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Pendred syndrome is a disorder characterized by a spectrum of symptoms, of which severe to profound hearing loss is most notable. Resulting from mutations in the *SLC26A4* gene, Pendred syndrome is estimated to account for between 5-10% of all hereditary hearing loss1. The *SLC26A4* gene encodes the transmembrane solute transporting protein Pendrin, which localizes to the plasma membrane of the inner ear, thyroid, and kidneys2. Recent research has identified over 200 different mutations of the *SLC26A4* gene2 that result in the formation of a mutant form of the Pendrin protein that exhibits a loss-of-function. The altered protein fails to transport anions in the normal capacity from conception, which in the inner ear manifests in atypical formation of an enlarged vestibular aqueduct in the temporal bone, along with a spectrum of other symptoms3. *While the physical phenotypes resulting from mutations in SLC26A4 are recognized and understood, additional genomic and proteomic research is required to elucidate the role of SLC26A4 in the sensory role of hearing, and also necessary to achieve a scientific understanding of the implications of variability at specific locations within the gene*.

**Here, I will test the *hypothesis* that location of nucleotide variability within the *SLC26A4* gene sequence will predict phenotypic outcomes associated with sensory hearing, as well as predict symptoms of congenital syndromic hearing loss attributed to Pendred syndrome.** This hypothesis was formulated through analysis of previously published cohort studies[2,4-6]in association with mouse model studies on *SLC26A4* expression[3,7-9]. The collective data reviewed in preparation for this proposal indicates that the location of the mutation within the *SLC26A4* gene influences Pendrin protein function in varying degrees, manifesting in different phenotypic symptoms.

The ***long-term* goal** is to understand the phenotypic manifestations of nucleotide variability within the *SLC26A4* gene depending on the mutation location within the gene. This understanding could then be applied on the order of population health in the diagnosis of Pendred syndrome and prediction of disorder phenotypes specific to individuals. The ***objective*** is to identify conserved regions of the *SLC26A4* gene between species with assorted hearing aptitudes as well as analyze of regions variability and constraint within a species. Focusing on genomic and proteomic perspectives, this study will pursue the following ***specific aims:***

1. **Identify regions of evolutionary constraint and variability within the *SLC26A4* gene between human and bat species.** I propose that regions of residue or nucleotide variability will correlate to regions within the *SLC26A4* gene that affect Pendrin function. In addition, I propose that the identified regions of variability between bats and humans account, in part, for the superior hearing abilities demonstrated by the bat species.
2. **Comparison of distinctive *SLC26A4* mutations and correlation to phenotypes between different geographical human populations**. Preliminary data insinuates that the location of mutation within the *SLC26A4* gene may predict the symptoms experienced by individuals with Pendred syndrome. My goal is to correlate domain or motif specific mutations with explicit phenotypic variants.
3. **Quantification of expression levels of Pendrin in longitudinal study and comparison of expression levels between species at defined developmental stages.** The congenital onset and irreversible nature of the disorder suggests that Pendrin expression levels peak in the embryonic or fetal phase of development. My goal is to determine expression patterns using a microarray assay followed by comparative analysis of expression levels between evolutionarily diverse species to determine the role *SLC26A4* in sensory hearing.

The *predicted outcomes* of the genomic and proteomic analyses conducted in this work will elucidate the roles of nucleotide variability correlation to phenotype on both individual and species platforms. The application of this work will have a positive impact, because exposition of the roles specific mutations within the *SLC26A4* gene*,* applied on the scale of population health, will allow for accurate prediction of Pendred syndrome symptoms on an individual basis, as well as enriching the scientific knowledge of the human genome and proteome.

**References**

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