

## **Rare Genetic Variation in Early Onset Presbycusis Patients and Their Offspring**

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Age-related sensorineural hearing loss (ARSHL), or presbycusis, is a major public health issue. ARSHL is heritable, yet common genetic variation identified via large-scale genome-wide association studies explains a small fraction of its phenotypic variance (sometimes referred to as the “missing heritability” problem). By contrast, recent work suggests that rare functional variation within genes previously identified for nonsyndromic congenital deafness may confer substantial risk for early onset ARSHL (EOARSHL). This study will collect phenotypic, whole-exome sequencing and copy–number variation data in EOARSHL probands, their normal-hearing offspring, and normal-hearing controls age- and sex-matched to the offspring. Variants will be annotated and partitioned into deafness gene networks. Aim 1 is to demonstrate that rare functional variants are preferentially located in deafness gene networks in EOARSHL. Aim 2 is to discover “early warning signs” of presbycusis by comparing various aspects of auditory function, such as cochlear synaptopathy, high-frequency thresholds, suprathreshold discrimination abilities, and self-reported real-world hearing experiences, in offspring who have inherited rare functional variants from probands (who are at high genetic risk for presbycusis) to controls (with normal genetic risk). This study has two innovative features. First, identifying genetic risk variants that are rare, functional, and of large effect via extreme cases of presbycusis may provide valuable insights because such variants are amenable to biological experimentation and may be leveraged to improve prediction, diagnosis, and treatment. Second, identifying warning signs of presbycusis years before the onset of primary symptoms would be a major boon for early detection, prediction, and management strategies.