Identification of Deafness-Causing Mutations Using Proteomics-Identified Candidates

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Abstract

This new project couples proteomics (Gillespie), human genomics (Richard J. Smith, University of Iowa), and mouse molecular genetics (Ulrich Müller, Scripps) in an integrated program for identification and description of molecules essential for hearing and balance. The proteomics work will be done at OHSU/PNNL and is described here. When studying monogenic and complex genetic diseases, standard linkage mapping and/or association approaches to identify disease-relevant genes suffer from low throughput and lack of insight into function. Our approach provides high throughput in a contextual functional framework. We begin by noting that specific organelles are often implicated in disease. Focusing on the auditory system, we will first define the complete proteome (especially the membrane proteome) of the hair bundle, the mechanically sensitive organelle of sensory hair cells, which comprises <<1% of total protein in inner-ear epithelia. This work will be carried out at OHSU/PNNL by the Gillespie lab. Second, to link new genes to auditory disease, we will use next-generation sequencing to interrogate *en masse* the genes encoding bundle proteins in hundreds of affected families with uncharacterized forms of hearing loss. Sequencing will be carried out at Iowa by the Smith lab. Third, we will generate mouse lines carrying the orthologous human mutations and analyze the functional consequences of these mutations on bundle-protein networks. These mice will be generated by the Müller lab at Scripps, then mutant hair bundles will be examined using proteomic techniques by the Gillespie lab at OHSU/PNNL. This project is iterative, so novel members of disrupted networks will be screened in human families as well. This composite approach provides an understanding of a disease phenotype at the molecular level, knowledge requisite to developing novel approaches to disease treatment.