Editorial

Barbara Vona* and Thomas Haaf

Hereditary auditory disorders

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Hearing loss (HL) is the most common sensory disorder and, from a human genetic perspective, an extremely heterogeneous and challenging disease. Recent statistics from the World Health Organization estimate that HL affects approximately 466 million individuals globally, which corresponds to roughly 6 % of the world population [1]. Its etiology falls under three umbrellas; namely, acquired, idiopathic, or genetic, with most idiopathic cases suspected to have a genetic cause. Especially in young children and adults, over half of HL is due to a genetic etiology, and there are several recently discovered associations of genetic susceptibility in age-related HL and other otological conditions such as otitis media. As a testament to its extreme genetic heterogeneity, with the notable exceptions of *GJB2* and *STRC*, even the most prevalently involved genes in HL are extremely rare. HL can be part of a syndrome or appear isolated, as in the case of non-syndromic HL. Two lines of evidence support that the field of auditory genetics is still in its infancy: Firstly, current diagnostic rates for HL patients underscore the poorly characterized genetic landscape for auditory disfunction, suggesting that gene discovery is still in the relatively early stages. Secondly, the most recent estimates from mouse studies suggest that as many as 1000 genes may play a critical role in hearing [2], many of which are presently uncharacterized in humans.

As with many other fields, scientific and technical advancements have propelled the field forward, in terms of uncovering novel genes involved in HL, disclosing the molecular genetic signatures in known genes, and the development of therapeutics. However, these advancements have yielded a new set of challenges with respect to comprehensive testing and variant interpretation, overcoming uncertainties that arise with syndromic features, addressing challenges in diagnostics for common and rare disorders of the inner ear, and finally, translational prospects for therapy development and delivery to the inner ear. This issue aims to provide an insight into several highly relevant and timely topics and underscores the importance of genetic testing for patients with hereditary HL.

The first article by Marina T. DiStefano and colleagues addresses the importance of collaborative efforts to curate genes associated with HL and develop expert, HL-tailored amendments to the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) guidelines to establish evidence-based specifications for variant interpretation. This article highlights the efforts of the ClinGen Hearing Loss Working Group and their expert panels that are tasked to curate variants and genes, through analysis of gene-disease relationships. These efforts only serve as the "tip of the iceberg" in terms of the enormous work that is required to improve genetic diagnoses of patients with HL.

Next, we summarize the clinical and diagnostic challenges involved in non-syndromic HL genetic diagnostics. Among one of the most challenging aspects impacting clinical management and counseling is the ability to diagnose and distinguish sub-clinical or pre-symptomatic syndromes for timely interventions. Worldwide diagnostic yields vary wildly according to patient ethnicity, with Africa, parts of Europe, Asia, and most of South America being "black boxes". Patients who achieve a molecular genetic diagnosis may benefit from tailored selection of the best currently available treatment modalities, and those under development in the future, as well as understanding about possible progression and prognosis.

The following article by Hanno J. Bolz describes one of the most relevant deafness syndromes. Usher syndrome is grouped into three clinical subtypes based on the coexistence of early onset, usually congenital, sensorineural HL, presence or absence of vestibular dysfunction, and age of onset of retinitis pigmentosa. A genetic diagnosis of Usher syndrome can be challenging and have tremendous implications in genetic counseling. Many diagnostic gaps that include the detection of all variants (i. e. deep intronic variants and CNVs) and interpretation of variants, as well as clinical overlap between Usher syndrome and other genetic disorders involving the auditory and visual systems will be discussed. Therapeutic developments in Usher syndrome have shown great promise in recent years.

***Corresponding author: Barbara Vona,** Tübingen Hearing Research Centre, Department of Otolaryngology – Head & Neck Surgery, Eberhard Karls University, Elfriede-Aulhorn-Strasse 5, 72076 Tübingen, Germany, e-mail: barbara.vona@uni-tuebingen.de
Thomas Haaf, Institute of Human Genetics, Julius-Maximilians University Würzburg, Biozentrum, Am Hubland, 97074 Würzburg, Germany, e-mail: thomas.haaf@uni-wuerzburg.de

Rare inner ear disorders with a genetic component are especially challenging to understand, diagnose, and treat. Martinez-Gomez and colleagues describe Meniere's disease, a heterogeneous inner ear disorder that is characterized by vertigo attacks, fluctuating sensorineural HL, tinnitus, and aural fullness. The authors summarize the clinical criteria and very recent insights into genetic findings linked to this debilitating disorder.

Finally, Morgan, Schott and colleagues provide a comprehensive look at therapeutic possibilities for hereditary HL. They describe considerations with respect to anatomical approaches, types of therapies, modes of delivery, and the current state of therapeutic developments. The field is moving toward the goal of translating genetic diagnoses to patient-tailored therapies in previously unimaginable ways, and this article is a fitting summary of the state of the art in the field.

We sincerely thank the authors for their valuable contributions to this issue that is dedicated to hereditary HL. We hope to increase visibility of an often underdiagnosed and invisible disorder and to foster interdisciplinary work to improve the healthcare of individuals with all forms of hereditary HL.

Conflict of interest: The authors declare that they have no competing interests.

References

[1] Davis AC, Hoffman HJ. Hearing loss: rising prevalence and impact. Bull World Health Organ. 2019;97:646.
[2] Ingham NJ, Pearson SA, Vancollie VE, Rook V, Lewis MA, Chen J, Buniello A, Martelletti E, Preite L, Lam CC, Weiss FD, Powis Z, Suwannarat P, Lelliott CJ, Dawson SJ, White JK, Steel KP. Mouse screen reveals multiple new genes underlying mouse and human hearing loss. PLoS Biol. 17(4):e3000194.

Dr. Barbara Vona
Tübingen Hearing Research Centre, Department of Otolaryngology – Head & Neck Surgery, Eberhard Karls University, Elfriede-Aulhorn-Strasse 5, 72076 Tübingen, Germany
barbara.vona@uni-tuebingen.de

Prof. Dr. Thomas Haaf
Institute of Human Genetics, Julius-Maximilians University Würzburg, Biozentrum, Am Hubland, 97074 Würzburg, Germany
thomas.haaf@uni-wuerzburg.de