HEARING IMPAIRMENT IS A HIGHLY PREVALENT DISORDER IN HUMANS, with significant hearing loss present in ~278 million people worldwide (7). Each year, approximately two in every 1,000 U.S. children are born either deaf or hard-of-hearing (4). Without appropriate intervention at an early age, undetected or untreated hearing loss results in delays in language development and subsequent issues with communication skills, reading abilities, and social-emotional development. For those born with hearing loss, it is estimated that >50% of cases have genetic causes, and most are inherited as an autosomal recessive trait. One of the implicated genes is SLC26A4, and as described by Dai et al. (2), mutations in this gene cause Pendred syndrome and nonsynonymous deafness.

Through the Early Hearing Detection and Intervention Program developed by the Joint Committee on Infant Hearing (3), great strides have been made over the past 10 years in physiological hearing screening of all infants prior to leaving the hospital. In addition to avoiding language delays in children, early detection of hearing loss and comprehensive characterization of the etiology is crucial for management of the patient. For example, the diagnosis of enlarged vestibular aqueduct, a phenotype described by Dai et al. (2), is important to know so that parents may be counseled to protect children from impacts to the head, as sudden deafness may occur as a result of even minor head trauma in these cases. Clinical protocols for infant hearing screening currently rely primarily on physiological tests that evaluate the auditory system to identify hearing loss in newborns. However, while often reliable, these physiological tests require specialized equipment and trained personnel to administer, they cannot predict whether hearing loss will develop over time, and in and of themselves they do not inform of potential syndromes or whether other diagnostic tests or counseling are warranted.

Due to these issues, infant hearing screening protocols stand to benefit significantly from the addition of genetic testing. Currently, DNA chips that screen for known hearing loss mutations across various genes are being developed for clinical use (1, 5). For many cases of congenital hearing loss, gene chip screenings are anticipated to be a cost-effective and efficient means of determining etiology and streamlining follow-up diagnostic evaluations and intervention strategies. One gene that is often included in genetic hearing screening is SLC26A4. Its gene product, pendrin, is a multi-ion transporter expressed in the inner ear, thyroid, and renal Type B intercalated cells. Mutations in SLC26A4 account for ~4–10% of cases of genetic hearing loss. For this reason, developing efficient and accurate assessment strategies of SLC26A4 mutations using genetic testing could help in the clinical diagnosis, assuming that mutations are shared among affected individuals and that the functional consequences of individual mutations on physiological function and hearing are understood. This detailed knowledge could have a positive impact clinical management and treatment of affected patients.

The study by Dai et al. (2) presents data from screening the SLC26A4 gene in hearing-impaired Chinese and U.S. subjects. They identified four novel mutations in Chinese subjects and six novel mutations in U.S. subjects, thus increasing the spectrum of known mutations for SLC26A4 in both populations. However, even more importantly, their analysis reveals only a limited overlap in the mutations identified in affected individuals between the two population groups. Given the wide range of the mutation spectrum, this study would suggest that targeted mutation analysis by resequencing may be required for comprehensive genetic analysis of affected individuals rather than testing a set of commonly shared allelic variants. While additional studies will be required to further characterize the frequency distribution of SLC26A4 mutations across other populations, it is highly unlikely that current attempts to define a limited set of mutations in this gene for genetic testing will be highly successful across continents.

In addition to the identification of novel mutations, Dai et al. (2) also performed functional testing of ion-exchange efficiency for the nontruncating mutations using a laboratory test system in Xenopus oocytes. Pendrin mediates Cl−/HCO3− exchange in the inner ear, and dysfunction may lead to disruption of the ionic balance of the inner ear and subsequent hearing loss (6). Two of the mutants identified in the current study, p.F354S and p.E737D, demonstrated hypofunctional Cl−/HCO3− exchange. One particularly interesting finding of this study is that one mutant, E303Q, was completely nonfunctional in both Cl−/Cl− and Cl−/HCO3− exchange, even though the protein was expressed at wild-type levels at the cell surface. This may indicate a critical role of E303Q in pendrin anion exchange, and further study of E303 will likely contribute to our understanding of ion exchange mechanisms not only in SLC26A4, but across the entire family of SLC26 transporters. The functional findings need to be validated at physiological conditions and at higher temperatures (~37°C) in mammalian cells, particularly given that other studies have shown rescue of ion exchange function at low temperatures for some pendrin mutations (8). However, this combined approach of comprehensive mutation profiling and functional characterization is likely to help in our understanding of the mechanisms by which genetic alterations lead to physiological imbalances and dysfunctions in the inner ear. Hopefully, technological advances will accelerate our discoveries, and we will be able to better define the clinical spectrum of hearing loss and other, similar genetic disorders.
In summary, the study by Dai et al. (2) outlines an exemplary effort to define and characterize the mutation spectrum of disease-causing mutations related to hearing loss. While further studies in other populations will be needed to fully assess the usefulness of genetic testing of SLC26A4 mutations in the clinical setting, the functional characterization of the mutations has the potential to help uncover with further study the pathophysiological causes and mechanisms of hearing loss. Moving forward, further integrated molecular investigations of the auditory system such as the one presented here stand to assist in early diagnosis and efficient management of patients. Ultimately, these efforts may lead to novel treatment options by pinpointing etiologies and identifying subsequent molecular intervention targets.

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REFERENCES