, Leo, A, Tursi, M, Grasso, A, Solfrizzi, V, Sobbà, C, Logroscino, G. 2014. The prevalence of peripheral and central hearing impairment and its relation to cognition in older adults. *Audiol Neurootol* 19 Suppl 1: 10–14.

Roche, JP, Hansen, MR. 2015. On the horizon: cochlear implant technology. *Otolaryngol. Clin. North Am.* 48: 1097–1116.

Shibata, SB, Raphael, Y. 2010. Future approaches for inner ear protection and repair. *J Commun Disord* 43: 295–310.

Willaredt, MA, Ebbers, L, Nothwang, HG. 2014. Central auditory function of deafness genes. *Hear. Res.* 312: 9–20.