Deep Phenotyping and Computational Modeling of Highly Diverse Forms of Hearing Loss Due to Specific Gene Mutations Identified in Families from Newfoundland, Canada

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ABSTRACT

Many diverse genetic disorders have been molecularly characterized from the genetically isolated human population of Newfoundland, Canada. In some of these disorders, unrelated patients have been found to carry the exact same underlying genetic mutation due to a recent shared ancestor, the result of natural population expansion from a limited number of English and Irish settlers in the late 1700s. Among these, four distinct forms of genetic hearing loss have been recently reported: a **CLDN14** autosomal recessive mutation, affecting the protein Claudin14 that regulates the formation of tight cellular junctions, produces precipitous mid/high frequency hearing loss at around 4-6 years of age; a **FOXL1** autosomal dominant mutation affecting the signaling protein FOXL1 gives rise to otosclerosis; a **KCNQ4** autosomal dominant mutation affecting the Kv7.4 ion channel leads to progressive high frequency hearing loss; and a **WFS1** autosomal dominant mutation, affecting the protein Wolframin that is involved in intracellular Ca^{2+} regulation, gives rise to a nonsyndromic low-frequency hearing loss.

The long-term goal of this project is to characterize the pathophysiology and resulting perceptual deficits experienced by affected family members. Computational models incorporating this pathology will then be utilized to develop improved hearing aid amplification strategies. The first stage of this project focuses on deep phenotyping of affected members of the KCNQ4 and WFS1 families, including the acquisition of advanced electrophysiological recordings (ABR and ECochG), psychophysical tuning curves, DPOAE growth functions, and word perception in quiet and noise, in addition to routine audiometric measures. The data from these recordings is being used, along with available animal models of the gene mutations, to inform the incorporation of appropriate pathology into the Bruce et al. (Hear. Res. 2018) model of the auditory periphery. Quantitative predictions of the electrophysiological and speech intelligibility data will be used for model validation. In this presentation, we will report on the analysis of deep phenotyping data collected from several members of each family and on computational models fit to those data. The impaired models will subsequently be used to optimize hearing aid amplification strategies to compensate for specific deficits caused by these genetic mutations, along with other individuals with similar patterns of pathophysiology.

AUDIOLOGICAL ASSESSMENT

A comprehensive assessment of each subject included:

- **Auditory Brainstem Response (ABR)** - Estimates of Waves I, III, and V at presentation rates of 19.5/s, 234.3/s, and 507.8/s of a 80 dB nHL alternating polarity 100 µs click using continuous loop average deconvolution (CLAD; Delgado and Ozdamar, 2004). CLAD sequences facilitated neural adaptation. Responses were acquired using vertical and horizontal montages with Etymotic ER3 transducers and foam-tip inserts.
- **Electrocochleography (ECochG)** - Estimates of cochlear microphonic, summation potential and action potential at presentation rates of 19.5/s, 234.3/s, and 507.8/s of a 80 dB nHL alternating polarity 100 µs click using CLAD. Responses were acquired using vertical and horizontal montages with an extratympanic wick electrode.
- **Sweeping Psychophysical Tuning Curves (SWPTC)** - Estimates of absolute threshold, Q10 and tip frequency of tuning curve at 0.5, 1, 2 and 4 kHz (Sęk and Moore, 2011). Broadened tuning indicates OHC impairment while tip shifts indicate cochlear dead regions.
- **Distortion Product Otoacoustic Emissions (DPOAEs)** - Kummer et al. (1998) protocol $2f1 - f2$ DPOAE frequency sweeps and input-output functions to estimate location of lesion boundaries.
- **Word Perception in Quiet and Noise** - NU-6 word test in quiet and in multi-talker babble.
- **Immittance Testing** - Comprehensive immittance and middle-ear reflexes tested using standard tympanogram, 3D tympanometry, wideband absorbance, and ipsi-lateral and contra-lateral reflexes at 0.5, 1, 2, 3, 4 kHz and wideband response.
- **Audiometric Thresholds** - Pure tone air conduction (0.125, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 kHz and high frequencies at 8, 9, 10, 11.2, 12.5, and 14 kHz) and bone conduction (0.25, 0.5, 1, 2 and 4 kHz) testing with masking. Clinical speech reception thresholds are also measured.

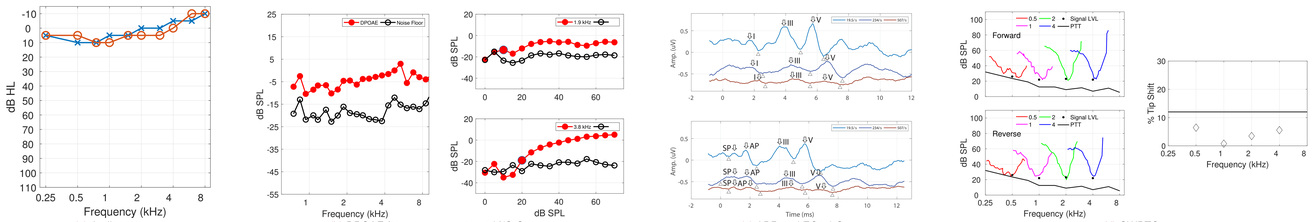
KCNQ4 AND WFS1 GENOTYPES

Deep phenotyping is being conducted on the families with the mutations:

- **KCNQ4** - This autosomal dominant mutation affects the Kv7.4 ion channel, part of a family of potassium channels found in cells of the inner ear and the auditory nerve pathway. Improper regulation of K^+ ions leads to nonsyndromic, progressive high frequency hearing loss. Approximately 16 individuals in this family appear to be affected. A complete test battery has been conducted on 6 subjects to date.
- **WFS1** - Another autosomal dominant mutation affecting the protein Wolframin that is involved in intracellular Ca^{2+} regulation. It gives rise to a nonsyndromic, low-frequency hearing loss. Approximately 28 individuals in this family appear to be affected. A complete test battery has been conducted on 2 subjects to date.

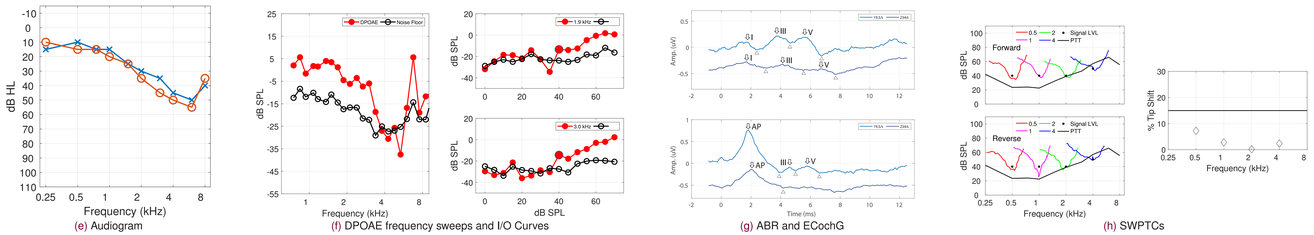
Complete datasets have also been collected for 5 normal hearing controls.

Example Normal Hearing Subject



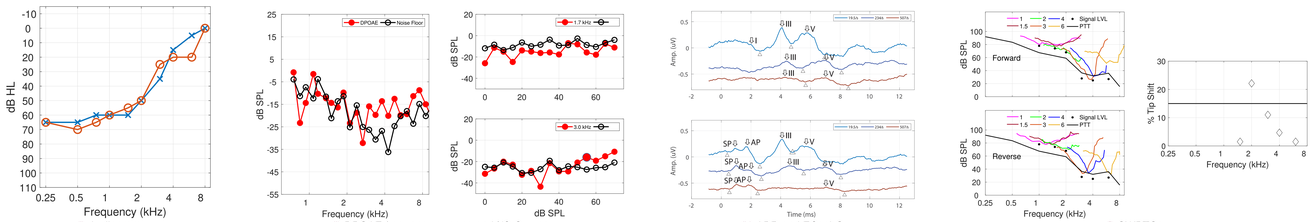
(a) Audiogram (b) DPOAE frequency sweeps and I/O Curves (c) ABR and ECochG (d) SWPTCs

Example KCNQ4 Subject



(e) Audiogram (f) DPOAE frequency sweeps and I/O Curves (g) ABR and ECochG (h) SWPTCs

Example WFS1 Subject



(i) Audiogram (j) DPOAE frequency sweeps and I/O Curves (k) ABR and ECochG (l) SWPTCs

ECochG POPULATION DATA

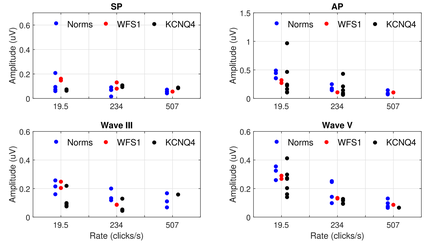


Figure 1: ECochG SP, AP, Wave III and Wave V amplitudes as a function of CLAD sequence click rate

MODELING APPROACH

Modeling of ABR and ECochG responses is based on a quantitative model that computes the convolution of the instantaneous discharge rates of the "humanized" nonlinear auditory-nerve model of Bruce, Erfani and Zilany (Bruce et al., 2018) and an empirically determined unitary response function that is assumed to reflect various cell contributions within the auditory brainstem (Rønne and Dau, 2012).

The unitary response function is determined by,

- Setting IHC, OHC & AN impairment in the auditory periphery model from assessments of audiogram, DPOAE and SWPTC data from a subject.
- Recording evoked potentials from the subject and generating a compound PSTH (cPSTH) from the model using CLAD and non-CLAD click sequences.
- Computing the unitary response by deconvolving the average cPSTH out of the subject's averaged evoked response.

A single deconvolution operation is required for non-CLAD click stimuli. Additional deconvolution operations are necessary for the CLAD click stimuli.

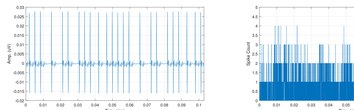
MODELING APPROACH - CONTINUED

Figures 2, 3 and 4 illustrate the empirical derivation of the unitary response from the PSTH generated using the auditory model and the subject's evoked response for CLAD click stimuli.

The steps required to compute the unitary response are,

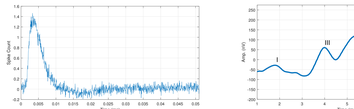
- A CLAD sequence is used to compute a PSTH using the auditory periphery model (see Fig. 2).
- The PSTH is deconvolved with the CLAD sequence, segmented and averaged to generate the compound PSTH. The D.C. offset of the compound PSTH is removed (see Fig. 3).
- The recorded subject evoked response is similarly deconvolved, segmented and averaged to produce the grand average evoked response.
- The unitary response is computed by deconvolving the cPSTH out of the evoked response (see Fig. 4). Fig. 4b shows the estimated UR function obtained via three different deconvolution methods compared to a ground-truth UR function from Rønne and Dau (2012) that was used to generate a test ABR signal.

MODELING APPROACH - CONTINUED



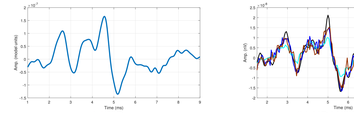
(a) CLAD Stimuli (b) PSTH

Figure 2: Step 1 of UR Computation



(a) cPSTH (b) Average Evoked Response

Figure 3: Step 2 of UR Computation



(a) UR (b) UR Validation

Figure 4: Step 3 of UR Computation and UR Validation

Similar UR functions across the normal hearing, KNCQ4 and WFS1 subjects will be indicative of pathophysiology that is primarily cochlear in nature. If this is the case, further refinement of the IHC, OHC & AN impairment in the model will be used to optimize the ABR and ECochG predictions.

If the UR functions in the KNCQ4 and/or WFS1 subjects vary greatly from the normal hearing controls, this will indicate central auditory deficits that will need to be described by a more detailed brainstem and midbrain neural circuit model.

The validity of the model parameters will also be assessed by predicting Words-in-Quiet and Words-in-Noise test data.

CONCLUSIONS

- Initial data suggest:
  - KNCQ4 mutation primarily affects OHCs in the base of the cochlea and possibly ANFs along the entire length.
  - WFS1 mutation has a mixed effect on OHCs & IHCs in the apex of the cochlea and possibly ANFs along the entire length.

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