Genetic Background Impacts the Severity of Hearing Loss in *Tecta* Mutant Mice

A. Monique Weaver[1]; Kevin T. Booth, PhD[1,2]; Hela Azaiez, PhD[1]; Richard J.H. Smith, MD[1]
[1]Molecular Otolaryngology and Renal Research Laboratories, University of Iowa, Iowa City, IA, USA
[2] Department of Neurobiology, Harvard Medical School, Boston, Massachusetts, USA

Introduction

- Alpha-tectorin is important for proper tectorial membrane (TM) structure and organization (Fig. 1).
- The *Tecta* mutant mouse has a disorganized TM that lacks all non-collagenous components the consequence of which is hearing loss.

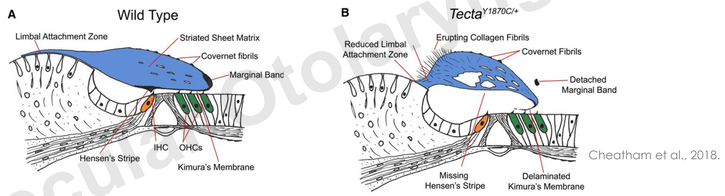

Figure 1. Tectorial membrane structure. Wild type TM structure (A) and mutant TM structure (B)

- Mutations in *TECTA* are also responsible for non-syndromic hearing loss in humans.
- Previous work in our lab has shown differences in audioprofiles between Japanese and European/American cohorts with *TECTA* mutations (Figure 2).
- These results suggest that either environmental or genetic factors are impacting the degree of hearing loss in these populations.
- Therefore, our objective was to investigate the hypothesis that other genes act as modifiers by altering *TECTA*-related hearing loss.

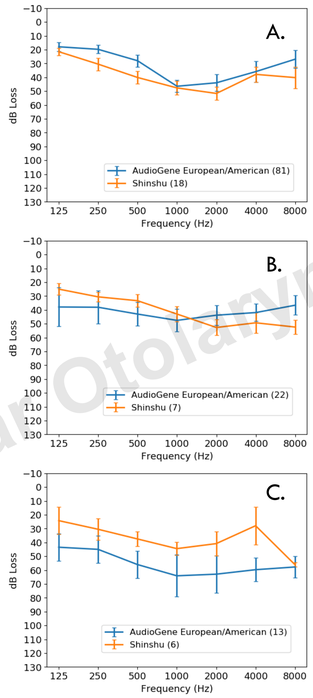

Figure 2. Audioprofiles of European/American and Japanese cohorts. Ages 0-19 (A), 20-39 (B), and 40-59(C). Significant differences were seen between the two cohorts (p = 0.0108871). Daniel Walls et al., pending publication

Materials and Methods

- Two *Tecta* mutant mice, *TECTA*^{C1619S} and *TECTA*^{C1837G} , were backcrossed to three background strains, resulting in the four mutant strains seen in Figure 3B.
- The cysteine-to-serine substitution occurs at the zonadhesin (ZA) domain, while the cysteine-to-glycine substitution occurs in the zona pellucida (ZP) domain (Figure 3A).
- CBA/J and FVB/NJ backgrounds were selected because of their relatively normal hearing, while C57BL/6 was selected because it is known to have age-related hearing loss.
- All hearing thresholds were obtained by measuring auditory brainstem responses (ABRs) on mice approximately 4 weeks old (p 27-32).
- Statistical analysis was done using MANCOVA and MANOVA tests.

Background-Specific Hearing Thresholds

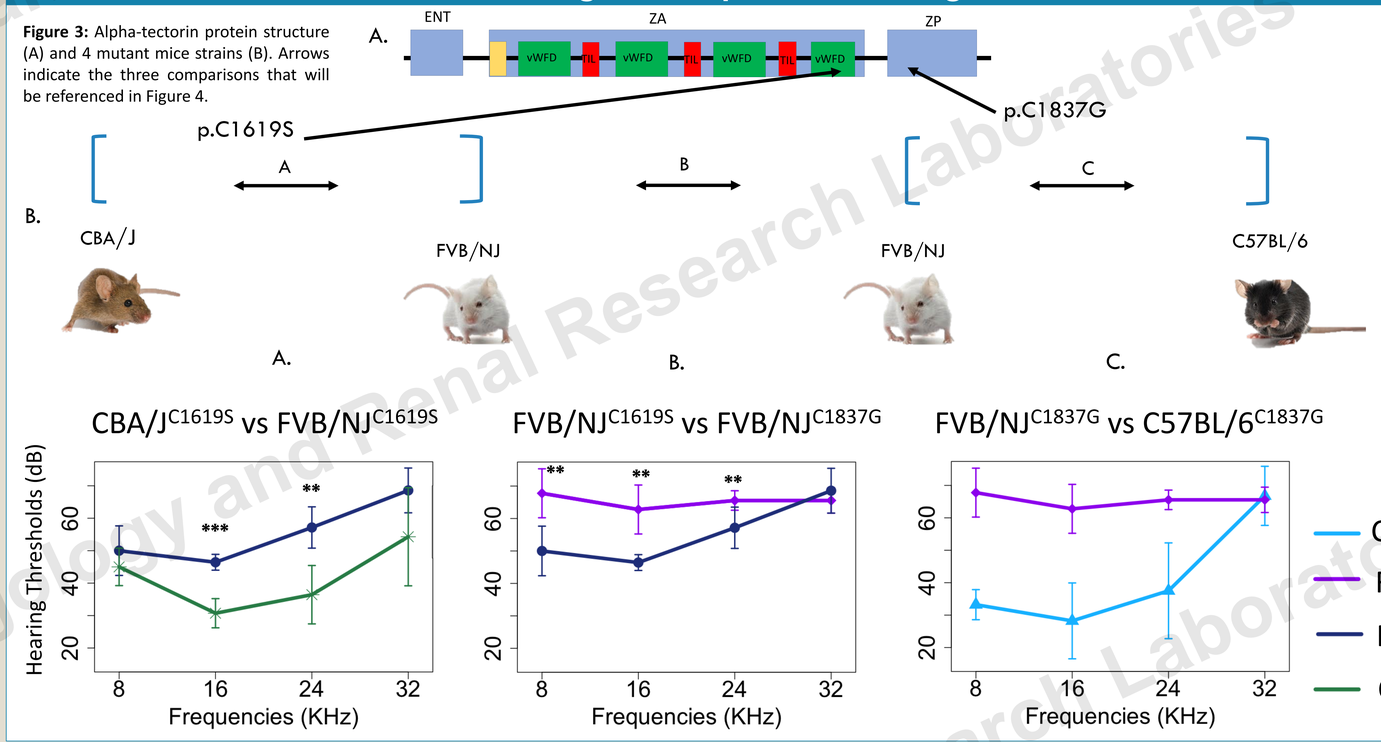

Figure 3: Alpha-tectorin protein structure (A) and 4 mutant mice strains (B). Arrows indicate the three comparisons that will be referenced in Figure 4.

Figure 4: Hearing thresholds of one-month-old hetero-zygous mice. Comparison between CBA/J and FVBN/J mice with the p.C1619S mutation (A), and between FVBN/J and C57BL/6 mice with the p.1837G mutation (C). Also, results in FVB/NJ mice with the two mutations (B). These comparisons are referred to in Figure 3B.

Results

Significant differences were observed between (Table 1):

- CBA/J and FVBN/J mice with p.C1619S mutations (Fig. 4A).
- C57BL/6 and FVB/NJ mice with p.C1837G mutations (Fig. 4B).
- p.C1837G and p.C1619S mutant mice (Fig. 4C)

No significant difference was observed between wild type mice (Fig. 5)

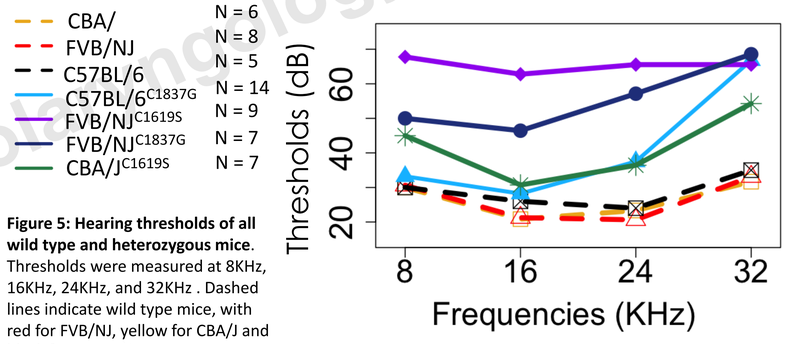

Figure 5: Hearing thresholds of all wild type and heterozygous mice. Thresholds were measured at 8KHz, 16KHz, 24KHz, and 32KHz . Dashed lines indicate wild type mice, with red for FVB/NJ, yellow for CBA/J and black for C57BL/6

Table 1.

Comparison	Overall P-value	8 KHz	16 KHz	24 KHz	32KHz
A	**2.937e-06 *** **	0.2085	**1.539e-06 *** **	**0.0005775 ** **	0.03032
B	**0.0001175 ** **	**0.0005154 ** **	**0.0001473 ** **	**0.004687 ** **	0.19633
C	**6.657e-09 *** **	**1.819e-11 *** **	**2.223e-07 *** **	**2.103e-05 *** **	0.7121

* p < .01, ** p < .005, *** p < .0001

Conclusions

- We present the novel finding that depending on genetic background, a single *Tecta* mutation can give rise to multiple phenotypes
  - Replicated with two distinct mutations
  - FVB/NJ mice demonstrated the most severe hearing loss
  - Further work is on-going to identify the specific genes acting as genetic modifiers

References

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Acknowledgements

Supported in part by NIDCD DC003544, DC002842 and DC012049 (RJHS) and NIH Predoctoral Tranining Grant T32GM008629 (AMW).