ARTICLE

Predominance of Genetic Diagnosis and Imaging Results as Predictors in Determining the Speech Perception Performance Outcome After Cochlear Implantation in Children

Chen-Chi Wu, MD, MMS; Yi-Chin Lee, MD, MPH; Pei-Jer Chen, MD, PhD; Chuan-Jen Hsu, MD, PhD

Objective: To investigate the roles of genetic diagnosis and imaging studies, as well as other prognostic factors, in predicting outcomes in children with cochlear implant.

Design: Prospective cohort study.

Setting: Tertiary referral center.

Participants: Sixty-seven consecutive children with sensorineural hearing impairment who had at least 3 years of experience with cochlear implant.

Interventions: Imaging of the inner ear was done with high-resolution computed tomography, and mutations were screened in 3 genes commonly associated with pediatric hearing impairment: *GJB2*, *SLC26A4*, and the mitochondrial 12S ribosomal RNA gene. Speech perception performance was compared according to genetic diagnosis and imaging data. A general linear model was constructed to demonstrate the predictive values of specific genetic and imaging results after adjusting for other factors.

Main Outcome Measure: Recognition scores on speech perception tests.

Results: Twenty-two children (33%) showed genetic mutations: 18 with *SLC26A4* and 4 with *GJB2* mutations. According to imaging findings, 33 children (49%) showed inner ear malformations: 9 with a narrow internal auditory canal and 24 with other malformations. All children with *SLC26A4* or *GJB2* mutations exhibited excellent speech recognition scores, whereas a narrow internal auditory canal was associated with poorer outcomes ($P<.001$ in all recognition scores). The general linear model confirmed that both a narrow internal auditory canal ($P<.001$) and *SLC26A4* mutations ($P=.04$) correlated with speech perception outcome.

Conclusions: Genetic diagnosis and imaging results are the 2 predominant factors determining the outcome in children with cochlear implants. In pediatric candidates for cochlear implantation, both genetic examination and imaging studies should be included in the battery of preoperative evaluations.

Arch Pediatr Adolesc Med. 2008;162(3):269-276

Author Affiliations: Division of Pediatric Otolaryngology, Departments of Otolaryngology (Drs Wu and Hsu) and Medical Genetics (Dr Wu), National Taiwan University Hospital and Graduate Institute of Clinical Medicine, College of Medicine (Drs Wu and Chen) and Division of Biostatistics, Graduate Institute of Epidemiology, College of Public Health (Dr Lee), National Taiwan University, Taipei.

PEDIATRIC SENSORINEURAL hearing impairment (SNHI) is a common defect affecting about 1 in 1000 children.[1,2] Research over time has shown that early identification of hearing loss followed by rehabilitation procedures, such as hearing aid use commencing during the first 6 months of life, significantly increases the level of language development, speech intelligibility, and emotional stability.[3] For those who get limited benefits from hearing aids and fail to reach communication milestones because of the severity of their hearing impairment, cochlear implantation has been demonstrated to be an effective intervention and is currently regarded as the treatment of last resort. Bypassing the sensory organ of the inner ear, cochlear implants (CIs) activate auditory nerve fibers directly, transmitting auditory signals through the central neural pathway and ultimately yielding speech understanding in the cortex. The performance outcome with CI, however, varies significantly among implantees. A plethora of factors, including age at implantation,[4,5] duration of implant use,[6] amount of residual hearing,[7-9] primary mode of communication before operation,[10] and presence of certain inner ear malformations (IEMs), such as a narrow internal auditory canal (IAC),[11,12] have been proposed to influence the outcome. Still, a panoramic prediction of CI results remains unavailable thus far, largely because pediatric SNHI is extremely heterogeneous in its etiology. As an invasive and expensive surgical procedure, identification of the most

crucial predictors of CI outcome is of paramount importance, since it may help steer appropriate rehabilitation programs and expectations by clinical workers, schools, and families.

With advances in molecular genetics, our understanding of the pathogenesis of pediatric SNHI has been greatly expanded in the past decade. With little doubt, genetic diagnosis provides direct clues about the pathogenesis of hearing loss in patients with hearing impairment. Recent studies have shown that patients with *GJB2* (or *Cx26*) (OMIM *121011) mutations usually exhibit excellent speech perception and language performance after cochlear implantation.[13-21] However, there is little evidence concerning the predictive value of other genetic mutations in cochlear implantation or the interplay of genetic diagnosis with the other prognostic factors. The aim of the present article was to elucidate the predominant factors that determine the long-term outcome after cochlear implantation in a prospective, longitudinal cohort consisting of pediatric cochlear implantees.

METHODS

SUBJECT RECRUITMENT AND PREIMPLANTATION EVALUATION

Sixty-seven consecutive and unrelated children with SNHI (31 boys and 36 girls) who underwent cochlear implantation from 1998 to 2003 were enrolled in this study. All children were native speakers of Mandarin Chinese and developed hearing impairment before the age of 3 years (ie, prelingual hearing impairment). Children with additional conditions that might interfere with speech/language development were excluded. Before implantation, a comprehensive clinical evaluation was conducted in each child, including a complete history, physical examination, audiological tests, and radiological studies of the temporal bone. Audiological results were assessed with air and bone conduction thresholds of pure tones using an audiometer (GSI 10; Grason-Stadler Inc, Milford, New Hampshire), thresholds of auditory brainstem response stimulated by tone bursts (Bravo; Nicolet, Madison, Wisconsin), or corrected thresholds of auditory steady state response with an auditory steady state response audiometer (ASSR; ERA Systems P/L, Melbourne, Australia), depending on age or neurological status. Thresholds obtained by auditory brainstem response (n=19) or auditory steady state response (n=2) were then correlated with visual reinforcement audiometry, and hearing levels of the ears to receive CIs were calculated by averaging the thresholds at 3 frequencies (500, 1000, and 2000 Hz). The temporal bone imaging results were determined using high-resolution computed tomographic (HRCT) scans. All HRCT images were scanned with 1-mm contiguous increments in both axial and coronal sections and were read independently by 2 pediatric otologists according to the criteria in the literature.[11,22,23] For instance, the width of the IAC was measured in the axial plane using a perpendicular line beginning on the posterior wall of the IAC and was described as narrow if it was less than 2 mm in diameter, whereas the width of vestibular aqueduct was measured in the axial plane in the midportion of the bony canal and was described as enlarged if it exceeded 2 mm.

All children were implanted with a Nucleus 24M or 24C CI (Cochlear Ltd, New South Wales, Australia), with age at implantation ranging from 1 to 14 years (mean, 4.7 years). Each patient received oral education in mainstream schools or rehabilitation facilities for at least 3 years after implantation and had a minimum of 3 years of experience with the device (duration of implant use, 3-10 years; mean, 4.4 years). The advanced combination encoding strategy with a stimulation rate of 900 ppspe (pulse per second on each electrode) or higher was used in all subjects. According to our previous study, this speech processing strategy was able to provide CI users with sufficient amounts of tonal information for Mandarin Chinese.[24] All subjects signed informed consent for participation in the project, and all procedures were approved by the Research Ethics Committee of the National Taiwan University Hospital.

GENETIC EXAMINATIONS

All implantees underwent mutation screening of 3 genes commonly associated with hearing impairment: *GJB2*, *SLC26A4* (OMIM *605646), and the mitochondrial 12S ribosomal RNA (rRNA) gene (*MTRNR1*) (OMIM *561000). In brief, after informed consent was obtained, genomic DNA was extracted from peripheral venous blood using standard procedures. Mutation screening was completed by polymerase chain reaction (PCR) amplification of both exons of *GJB2*, all 21 exons of *SLC26A4*, and the whole mitochondrial 12S rRNA gene, followed by direct sequencing of the PCR products. For those who carried only 1 nonpolymorphic *GJB2* allele variant, the DNA samples were further studied for mutations in the coding region of *GJB6* (or *Cx30*) (OMIM *604418) by direct sequencing and for Δ(*GJB6*-D13S1830) by gap PCR. Primer sequences and amplification conditions for PCR were described in previous reports.[25-27] Reaction products were purified and subjected to bidirectional sequencing in a semiautomated DNA sequencer (ABI PRISM 377; Perkin Elmer–Cetus, Foster City, California). The data were subsequently compared with the wild-type sequence of each gene in RefSeq (accession numbers: *GJB2*, NT_024524 [genomic DNA (gDNA)], NM_004004 [complementary DNA (cDNA)]; *GJB6*, NW_925473 [gDNA], NM_006783 [cDNA]; *SLC26A4*, NT_007933 [gDNA], NM_000441 [cDNA]; mitochondrial genome, NC_001807). Each variant allele was then analyzed in pedigrees, as well as compared with a panel of 120 controls with normal hearing and international databases (*GJB2* and *GJB6*: the Connexin-deafness homepage, davinci.crg.es/deafness; *SLC26A4*: Pendred/BOR Home Page, www.medicine.uiowa.edu/pendredandbor; and mitochondrial genome: MITOMAP, www.mitomap.org), to clarify whether it was a true mutation. Samples from parents and siblings were analyzed whenever possible to determine the meiotic phase of each mutation. The whole genotyping procedure was completed in the central laboratory of the National Taiwan University Hospital.

EVALUATION OF AUDITORY SPEECH PERCEPTION PERFORMANCE

Auditory speech perception performance was conducted with closed-set (ie, test with visual clues) and open-set (ie, test without visual clues) Mandarin speech recognition tests as described elsewhere.[24] As a tonal language, Mandarin Chinese has 4 tonal patterns, and each tonality of a monosyllable might represent a different meaning lexically. For example, the monosyllable /ma/, pronounced using tone 1, 2, 3, or 4, can mean "mother," "hemp," "horse," or "scold," respectively, making the tonal information an important clue in speech perception of Mandarin in addition to consonants and vowels. The results of auditory speech perception performance in the present study were expressed in terms of the recognition scores of 5 parameters: consonant, vowel, tone, phonetically balanced (PB) word, and sentence. For Mandarin speech recognition tests, the test materials were developed at National Tai-

wan University Hospital and recorded at House Ear Institute. All test materials were digitized using a 16-bit A/D converter at a 16-kHz sampling rate without high-frequency preemphasis. The test materials were recorded on a CD and were presented to the subjects at a level of 65 dBA via a single speaker in a quiet room. These Mandarin recognition tests were used in previous studies.[24,28]

For the Mandarin sentence recognition test, 6 sentence lists each containing 25 sentences were used for open-set testing. During the test, a sentence list was chosen pseudorandomly from among the 6 lists and sentences were chosen randomly, without replacement, from among the 25 sentences within that list and presented to the subject. The subject responded by repeating the sentence as accurately as possible. For the Mandarin word recognition test, 2 word lists each containing 50 PB words were used for open-set testing. During the test, a word list was chosen pseudorandomly and words were chosen randomly from among the 50 words within that list and presented to the subject. The subject responded by repeating the word. The answers were recorded with an IC recorder (ICD-SX30; Sony, Tokyo, Japan) and were analyzed by 2 different researchers. A sentence recognition score was measured according to the percentage of words correctly identified. Word, tone, vowel, and consonant recognition scores were measured according to the percentage of words, tones, vowels, and consonants correctly repeated in the Mandarin word recognition test.

STATISTICS

All statistical analyses were carried out using SPSS software (version 13.0; SPSS Inc, Chicago, Illinois). Speech perception performance outcome, as expressed in speech recognition scores of the 5 parameters, were compared according to genetic diagnosis and imaging results, respectively. A general linear model, with the sum of the 5 speech recognition scores set as the dependent (outcome) variable, was then constructed to evaluate the effects of specific imaging or genetic results on speech perception performance by controlling for the confounding of other prognostic factors, including age at implantation, duration of implant use, and residual hearing (ie, pure-tone average before implantation). All tests were 2-tailed and differences were reported as significant if the *P* value was less than 0.05.

RESULTS

GENETIC VARIANTS IDENTIFIED AND GENOTYPES OF PATIENTS

Mutated alleles of the screened genes in the 67 children with CI are summarized in **Table 1**. *SLC26A4* mutations were more prevalent than *GJB2* mutations in the present cohort, while no patients harbored mutations in the mitochondrial 12S rRNA gene or *GJB6*. The most common mutation was IVS7-2A>G of *SLC26A4* (allele frequency, 22/134), followed by 235delC of *GJB2* (allele frequency, 3/134) and T410M and H723R of *SLC26A4* (both allele frequencies, 3/134), and other mutations.

When categorized by genetic results, 22 of the 67 patients (33%) had mutations, including 18 with *SLC26A4* mutations and 4 with *GJB2* mutations. The genotypes of these 22 patients are detailed in **Table 2**. Sixteen patients were homozygous or compound heterozygous for *SLC26A4* mutations, 2 patients were heterozygous for *SLC26A4* mutation (only 1 IVS7-2A>G allele detected), 1 patient was homozygous for the *GJB2* 235delC mutation, and 3 patients were heterozygous for *GJB2* mutation (the only detected mutations: V63L, 235delC, and R143W). In the families of the 2 *SLC26A4* and 3 *GJB2* heterozygotes, the mutation cosegregated with the phenotype of hearing loss in affected family members, implying that the other allele of *SLC26A4* or *GJB2* in these heterozygotes might harbor an undetected, hidden mutation, as postulated by Kimberling.[29] Alternatively, V63L and R143W of *GJB2* alone might lead to hearing impairment, since many *GJB2* mutations are inherited in an autosomal dominant manner.[30]

Table 1. Genetic Variants Identified in the 67 Cochlear Implantees

Exon	Nucleotide Change	Codon Change	No. of Mutated Alleles
SLC26A4			
3	230A>T	K77I	1
3′ Int 7	IVS7-2A>G	Splice acceptor	22
5′ Int 8	IVS8 + 5G>C	Splice donor	1
10	1160C>T	A387V	1
10	1229C>T	T410M	3
12	1343C>T	S448L	2
19	2162C>T	T721M	1
19	2168A>G	H723R	3
GJB2			
2	187G>T	V63L	1
2	235delC	Frameshift	3
2	427C>T	R143W	1

Table 2. Genotypes of Patients With Genetic Mutations

Gene	Genotype	No. of Patients
SLC26A4		
Homozygous	IVS7-2A>G/IVS7-2A>G	7
	T410M/T410M	1
	H723R/H723R	1
Compound heterozygous	K77I/IVS7-2A>G	1
	IVS7-2A>G/IVS8 + 5G>C	1
	IVS7-2A>G/A387V	1
	IVS7-2A>G/S448L	2
	IVS7-2A>G/H723R	1
	T410M/T721M	1
Heterozygous	IVS7-2A>G/wt	2
GJB2		
Homozygous	235delC/235delC	1
Heterozygous	V63L/wt	1
	235delC/wt	1
	R143W/wt	1

Abbreviation: wt, wild type.

IMAGING RESULTS OF THE INNER EAR

Among the 67 children with CI, 33 (49%) had IEMs on temporal bone HRCT. When classified according to the types of IEMs, 9 patients had a narrow IAC, either as an isolated finding (n=2) or in combination with other malformations (n=7) (**Table 3**). The remaining 24 children had other types of IEMs, of which the more com-

Table 3. Types of IEMs

Type of IEM	Patients With a Narrow IAC (n=9)	Patients With Other IEMs (n=24)
No. of IEMs		
Isolated IEM	2	12[a]
Multiple malformations	7	12
Cochlea		
Aplasia	1	0
Hypoplasia	1	2
Common cavity	3	0
Incomplete partition	0	11
Vestibule		
Aplasia	0	0
Hypoplasia	4	0
Enlargement	0	6
Semicircular canal		
Aplasia	1	0
Dysplasia	6	4
Aqueduct		
EVA	0	19
IAC		
Narrow IAC	9	0
Wide IAC	0	2

Abbreviations: EVA, enlarged vestibular aqueduct; IAC, internal auditory canal; IEM, inner ear malformation.
[a] Includes 9 patients with EVA, 2 patients with incomplete partition of the cochlea, and 1 patient with a wide IAC.

mon included an enlarged vestibular aqueduct (EVA) (n=19), incomplete partition of the cochlea (or Mondini dysplasia) (n=11), large vestibule (n=6), and semicircular canal dysplasia (n=4) (Table 3).

COMPARISON OF SPEECH PERCEPTION PERFORMANCE ACCORDING TO GENETIC DIAGNOSIS AND IMAGING RESULTS

To investigate the roles of genetic diagnosis and imaging results in predicting speech perception performance with CI, the achievement rate of open-set speech recognition and speech recognition scores were compared according to the genotypes and IEM types of the patients, respectively. As shown in **Table 4**, there was a significant difference in the percentage of achievement of open-set speech recognition among patients with *SLC26A4* mutations (100%), those with *GJB2* mutations (100%), and those without mutation (76%) (Fisher exact test, $P=.04$), although the 3 groups did not differ in age at implantation, duration of CI use, or residual hearing (analysis of variance [ANOVA], all $P>.10$). Similar to the percentage of achievement of open-set speech recognition, average recognition scores of consonants, vowels, PB words, and sentences were also different among the 3 groups (ANOVA, all $P<.05$). A post hoc test with the Tukey multiple comparison procedure revealed a significant difference in these speech recognition scores between patients with *SLC26A4* mutations and those without mutations (all $P<.05$).

By comparing speech perception performance according to imaging results, there was also a significant difference in the percentage of achievement of open-set speech recognition among patients with a narrow IAC (22%), those with other types of IEMs (96%), and those without IEMs (91%) (Fisher exact test, $P<.001$), although the 3 groups did not differ in age at implantation, duration of CI use, or residual hearing (ANOVA, all $P>.05$) (**Table 5**). Likewise, average recognition scores of consonants, vowels, tones, PB words, and sentences were different among the 3 groups (ANOVA, all $P<.001$), and a post hoc test with the Tukey multiple comparison procedure revealed a significant difference in the speech recognition scores between patients with a narrow IAC and each of the other 2 groups (all $P<.001$).

GENERAL LINEAR MODEL

Since there was an association between specific genetic diagnosis and imaging results, such as the association between *SLC26A4* mutations and EVA and/or incomplete partition of the cochlea, confounding might arise when investigating the correlation between CI outcome and genetic diagnosis or imaging results. To control the confounding, a general linear model was established, and the predictive values of specific genetic and imaging results in the presence of other prognostic factors was assessed. As shown in **Table 6**, with other prognostic factors being adjusted, both the presence of a narrow IAC ($P<.001$) and the presence of *SLC26A4* mutations ($P=.04$) were still significantly correlated with the sum of speech recognition scores.

GENOTYPES, PHENOTYPES, AND SPEECH PERCEPTION PERFORMANCE IN SUBJECTS WITH EVA AND/OR INCOMPLETE PARTITION OF THE COCHLEA

To elucidate the correlation between CI outcome and *SLC26A4* mutations, *SLC26A4* genotypes in the 21 patients who had EVA and/or incomplete partition of the cochlea on HRCT, the corresponding radiological findings, and average speech recognition scores of 5 parameters are summarized in **Table 7**. As reported in our previous studies,[25,31] there was no clear correlation between *SLC26A4* genotypes and radiological phenotypes. Patients with *SLC26A4* mutations, regardless of the associated IEMs, exhibited excellent recognition scores, whereas 1 patient without *SLC26A4* mutations did not achieve open-set speech recognition after implantation.

COMMENT

In the present study, we identified that genetic diagnosis and imaging results were the principal factors determining the long-term speech perception performance in children after cochlear implantation. Other variables that have been documented to affect the outcome, such as age at implantation, duration of CI use, and preoperative residual hearing, did not appear to play substantial roles in our cohort (Table 6). There are 2 probable reasons. Early identification of hearing impairment as a consequence of a nationwide hearing screening program in new-

Table 4. Comparison of Speech Perception Performance According to Genetic Diagnosis

Variable	Mean (SD)			
	SLC26A4 Mutation (n=18)	*GJB2* Mutation (n=4)	No Mutation (n=45)	*P* Value
Male, No. (%)	7 (39)	3 (75)	21 (47)	.46[a]
Age, y	9.7 (3.6)	8.3 (2.3)	9.5 (3.0)	.74[b]
Age at implantation, y	5.7 (3.2)	3.2 (1.0)	4.4 (2.8)	.18[b]
Duration of implant use, y	3.7 (1.4)	4.7 (2.0)	4.6 (1.7)	.12[b]
Pure-tone average before implantation, dBHL	98.7 (10.6)	103.5 (4.4)	103.0 (9.5)	.27[b]
Achievement of open-set speech recognition, No. (%)	18 (100)	4 (100)	34 (76)	.04[a]
Speech recognition scores, %				
Consonant	88.0 (7.2)	90.5 (1.9)	66.2 (38.6)	.04[c]
Vowel	86.2 (6.1)	81.5 (8.4)	64.6 (38.0)	.047[c]
Tone	91.7 (6.3)	95.5 (1.9)	71.0 (41.3)	.06[c]
Phonetically balanced word	79.2 (10.5)	73.5 (6.8)	56.3 (34.4)	.02[c]
Sentence	89.9 (10.8)	93.3 (5.4)	58.3 (37.7)	.001[c]

Abbreviation: dBHL, decibel hearing level.
[a] Fisher exact test.
[b] Analysis of variance.
[c] Analysis of variance, post hoc test for significance with the Tukey multiple comparison procedure: consonant, *SLC26A4* mutation vs no mutation, $P=.047$; vowel, *SLC26A4* mutation vs no mutation, $P=.04$; phonetically balanced word, *SLC26A4* mutation vs no mutation, $P=.02$; and sentence, *SLC26A4* mutation vs no mutation, $P=.002$.

Table 5. Comparison of Speech Perception Performance According to Imaging Results

Variable	Mean (SD)			
	Narrow IAC (n=9)	Other IEMs (n=24)	No IEMs (n=34)	*P* Value
Male, No. (%)	3 (33)	10 (42)	18 (53)	.52[a]
Age, y	7.3 (2.0)	9.0 (3.3)	9.9 (3.4)	.34[b]
Age at implantation, y	3.4 (1.3)	4.9 (3.1)	4.9 (3.1)	.40[b]
Duration of implant use, y	4.6 (1.6)	3.8 (1.4)	4.8 (1.8)	.08[b]
Pure-tone average before implantation, dBHL	106.3 (9.7)	98.4 (11.5)	103.1 (7.5)	.06[b]
Achievement of open-set speech recognition, No. (%)	2 (22)	23 (96)	31 (91)	<.001[a]
Speech recognition scores, %				
Consonant	17.8 (35.3)	82.4 (19.1)	81.1 (26.4)	<.001[c]
Vowel	18.0 (35.7)	81.7 (18.3)	78.0 (26.3)	<.001[c]
Tone	21.3 (42.3)	88.2 (19.8)	85.7 (27.9)	<.001[c]
Phonetically balanced word	14.7 (29.1)	73.2 (19.0)	68.8 (25.2)	<.001[c]
Sentence	15.7 (31.1)	80.3 (23.8)	73.4 (29.4)	<.001[c]

Abbreviations: dBHL, decibel hearing level, IAC, internal auditory canal; IEM, inner ear malformation.
[a] Fisher exact test.
[b] Analysis of variance.
[c] Analysis of variance, post hoc test for significance with the Tukey multiple comparison procedure: consonant, vowel, tone, phonetically balanced word, and sentence: narrow IAC vs other IEMs, all $P<.001$ and narrow IAC vs no IEMs, all $P<.001$.

borns and a growing consensus internationally about the indications for cochlear implantation might lead to a more homogeneous distribution in age at implantation and residual hearing among CI candidates. Lack of correlation between speech perception performance and duration of CI use, on the other hand, might result from the more stringent enrollment criteria we adopted in the current study: we only recruited patients with a sufficient period of rehabilitation to reach their learning plateau with the device, namely 3 years. Accordingly, in terms of the long-term outcome, genetic diagnosis and imaging findings were the 2 key prognostic factors in children with CI. For an invasive and expensive procedure like cochlear implantation, which requires long-term and labor-

Table 6. General Linear Model Analyzing the Relations Between Sum of Speech Recognition Scores and the Prognostic Factors

Variable	β	SE	*t* Test	*P* Value
Interception	231.82	168.84	1.37	.17
Narrow IAC	−315.01	46.57	−6.76	<.001
Other IEMs	−62.91	55.60	−1.13	.26
SLC26A4 mutation	124.40	59.98	2.07	.04
GJB2 mutation	52.50	64.17	0.82	.42
Age at implantation, y	−8.37	5.43	−1.54	.13
Duration of implant use, y	−7.40	9.41	−0.79	.43
Residual hearing, dBHL	2.20	1.61	1.36	.18

Abbreviations: See Table 5.

Table 7. Genotypes, Radiologic Phenotypes, and Speech Perception Performance in Implantees With EVA and/or Incomplete Partition of the Cochlea

Patient No.	*SLC26A4* Genotype	Inner Ear Malformation	Achievement of Open-set Speech Recognition	Average Speech Recognition Score[a]
1	T410M/T721M	EVA, M, V, S	Yes	78.4
2	IVS7-2A>G/S448L	EVA, M, V, S	Yes	91.2
3	IVS7-2A>G/IVS7-2A>G	EVA	Yes	96.4
4	IVS7-2A>G/H723R	EVA, V, S	Yes	91.0
5	IVS7-2A>G/IVS7-2A>G	EVA	Yes	96.0
6	IVS7-2A>G/IVS7-2A>G	EVA, M, V	Yes	89.0
7	IVS7-2A>G/A387V	EVA	Yes	82.4
8	IVS7-2A>G/IVS7-2A>G	EVA, M	Yes	87.6
9	K77I/IVS7-2A>G	EVA, M	Yes	77.0
10	IVS7-2A>G/wt	EVA	Yes	79.6
11	IVS7-2A>G/S448L	EVA	Yes	92.8
12	IVS7-2A>G/wt	EVA	Yes	85.2
13	H723R/H723R	EVA	Yes	81.0
14	IVS7-2A>G/IVS7-2A>G	EVA	Yes	91.2
15	IVS7-2A>G/IVS8 + 5G>C	EVA, M	Yes	91.0
16	T410M/T410M	EVA, M, V	Yes	89.0
17	IVS7-2A>G/IVS7-2A>G	EVA, M	Yes	87.6
18	IVS7-2A>G/IVS7-2A>G	EVA, M	Yes	79.6
19	wt/wt	M	Yes	88.2
20	wt/wt	EVA	Yes	79.2
21	wt/wt	M, V, S	No	0

Abbreviations: EVA, enlarged vestibular aqueduct; M, incomplete partition of the cochlea (Mondini dysplasia); S, semicircular canal dysplasia; V, vestibular enlargement; wt, wild type.

[a] Average of the 5 speech recognition scores.

intensive postoperative rehabilitation, including genetic screening and imaging studies into the battery of preoperative evaluations might be mandatory.

All 22 patients with genetic mutations, both the 18 patients with *SLC26A4* mutations and the 4 patients with *GJB2* mutations, demonstrated excellent speech perception performance with CI. Accordingly, a significant positive correlation was observed between the presence of *SLC26A4* mutations and the sum of speech recognition scores in the general linear model. One reasonable explanation is that the pathogenic consequences of mutations in both genes are confined to the inner ear and spare the integrity of the auditory nerve and central auditory pathway, which are essential for the function of CI. Indeed, previous research revealed that *GJB2* mutations lead to hearing impairment via blockade of potassium recycling in the inner ear,[32] whereas *SLC26A4* mutations induce hearing loss by affecting pH in the space within the stria vascularis and result in the loss of endocochlear potential in the inner ear.[33] Satisfactory speech performance outcome has also been documented in patients with other genetic mutations for which the pathogenetic process is confined to the inner ear, including patients with the mitochondrial m.1555A>G mutation,[34] those with *OTOF* (OMIM *603681) mutations,[35] those with Usher syndrome type 1,[36] patients with *DFNA9* (OMIM #601369),[37] and patients with *DFNA17* (OMIM #603622).[38] Following this line of reasoning, identification of patients with genetic mutations that exclusively involve the inner ear might assist in selecting CI candidates in whom a success rate of nearly 100% is to be anticipated, as demonstrated in the present study.

The correlation between poor CI outcome and the presence of a narrow IAC has been verified in several recent studies.[11,12] Other types of IEMs, such as EVA and incomplete partition of the cochlea or common cavity, did not appear to impact the long-term outcome with CI.[11,12] Consistent with previous studies, children with a narrow IAC performed much more poorly in speech perception as compared with those with other types of IEMs and those without IEMs in our cohort (Table 5) ($P < .001$ in all speech recognition scores). Although the difference was exceedingly significant, a narrow IAC is an uncommon imaging finding that has only been identified in less than 10% of children with hearing impairment,[11,12,39] thus limiting its application in a general clinical setting. By contrast, as revealed in the current and previous reports,[13,15,20] one-third to one-half of CI candidates harbored mutations in common deafness genes. Unlike the imaging finding of a narrow IAC, patients with common genetic mutations are associated with an excellent outcome of CI. From this perspective, genetic diagnosis has important clinical implications in predicating CI outcome in a population that could not be addressed by imaging studies before implantation.

To our knowledge, this pilot report might be among the first to investigate the impact of genetic diagnosis on the outcome of CI by pooling together the results of common genetic mutations, which mainly involve the inner ear, and inspecting the interplay of genetic diagnosis with other prognostic factors by constructing regression models. In contrast to previous literature, which reported good CI outcome among patients with *GJB2* mutations,[13-21] the current article additionally

found that mutations in another common deafness gene, *SLC26A4*, might also represent a good prognostic factor in pediatric CI candidates. The power of the present study, however, might be compromised by its limited number of cases and the single ethnic background of the studied cohort, since common deafness genetic mutations differ remarkably among various populations. As exemplified in the general linear model, a significant correlation between the sum of speech recognition scores and the presence of *GJB2* mutations could not be identified, probably owing to the limited number of children with *GJB2* mutations in the present cohort, which in turn might be attributed to the low prevalence of *GJB2* mutations in the Taiwanese population.[26] Multicenter studies on the long-term results with CI might be warranted to validate the preliminary observations of the current study and to collect more comprehensive data for establishing a predictive model that could tailor individual estimation of postimplantation outcome for each CI candidate.

In conclusion, by comparing the speech perception performance according to genetic and imaging results and controlling possible confounding prognostic variables in the general linear model, the present study revealed that genetic diagnosis and imaging results were the 2 predominant factors determining the long-term speech perception performance in children with CI. Specifically, children with a narrow IAC on imaging studies were usually associated with poor outcome, whereas children with either *SLC26A4* or *GJB2* mutations always excelled in speech perception performance after cochlear implantation. The predictive values of these 2 prognostic indicators appear complementary to each other. Accordingly, in pediatric CI candidates, a combination of both genetic examination and imaging studies is recommended to be included in the battery of preoperative evaluations before proceeding to implantation.

Accepted for Publication: September 7, 2007.
Correspondence: Chuan-Jen Hsu, MD, PhD, Division of Pediatric Otolaryngology, Department of Otolaryngology, National Taiwan University Hospital, 7 Chung-Shan S Rd, Taipei 100, Taiwan (cjhsu@ntu.edu.tw).
Author Contributions: Dr Hsu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Wu, Chen, and Hsu. *Acquisition of data:* Wu and Hsu. *Analysis and interpretation of data:* Wu and Lee. *Drafting of the manuscript:* Wu. *Critical revision of the manuscript for important intellectual content:* Lee, Chen, and Hsu. *Statistical analysis:* Lee. *Obtained funding:* Hsu. *Administrative, technical, and material support:* Chen and Hsu. *Study supervision:* Chen and Hsu.
Financial Disclosure: None reported.
Funding/Support: This study was supported by research grant NSC-94-2314-B-002-040 from the National Science Council of the Executive Yuan of the Republic of China.
Previous Presentation: This work was presented at the 6th Molecular Biology of Hearing and Deafness Conference; July 12, 2007; Cambridge, England.
Additional Contributions: M. J. Horng, MAud, and the NWL Foundation for the Hearing Impaired, Taipei, Taiwan, assisted in recording the speech performance results.

REFERENCES

1. Nadol JB Jr. Hearing loss. *N Engl J Med*. 1993;329(15):1092-1102.
2. Marazita ML, Ploughman LM, Rawlings B, Remington E, Arnos KS, Nance WE. Genetic epidemiological studies of early-onset deafness in the US school-age population. *Am J Med Genet*. 1993;46(5):486-491.
3. Yoshinaga-Itano C, Sedey AL, Coulter DK, Mehl AL. Language of early- and later-identified children with hearing loss. *Pediatrics*. 1998;102(5):1161-1171.
4. Hammes DM, Novak MA, Rotz LA, Willis M, Edmondson DM, Thomas JF. Early identification and cochlear implantation: critical factors for spoken language development. *Ann Otol Rhinol Laryngol Suppl*. 2002;189:74-78.
5. McConkey Robbins A, Koch DB, Osberger MJ, Zimmerman-Phillips S, Kishon-Rabin L. Effect of age at cochlear implantation on auditory skill development in infants and toddlers. *Arch Otolaryngol Head Neck Surg*. 2004;130(5):570-574.
6. Nicholas JG, Geers AE. Effects of early auditory experience on the spoken language of deaf children at 3 years of age. *Ear Hear*. 2006;27(3):286-298.
7. Cullen RD, Higgins C, Buss E, Clark M, Pillsbury HC III, Buchman CA. Cochlear implantation in patients with substantial residual hearing. *Laryngoscope*. 2004; 114(12):2218-2223.
8. Gantz BJ, Turner CW. Combining acoustic and electrical hearing. *Laryngoscope*. 2003;113(10):1726-1730.
9. Rubinstein JT, Parkinson WS, Tyler RS, Gantz BJ. Residual speech recognition and cochlear implant performance: effects of implantation criteria. *Am J Otol*. 1999;20(4):445-452.
10. Geers A, Brenner C, Davidson L. Factors associated with development of speech perception skills in children implanted by age five. *Ear Hear*. 2003; 24(1)(suppl):24S-35S.
11. Papsin BC. Cochlear implantation in children with anomalous cochleovestibular anatomy. *Laryngoscope*. 2005;115(1, pt 2)(suppl 106):1-26.
12. Kim LS, Jeong SW, Huh MJ, Park YD. Cochlear implantation in children with inner ear malformations. *Ann Otol Rhinol Laryngol*. 2006;115(3):205-214.
13. Cullen RD, Buchman CA, Brown CJ, et al. Cochlear implantation for children with GJB2-related deafness. *Laryngoscope*. 2004;114(8):1415-1419.
14. Lustig LR, Lin D, Venick H, et al. GJB2 gene mutations in cochlear implant recipients: prevalence and impact on outcome. *Arch Otolaryngol Head Neck Surg*. 2004;130(5):541-546.
15. Taitelbaum-Swead R, Brownstein Z, Muchnik C, et al. Connexin-associated deafness and speech perception outcome of cochlear implantation. *Arch Otolaryngol Head Neck Surg*. 2006;132(5):495-500.
16. Dahl HH, Wake M, Sarant J, Poulakis Z, Siemering K, Blamey P. Language and speech perception outcomes in hearing-impaired children with and without connexin 26 mutations. *Audiol Neurootol*. 2003;8(5):263-268.
17. Green GE, Scott DA, McDonald JM, et al. Performance of cochlear implant recipients with GJB2-related deafness. *Am J Med Genet*. 2002;109(3):167-170.
18. Fukushima K, Sugata K, Kasai N, et al. Better speech performance in cochlear implant patients with GJB2-related deafness. *Int J Pediatr Otorhinolaryngol*. 2002; 62(2):151-157.
19. Matsushiro N, Doi K, Fuse Y, et al. Successful cochlear implantation in prelingual profound deafness resulting from the common 233delC mutation of the GJB2 gene in the Japanese. *Laryngoscope*. 2002;112(2):255-261.
20. Sinnathuray AR, Toner JG, Clarke-Lyttle J, Geddis A, Patterson CC, Hughes AE. Connexin 26 (GJB2) gene-related deafness and speech intelligibility after cochlear implantation. *Otol Neurotol*. 2004;25(6):935-942.
21. Sinnathuray AR, Toner JG, Geddis A, Clarke-Lyttle J, Patterson CC, Hughes AE. Auditory perception and speech discrimination after cochlear implantation in patients with connexin 26 (GJB2) gene-related deafness. *Otol Neurotol*. 2004; 25(6):930-934.
22. Jackler RK, Luxford WM, House WF. Congenital malformations of the inner ear: a classification based on embryogenesis. *Laryngoscope*. 1987;97(3, pt 2) (suppl 40):2-14.
23. McClay JE, Tandy R, Grundfast K, et al. Major and minor temporal bone abnormalities in children with and without congenital sensorineural hearing loss. *Arch Otolaryngol Head Neck Surg*. 2002;128(6):664-671.
24. Fu QJ, Hsu CJ, Horng MJ. Effects of speech processing strategy on Chinese tone recognition by nucleus-24 cochlear implant users. *Ear Hear*. 2004;25(5):501-508.
25. Wu CC, Chen PJ, Hsu CJ. Specificity of SLC26A4 mutations in the pathogenesis of inner ear malformations. *Audiol Neurootol*. 2005;10(4):234-242.
26. Hwa HL, Ko TM, Hsu CJ, et al. Mutation spectrum of the connexin 26 (GJB2) gene in Taiwanese patients with prelingual deafness. *Genet Med*. 2003;5(3): 161-165.

27. Wu CC, Chiu YH, Chen PJ, Hsu CJ. Prevalence and clinical features of the mitochondrial m.1555A>G mutation in Taiwanese patients with idiopathic sensorineural hearing loss and association of haplogroup f with low penetrance in three families. *Ear Hear*. 2007;28(3):332-342.
28. Liu TC, Hsu CJ, Horng MJ. Tone detection in Mandarin-speaking hearing-impaired subjects. *Audiology*. 2000;39(2):106-109.
29. Kimberling WJ. Estimation of the frequency of occult mutations for an autosomal recessive disease in the presence of genetic heterogeneity: application to genetic hearing loss disorders. *Hum Mutat*. 2005;26(5):462-470.
30. Connexins and deafness. The Connexin-deafness homepage Web site. http://davinci.crg.es/deafness. Accessed September 1, 2007.
31. Wu CC, Yeh TH, Chen PJ, Hsu CJ. Prevalent SLC26A4 mutations in patients with enlarged vestibular aqueduct and/or Mondini dysplasia: a unique spectrum of mutations in Taiwan, including a frequent founder mutation. *Laryngoscope*. 2005;115(6):1060-1064.
32. Spicer SS, Schulte BA. The fine structure of spiral ligament cells relates to ion return to the stria and varies with place-frequency. *Hear Res*. 1996;100(1-2):80-100.
33. Wangemann P, Itza EM, Albrecht B, et al. Loss of KCNJ10 protein expression abolishes endocochlear potential and causes deafness in Pendred syndrome mouse model. *BMC Med*. 2004;2:30.
34. Tono T, Ushisako Y, Kiyomizu K, et al. Cochlear implantation in a patient with profound hearing loss with the A1555G mitochondrial mutation. *Am J Otol*. 1998;19(6):754-757.
35. Rouillon I, Marcolla A, Roux I, et al. Results of cochlear implantation in two children with mutations in the OTOF gene. *Int J Pediatr Otorhinolaryngol*. 2006;70(4):689-696.
36. Pennings RJ, Damen GW, Snik AF, Hoefsloot L, Cremers CW, Mylanus EA. Audiologic performance and benefit of cochlear implantation in Usher syndrome type I. *Laryngoscope*. 2006;116(5):717-722.
37. Vermeire K, Brokx JP, Wuyts FL, et al. Good speech recognition and quality-of-life scores after cochlear implantation in patients with DFNA9. *Otol Neurotol*. 2006;27(1):44-49.
38. Hildebrand MS, de Silva MG, Gardner RJ, et al. Cochlear implants for DFNA17 deafness. *Laryngoscope*. 2006;116(12):2211-2215.
39. Wu CC, Chen YS, Chen PJ, Hsu CJ. Common clinical features of children with enlarged vestibular aqueduct and Mondini dysplasia. *Laryngoscope*. 2005;115(1):132-137.

Announcement

Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), *Archives of Pediatrics and Adolescent Medicine* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 15, 2004 (2004;292(11):1363-1364) and June 15, 2005 (2005;293(23):2927-2929) issues of *JAMA*. Also see the Instructions to Authors on our Web site: www.archpediatrics.com.