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18.08.2024 **Date**

## **RE: Application for the Research Award Tinnitus & Hearing 2024**

Dear Professor Dr. Christian Dobel,  
Dear Professor Dr. Birgit Mazurek,

I am pleased to submit the study titled "PKHD1L1, a gene involved in the stereocilia coat, causes autosomal recessive nonsyndromic hearing loss" for consideration for the Research Award Tinnitus & Hearing 2024. I had the pleasure to co-lead this study with two investigators from Harvard Medical School: Prof. Artur A. Indzhykulia (Mass Eye & Ear) and Prof. A. Eliot Shearer (Boston Children's Hospital). Through the identification of four families with recessive genetic variants in *PKHD1L1*, we were able to provide conclusive evidence to assert that *PKHD1L1* is a novel gene for human sensorineural hearing loss (DFNB124) for the first time with implications that will improve the molecular genetic diagnoses of patients around the world. We carefully reviewed the history of hearing loss in the affected individuals and determined that all individuals had congenital, sensorineural hearing loss that was progressive. Progressive forms of autosomal recessive hearing loss are rather rare and of particular interest with a potentially large window for therapeutic intervention. We functionally investigated the function of each variant identified in the patients. Briefly, the missense variants reduced protein folding and stability. One of these was also identified as causing aberrant RNA splicing. Finally, as an immense honor, this work was featured in the Spring 2024 issue of Harvard Otolaryngology Magazine and highlighted the collaborative efforts between Mass Eye and Ear, Boston Children's Hospital and the University Medical Center Göttingen (<https://oto.hms.harvard.edu/harvard-otolaryngology>).

This work will undoubtedly further improve genetic diagnostic rates in individuals with hearing loss around the world. As a future outlook, our work is currently focused on going deeper with the natural

history of disease to refine understanding of the therapeutic window, as well as exploring pre-clinical therapeutic development to delay or prevent progressive decline of hearing thresholds.

This work is not under consideration for another award elsewhere and represents an important finding on the quest to uncover all molecular targets of the inner ear.

If further information is requested, please let me know. Thank you in advance for your time and support.

Sincerely yours,



Dr. Barbara Vona

**Enclosures:**

- Short description of the submitted scientific work and significance
- Curriculum vitae with description of academic career
- List of publications
- Published work "PKHD1L1, a gene involved in the stereocilia coat, causes autosomal recessive nonsyndromic hearing loss" by Redfield...Vona, 2024
- Confirmation that the work has not been submitted for any other prize with signature assurance that all co-authors agree to submission for the research award