Hearing Preservation and Spatial Hearing Outcomes After Cochlear Implantation in Children With TMPRSS3 Mutations

*Z. Ellen Peng, †Alejandro Garcia, *Shelly P. Godar, ‡Jeffrey R. Holt, †Daniel J. Lee, and *§Ruth Y. Litovsky

*Waisman Center, University of Wisconsin-Madison, Madison, Wisconsin; †Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts; ‡Boston Children's Hospital & Harvard Medical School, Boston, Massachusetts; and §Department of Communication Sciences & Disorders, University of Wisconsin-Madison, Madison, Wisconsin

Objective: Investigate hearing preservation and spatial hearing outcomes in children with TMPRSS3 mutations who received bilateral cochlear implantation.
Study Design and Methods: Longitudinal case series report. Two siblings (ages, 7 and 4 yr) with TMPRSS3 mutations with downsloping audiograms received sequential bilateral cochlear implantation with hearing preservation with low-frequency acoustic amplification and high-frequency electrical stimulation. Spatial hearing, including speech perception and localization, was assessed at three time points: preoperative, postoperative of first and second cochlear implant (CI).
Results: Both children showed low-frequency hearing preservation in unaided, acoustic-only audiograms. Both children demonstrated improvements in speech perception in both quiet and noise after CI activations. The emergence of spatial hearing was observed. Each child's overall speech perception and spatial hearing when listening with bilateral CIs were within the range or better than published group data from children with bilateral CIs of other etiology.
Conclusion: Bilateral cochlear implantation with hearing preservation is a viable option for managing hearing loss for pediatric patients with TMPRSS3 mutations.
Key Words: Cochlear implantation—Electric acoustic stimulation—Hearing preservation—Pediatric—Sound localization—Spatial hearing—Speech perception—TMPRSS3.

Otol Neurotol **44:**21–25, 2023.

INTRODUCTION

Autosomal recessive nonsyndromic hearing loss (ARNSHL) accounts for 70% of hereditary deafness (1). The most commonly identified cause of nonsyndromic hearing loss (NSHL) is a mutation of gap junction protein beta 2 (*GJB2)* encoding connexin 26 associated with nonprogressive bilateral sensorineural hearing loss (SNHL) (2). Progressive ARNSHL is less common and has been associated with mutations of the transmembrane protease serine 3 (TMPRSS3) gene on chromosome 21q22.3, causing DFNB8 (3). More severe TMPRSS3 mutations cause profound congenital SNHL, known as DFNB10. Pediatric patients with DFNB8 and biallelic TMPRSS3 mutations often pass newborn hearing screening but quickly develop SNHL during early childhood. There are also reports of families affected by compound heterozygotes mutations (p.V116M and c.323-6G > A, p.Glu104Lys and p.Ala306Thr) (4,5). Further, these children may present with downsloping severe to profound SNHL in frequencies over 1000 to 2000 Hz and mild to moderate thresholds in lower frequencies.

Pathogenic variants of TMPRSS3 affect hair cell and spiral ganglion neuron (SGN) function (6,7). Outcomes following CI in adults with TMPRSS3 mutations are scarce but suggest modest performance compared with other etiologies of genetic hearing loss (8). Few studies have examined children with TMPRSS3 mutations, demonstrating favorable word discrimination scores in the electric-acoustic stimulation (EAS) condition (9). The present study examines speech perception and spatial hearing abilities in two children who are siblings with pathegenetic variants of TMPRSS3 associated with DFNB8 at three time points: 1) before implantation, 2) 9 months after activation of first CI with EAS (i.e., bimodal listening with one CI and one hearing aid [HA]), and 3) 9 months after activation of second CI with EAS (24 months after first CI).

METHODS

Patients I and II are otherwise healthy female siblings with progressive childhood onset ARNSHL associated with DFNB8 and

Address Correspondence and reprint requests to Z. Ellen Peng, Ph.D. Boys Town National Research Hospital, 555 North 30th Street, Omaha, NE 68131; E-mail: ellen.peng@boystown.org

J.R.H. is a consultant for Rescue Hearing and several other biotech companies developing inner ear therapeutics. The remaining authors disclose no conflicts of interest.

Sources of support and disclosure of funding: This work was supported by the National Institute of Health (NIH) National Institute on Deafness and Other Communication Disorders grants R01DC003083, R01DC008365 (RYL), R01DC013521 (JRH) and in part by a core grant to the Waisman Center at University of Wisconsin-Madison from the NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development grant P50HD105353.

DOI: 10.1097/MAO.0000000000003747

mutations of TMPRSS3 who initially passed their newborn hearing screening. There was no family history of hearing loss. Parents were from European origin. Genetic testing confirmed compound heterozygous variants for TMPRSS3, including a c.208delC and c.595G>A trans missense mutation previously described in the literature (10).

Patient I was diagnosed with a normal to profound SNHL at age 2 years and received binaural amplification with hearing aids. Patient II was fitted with hearing aids at 9 months of age. Both presented to (institution redacted for blind review) with downsloping severe to profound high-frequency HL above 1000 Hz with normal to moderate low-frequency HL (Fig. 1). Patient I and Patient II underwent sequential bilateral implantation at age 7 and age 4, due to differences in SNHL progression, respectively (Med-El Synchrony receiver stimulator with Flex 28 array, Sonnet external speech processor) at (institution redacted for blind review). Full insertion was achieved in all four ears using a round window approach (Fig. 1), with application of dexamethasone-hyaluronate gel locally during each surgery and the administration of oral steroids postoperatively. A test battery of behavioral assessments was performed at (institution redacted for blind review) at three time points: 1) before implantation, 2) 9 months after first CI activation, and 3) 9 months after second CI activation (also in Table 1). All auditory tasks were conducted in a sound attenuated booth with loudspeakers positioned at ear height of the patient. Patients wore their hearing devices with everyday settings during testing. The acoustic-electric cutoff frequency was 812 Hz for Patient I (only in Visit 2) and 215 Hz for Patient II, below which acoustic amplification was provided through the CI. For Visit 3, data logging showed that Patient I with bilateral CIs did not use the program with acoustic-electric stimulation (EAS). All experimental procedures were approved by the Health Sciences Institutional Review Board at (institution redacted for blind review). Written informed consent was obtained before testing.

RESULTS

Hearing Preservation

There was hearing preservation indicated a low-frequency and mid-frequency (150–500 Hz) threshold drop of less than 30 dB in most frequencies from preoperative to postoperative unaided audiograms. Postoperative acoustic-only pure tone average (PTA) was 45 dB for Patient I for both ears and 68 to 73 dB for Patient II after bilateral CI insertion. There was an overall improvement in hearing thresholds after bilateral CI activation (Fig. 1, postoperative CI only audiograms). Patient I showed improvement in word recognition scores with a preoperative consonant nucleus consonant of 24% in both ears to 74% in the right ear and 80% in the left ear with CI only. Patient II had preoperative pattern perception of 75% in the right ear and 66% in

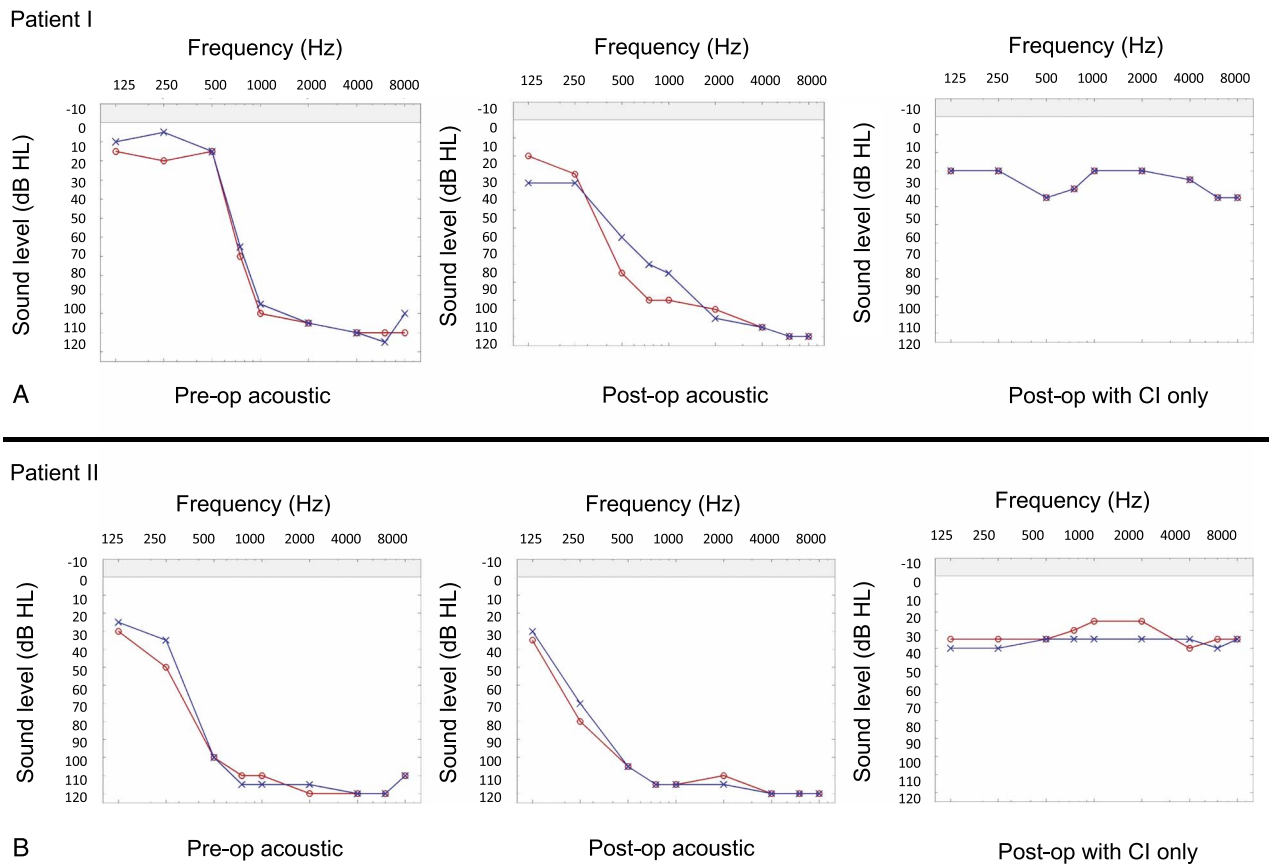

FIG. 1. Preoperative acoustic audiogram, postoperative left and right reverse Stenvers x-ray demonstrating bilateral flex 28 straight electrode array inserted through a round window approach, postoperative acoustic audiogram and postoperative with CI only audiogram for patient I (*A*) and patient 2 (*B*) obtained at (institution redacted for blind review). CI indicates cochlear implant.

TABLE 1. *Age, device status, and behavioral tasks assessed*

		Visit 1	Visit 2	Visit 3
Patient I	Chronological age (yr; mo)	7; 6	8; 5	9; 9
	Devices worn	Bilateral HAs	HA (left ear) + CI (right ear)	Bilateral CIs
	Post-CI activation	Pre-CI	9 mo post first CI	24 mo. post first CI; 9 mo. post second CI
	Behavioral tasks tested	1) Speech perception 2) Spatial acuity	Same as Visit 1 + 3) Localization	Same as Visit 2
Patient II	Chronological age (yr; mo)	4; 3	5; 1	6; 6
	Devices worn	Bilateral HAs	HA (left ear) + CI (right ear)	Bilateral CIs
	Post-CI activation	Pre-CI	9 mo post first CI	24 mo post first CI; 14 mo post second CI
	Behavioral tasks tested	1) Speech perception 2) Spatial acuity	Same as Visit 1	Same as Visit 1 + 3) Localization

the left ear to a consonant nucleus consonant of 76% in the right ear and 90% in the left ear with the CI only.

Speech Perception

Speech perception in quiet and noise was assessed using the age-appropriate version of the Children's Realistic Index for Speech Perception (CRISP) task (11–13). On each trial, the patient heard a "Ready …" call sign, followed by a bisyllabic target word (male voice). The task was to select one of the four icons that matched the target word. After determining which of 25 possible target words were recognized by each patient, the full corpus of 25 words was used for Patient I and 16 words for Patient II. The testing procedure was the same as in previous studies by Litovsky and

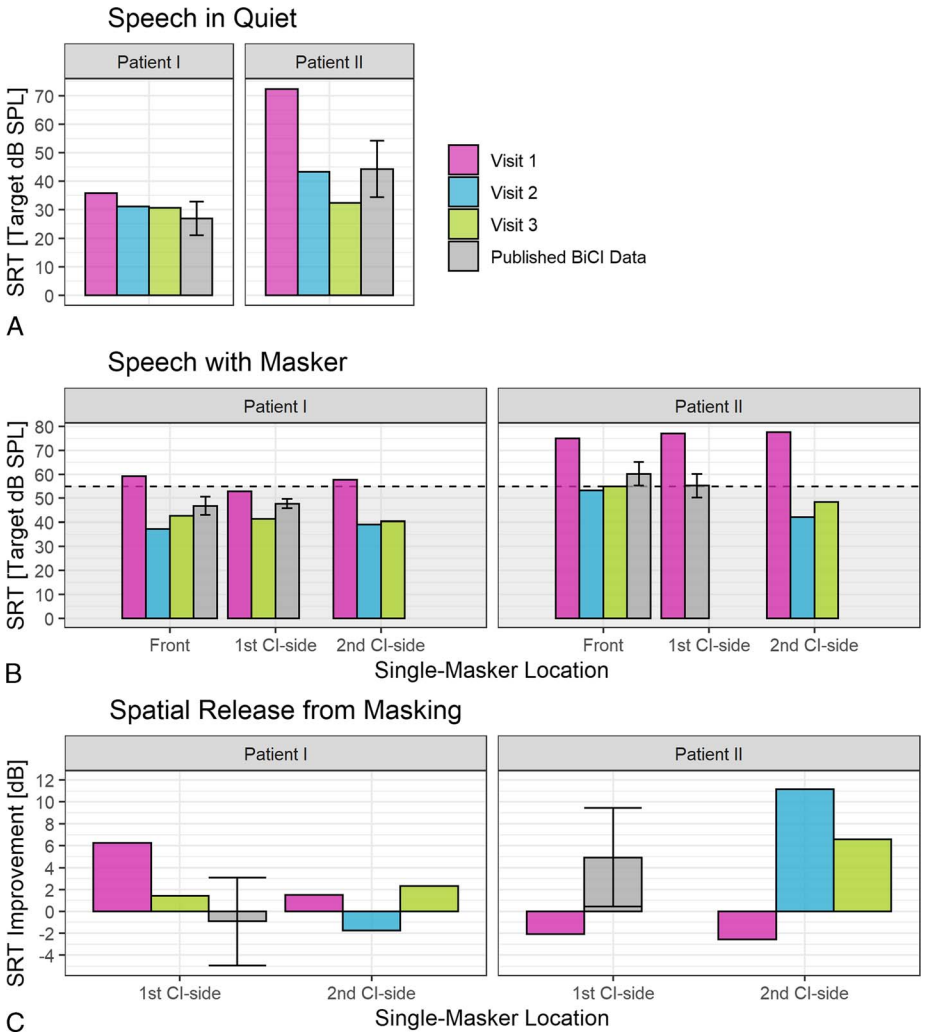

FIG. 2. Speech perception (*A* and *B*) and spatial release from masking (*C*) across visits (*color bars*), comparing with published data from children with BiCIs (12,13) (*gray bars*).

colleagues (11,12,14). The target speaker was always located in front at 0° azimuth. For each experimental run, the target was presented at 60 dB sound pressure level (SPL) and varied adaptively based on the patient's performance. Speech reception threshold (SRT) was estimated as the target speech SPL at which 79.4% was achieved for each condition. For each patient, speech in quiet was tested first, followed by conditions with maskers pseudo-randomly assigned. Maskers consisted of the Harvard/IEEE sentences (15) (female voice) fixed at 55 dB SPL. Maskers were either co-located with the target (0° front), or at 90° toward the patient's first CI, or 90° toward the second CI.

Figure 2 shows SRTs target speech SPL in quiet and with a masker as compared with average published data using the same task in a group of children with bilateral cochlear implants (BiCIs) (11,12,14). Patient I showed similar preoperative and postoperative performance in quiet, and improved (reduced) SRTs with maskers after first CI implantation. Patient II showed drastic improvement of over 20 dB SRT in both quiet and masked conditions after the first CI implantation, with stable performance after the second CI. Both patients performed similar to children with BiCIs after their first CI implantation (listening in EAS mode). Figure 2C shows benefit of spatial cues known as spatial release from masking (SRM), derived as SRT improvement with maskers displacement from 0° to 90°. Patient I showed SRM at visit 1, with bilateral hearing aid use, which was not observed after CI activation. Patient II demonstrated a substantial increase in SRM with the first CI, and slight reduction in SRM after the second CI.

Spatial Acuity and Sound Localization

Spatial acuity was assessed in a right-left discrimination task following procedures published by Litovsky and colleagues (16–18). On each trial, the token word "baseball" was played from a loudspeaker either on the right or left at a fixed spatial separation from 0° azimuth, at 60 dB SPL with intensity roving between 56 and 64 dB. The patient was asked to indicate the side from which the sound was heard. Testing was conducted in blocks of 20 trials, at a fixed angle separation with equal number of trials in random order to the right and left. Testing was initially conducted with sounds at ±90° from front, with adaptive change in angles, i.e., reduction on subsequent blocks if ≥75% correct, and increased angles if <75% correct. The minimum audible angle (MAA) is interpolated at 75%

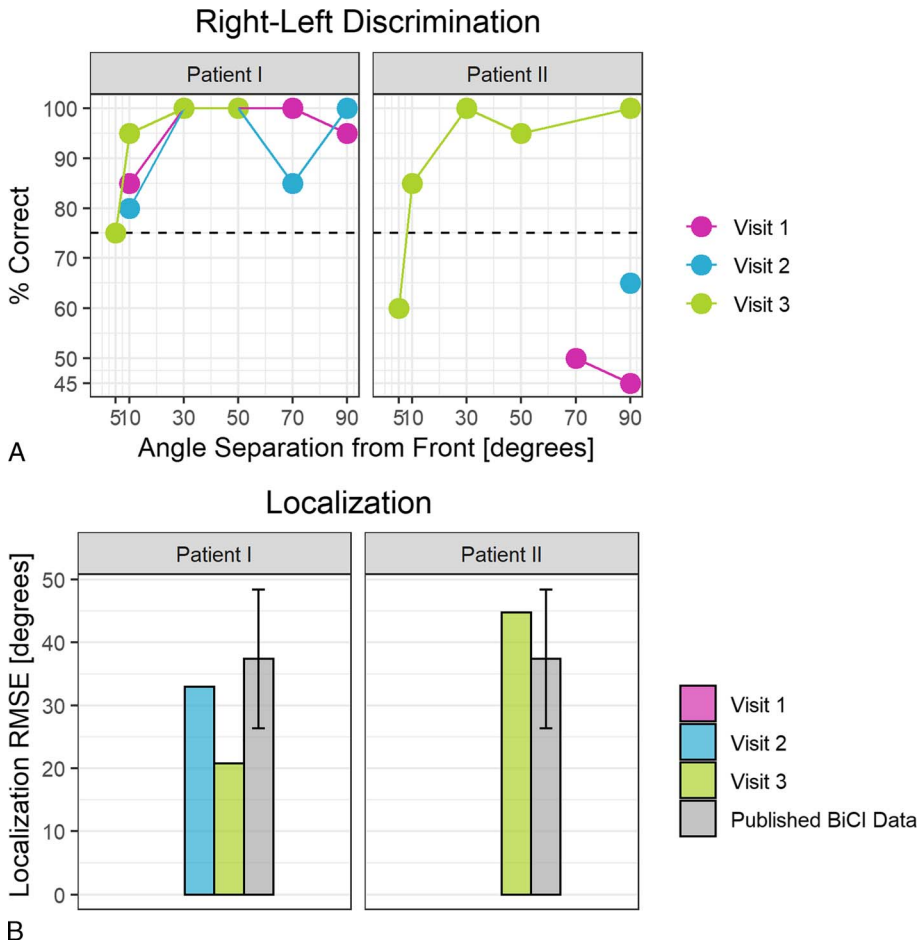

FIG. 3. Spatial acuity in a right-left discrimination task across visits showing % correct data as a function of angle separation across visits (*A*). Sound localization in RMSE in degrees (*color bars*) (*B*), with published data from children with BiCIs (19) (*gray bars*). RMSE indicates root mean squared error.

correct. Patient I demonstrated high accuracy across the first two visits (bilateral HAs and bimodal CI-HA) with an estimated MAA ≤10° (Fig. 3A). Accuracy increased in the 10° separation at Visit 3 (BiCIs), with MAA ~5°. For Patient II, performance was near chance level during the first two visits, even without sound intensity roving applied. With BiCIs, Patient II showed drastic improvement and emergence of right-left discrimination ability with MAA ~7.8°. Previous studies reported average MAA between 18.6° and 30.5° (16–18) in children with BiCIs.

Sound localization was assessed following previously published procedures (20,21). On each trial, the word "baseball" was presented from one of the 19 loudspeakers from 90° to +90° in 10° spacing. Levels were set at 60 dB SPL roved between 56 and 64 dB, with 10 to 15 repetitions from each location. Each loudspeaker was marked by a unique color-symbol combination. The patient was asked to indicate the symbol corresponding to the perceived location. Localization accuracy was computed as root mean square error (RMSE) (deviation between responses and target). Due to time constraint, the localization task was only tested during Visits 2 and 3 for Patient I, and Visit 3 for Patient II. Patient I showed improved RMSE at Visit 3, after BiCI intervention as compared with bimodal CI-HA listening, with RMSE better than children with BiCIs (Fig. 3B). Patient II had localization ability that is still emerging, i.e., able to perform the localization task during Visit 3 but greater RMSE than children with BiCIs.

DISCUSSION

For both patients, we observed benefits from BiCI intervention with EAS for Patient II and electric stimulation for Patient I with improved performance across visits, as they progressed from listening with bilateral HAs (Visit 1) to bimodal CI-HA (Visit 2) to BiCIs (Visit 3). Both patients performed similar to or better than published data from children with BiCIs (12,13,17,19) by Visit 3, a trend that is consistent with previous report of EAS treatment on pediatric patients with TMPRSS3 (9). After the first CI intervention, Patient II showed more drastic improvement on speech SRTs and SRM, as well as emergence of left-right discrimination by 14 months after BiCI listening with EAS.

To date, there is no long-term CI outcome data in children with TMPRSS3 mutations. Here, we demonstrated hearing preservation with CIs in children with downsloping progressive SNHL associated with DFNB8 and compound heterozygous variants for TMPRSS3. Both patients used daily CI listening programs that included options for acoustic amplification and electric stimulation. The impact of low-frequency acoustic amplification on listening outcomes remains for future investigation. Future work is warranted to study a larger sample of pediatric patients with TMPRSS3 mutations (both DFNB8 and DFNB10) to provide additional support on the long-term efficacy of similar treatments of bilateral cochlear implants with hearing preservation.

REFERENCES

1. Gao X, Huang SS, Yuan YY, et al. Identification of TMPRSS3 as a significant contributor to autosomal recessive hearing loss in the Chinese population. *Neural Plast* 2017;2017:3192090.
2. Oguchi T, Ohtsuka A, Hashimoto S, et al. Clinical features of patients with GJB2 (connexin 26) mutations: severity of hearing loss is correlated with genotypes and protein expression patterns. *J Hum Genet* 2005;50:76–83.
3. Bademci G, Foster J, Mahdieh N, et al. Comprehensive analysis via exome sequencing uncovers genetic etiology in autosomal recessive nonsyndromic deafness in a large multiethnic cohort. *Genet Med* 2016;18:364–71.
4. Ganapathy A, Pandey N, Srisailapathy CRS, et al. Non-syndromic hearing impairment in India: high allelic heterogeneity among mutations in TMPRSS3, TMC1, USHIC, CDH23 and TMIE. *PLoS One* 2014;9:e84773.
5. Moon IS, Grant AR, Sagi V, Rehm HL, Stankovic KM. TMPRSS3 gene variants with implications for auditory treatment and counseling. *Front Genet* 2021;12:780874.
6. Fasquelle L, Scott HS, Lenoir M, et al. Tmprss3, a transmembrane serine protease deficient in human DFNB8/10 deafness, is critical for cochlear hair cell survival at the onset of hearing. *J Biol Chem* 2011;286:17383–97.
7. Shearer AE, Tejani VD, Brown CJ, et al. In vivo electrocochleography in hybrid cochlear implant users implicates TMPRSS3 in spiral ganglion function. *Sci Rep* 2018;8:14165.
8. Eppsteiner RW, Shearer AE, Hildebrand MS, et al. Prediction of cochlear implant performance by genetic mutation: the spiral ganglion hypothesis. *Hear Res* 2012;292:51–8.
9. Holder JT, Morrel W, Rivas A, Labadie RF, Gifford RH. Cochlear implantation and electric acoustic stimulation in children with TMPRSS3 genetic mutation. *Otol Neurotol* 2021;42:396–401.
10. Weegerink NJ, Schraders M, Oostrik J, et al. Genotype-phenotype correlation in DFNB8/10 families with TMPRSS3 mutations. *J Assoc Res Otolaryngol* 2011;12:753–66.
11. Litovsky RY. Speech intelligibility and spatial release from masking in young children. *J Acoust Soc Am* 2005;117:3091–9.
12. Hess CL, Misurelli SM, Litovsky RY. Spatial release from masking in 2-year-olds with normal hearing and with bilateral cochlear implants. *Trends Hear* 2018;22:233121651877556.
13. Misurelli SM, Litovsky RY. Spatial release from masking in children with bilateral cochlear implants and with normal hearing: effect of target-interferer similarity. *J Acoust Soc Am* 2015;138:319–31.
14. Misurelli SM, Litovsky RY. Spatial release from masking in children with normal hearing and with bilateral cochlear implants: effect of interferer asymmetry. *J Acoust Soc Am* 2012;132:380–91.
15. Rothauser EH, Chapman WD, Guttman N, et al. IEEE recommended practice for speech quality measurements. *IEEE Trans Audio Electroacoust* 1969;17:225–46.
16. Litovsky RY, Johnstone PM, Godar S, et al. Bilateral cochlear implants in children: localization acuity measured with minimum audible angle. *Ear Hear* 2006;27:43–59.
17. Godar SP, Litovsky RY. Experience with bilateral cochlear implants improves sound localization acuity in children. *Otol Neurotol* 2010; 31:1287–92.
18. Grieco-Calub TM, Litovsky RY. Spatial acuity in 2-to-3-year-old children with normal acoustic hearing, unilateral cochlear implants, and bilateral cochlear implants. *Ear Hear* 2012;33:561–72.
19. Litovsky RY, Gordon K. Bilateral cochlear implants in children: effects of auditory experience and deprivation on auditory perception. *Hear Res* 2016;338:76–87.
20. Zheng Y, Godar SP, Litovsky RY. Development of sound localization strategies in children with bilateral cochlear implants. *Plos One* 2015; 10:e0135790.
21. Grieco-Calub TM, Litovsky RY. Sound localization skills in children who use bilateral cochlear implants and in children with normal acoustic hearing. *Ear Hear* 2010;31:645–56.