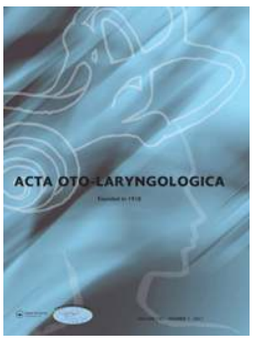

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ORIGINAL ARTICLE

Outcomes of cochlear implantation for the patients with specific genetic etiologies: a systematic literature review

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ABSTRACT

Conclusion: Most of the cases with gene mutations of intra-cochlear etiology showed relatively good CI outcomes. To progress toward more solid evidence-based CI intervention, a greater number of reports including CI outcomes for specific gene mutations are desired.

Background: Cochlear implantation (CI) is the most important and effective treatment for patients with profound sensorineural hearing loss. However, the outcomes of CI vary among patients. One of the reasons of this heterogeneous outcome for cochlear implantation is thought to be the heterogeneous nature of hearing loss. Indeed, genetic factors, the most common etiology in severe-to-profound hearing loss, might be one of the key determinants of outcomes for CI and electric acoustic stimulation (EAS). Patients with genetic causes involving an 'intra-cochlear' etiology show good CI/EAS outcomes.

Review: This review article aimed to summarize the reports on CI/EAS outcomes in patients with special genetic causes as well as to assist in future clinical decision-making. Most of the cases were suspected of an intra-cochlear etiology, such as those with *GJB2*, *SLC26A4*, and *OTOF* mutations, which showed relatively good CI outcomes. However, there have only been a limited number of reports on patients with other gene mutations.

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Cochlear implantation; electric acoustic stimulation; GJB2; SLC26A4; CDH23; OTOF; ACTG1; TMPRSS3; Usher syndrome; Waardenburg syndrome

Introduction

Congenital sensorineural hearing loss is the most common sensory disorder, with ~1 in every 1000 newborns in developed countries suffering severe-to-profound hearing loss. With regard to the etiology of hearing loss, at least 50% of cases are attributable to genetic causes [1].

Cochlear implantation (CI) is the most important and effective treatment for patients with profound sensorineural hearing loss. However, the outcomes of CI vary among patients. One of the reasons of this heterogeneous outcome for cochlear implantation is thought to be the heterogeneous nature of hearing loss. Indeed, genetic factors, the most common etiology in severe-to-profound hearing loss, might be one of the key determinants of outcomes for CI and electric acoustic stimulation (EAS). Recently, we reported a comprehensive study on the etiology of patients receiving CI/EAS, with special emphasis on genetic epidemiology, and revealed that the patients with genetic causes involving an 'intra-cochlear' etiology showed good CI/EAS outcomes [2]. In addition, our recent series of studies on satisfactory auditory performance after receiving CI/EAS in patients with specific deafness gene mutations indicates that genetic testing will be helpful in predicting CI/EAS outcomes, as well as in deciding treatment choices [3,4].

However, because of the extreme genetic heterogeneity of deafness, the clinical application of genetic testing and subsequent decision-making based on genetic testing information in clinical settings remain difficult. To date, more than 80 genes have been reported to be associated with non-syndromic sensorineural hearing loss (SNHL) (http://hereditaryhearingloss.org). Recent advances in targeted exon-sequencing of selected genes using Massively Parallel DNA Sequencing (MPS) technology have enabled us to identify causative mutations in a relatively short time. Further, it now appears possible to identify the etiology of every hearing loss patient prior to clinical decision-making.

In this review article, we aimed to summarize the reports on CI/EAS outcomes in patients with special genetic causes, as well as to assist in future clinical decision-making.

Methods

Literature search

The PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) was searched from April 1996 to December 2016. The following key words were used to identify all studies reporting on cochlear implantation outcomes and genetic mutations, respectively: 'GJB2' + 'cochlear implantation', 'SLC26A4' + 'cochlear implantation', 'CDH23' + 'cochlear implantation', 'CDH23' + 'electric acoustic stimulation', 'OTOF' + 'cochlear implantation', 'Mitochondria' + 'cochlear implantation', 'Mitochondria' + 'electric acoustic stimulation', 'COCH' + 'cochlear implantation', 'ACTG1' +

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'cochlear implantation', 'ACTG1' + 'electric acoustic stimulation', 'TMPRSS3' + 'cochlear implantation', 'TMPRSS3' + 'electric acoustic stimulation', 'Usher syndrome' + 'cochlear implantation', and 'Waardenburg syndrome' + 'cochlear implantation'.

Inclusion criteria

Titles and abstracts of the candidate articles identified in the database search mentioned above were screened, and we selected the articles reporting on CI/EAS outcomes. Subsequently, a full-length article review was performed according to the following criteria.

1. The article was published in a peer-reviewed journal in the English language.
2. The article reported not only CI/EAS hearing thresholds with CI/EAS, but also other CI/EAS outcome measurements.

Results and discussion

Cochlear implantation outcomes in patients with GJB2 mutations

Mutation in the *GJB2* gene is the most prevalent genetic cause of congenital severe-to-profound hearing loss worldwide. A series of studies has demonstrated that 15–25% of patients with congenital hearing loss have a *GJB2* mutation [5,6]. Due to this high frequency and the small size of the *GJB2* gene, which has only one coding exon, making analysis possible using conventional Sanger sequencing, many reports on *GJB2* gene mutations are available. To date, more than 100 *GJB2* variations have been reported (see the Connexin-deafness homepage: http://www.davinc.crg.es/deafness).

For the same reason, there are many reports concerning CI outcomes for patients with *GJB2* mutations. In the database search, we identified 82 articles including the selected keywords, with 35 of them mentioning CI outcomes (Table 1). Most reports were retrospective analyses of CI patients, and patients with *GJB2* mutations showed good or identical CI performance to those in other groups. Considering the fact that one out of four-to-five congenital deafness patients carry biallelic *GJB2* mutations, it is understandable that the CI performance of *GJB2* patients is considered to be equivalent to or slightly better than the overall average for CI patients. (In general, non-*GJB2* patients consist of those with inner ear malformation, cochlear nerve deficiency, and associated mental retardation or pervasive developmental disorder, thus limiting the CI outcomes for the non-*GJB2* group).

It is worth noting that Lalwani et al. [7] reported that the CI outcomes of patients with *GJB2* mutations, measured using many kinds of assessment tests, were worse than the average for normal CI patients with regard to certain rehabilitation outcomes based on certain test results. Thus, detailed outcome studies using many kinds of outcome measures are required to confirm the outcomes for *GJB2* patients.

Cochlear implantation outcomes in patients with SLC26A4 mutations

Mutations in the *SLC26A4* gene are known to be responsible for Pendred syndrome and non-syndromic hearing loss with enlarged vestibular aqueduct (EVA). The *SLC26A4* mutation is the second most frequent mutation in patients with severe-to-profound sensorineural hearing loss. However, there have been only a limited number of studies performed on *SLC26A4* mutations in comparison with those on *GJB2* mutations. Studies on non-syndromic hearing loss have revealed that biallelic *SLC26A4* mutations are present in 2–3.5% of Caucasian patients, whereas 5.5–12.6% of East Asian patients with NSHL have biallelic *SLC26A4* mutations [6].

In the database search, we identified 22 articles including the selected keywords, with nine of them mentioning CI outcomes (Table 2). Most reports were retrospective analyses or case reports of CI patients, and patients with *SLC26A4* mutations showed good or identical CI performance to those of other groups. Yan et al. [8] reported that CI outcomes in patients with *SLC26A4* mutations were worse than those in patients with *GJB2* mutations, but better than those in other patients.

Kim et al. [9] reported that patients experiencing gusher during CI surgery had vestibular aqueducts of 3.65 ± 1.12 mm in width, whereas the width in patients without gusher was 2.03 ± 0.66 mm in width. Yamazaki et al. [10] reported that patients with biallelic *SLC26A4* mutations with EVA and incomplete partitioning type II also experience gusher during CI surgery. Combining all previous data, patients with *SLC26A4* biallelic mutations appear to be good candidates for CI surgery; however, surgeons should take appropriate care, due to the potential for intra-operative gusher.

Cochlear implantation outcomes in patients with CDH23 mutations

The *CDH23* mutation is the second or third most frequent mutation in patients with severe-to-profound sensorineural hearing loss [11]. However, there have been only a limited number of studies on *CDH23* mutations performed, as it has many exons and the analysis of *CDH23* is time-consuming.

In the database search, we identified five articles including the selected keywords; however, three of them described Usher syndrome patients, so we were able to find only one article that mentioned CI/EAS outcomes (Table 3) [3]. In this report, the patients with biallelic *CDH23* mutations showed good EAS performance.

Cochlear implantation outcomes in patients with OTOF mutations

Mutations in the *OTOF* gene are reported to be a major cause of non-syndromic recessive auditory neuropathy

Table 1. Cochlear implantation outcomes in patients with *GJB2* mutations.

First author	Title	Journal	Number of patients	Summary
Wu CM	Long-term cochlear implant outcomes in children with *GJB2* and *SLC26A4* mutations.	PLoS One 2015;10:e0138575.	25	Genetic analysis was conducted on 222 cochlear implant patients, and identified 25 patients with *GJB2* gene mutations, and 23 cases of *SLC26A4* gene mutation. Auditory performance of the *GJB2* and *SLC26A4* mutation groups were favorable.
Busi M	Cochlear implant outcomes and genetic mutations in children with ear and brain anomalies.	Biomed Res Int 2015;2015:696281	22	Genetic analysis was conducted on 426 cochlear implant patients, and identified 22 patients with *GJB2* gene mutations, four cases of *SLC26A4* gene mutation, and one mitochondrial mutation case. A comparison of cases with a genetic etiology with the other cases showed that the *GJB2* and *SLC26A4* mutation groups showed significantly better outcomes.
Varga L	Is deafness etiology important for prediction of functional outcomes in pediatric cochlear implantation?	Acta Otolaryngol 2014;134:571–8	45	Genetic analysis was conducted on 92 cochlear implant patients, and identified 42 cases with *GJB2* mutations and 18 syndromeic hearing loss cases. The Category of Auditory Performance (CAP) score of the *GJB2* group was the most favorable, followed by the unknown group and syndromic hearing loss group.
Black J	Paediatric cochlear implantation: adverse prognostic factors and trends from a review of 174 cases.	Cochlear Implants Int 2014;15:62–77	15	Examined the factors for cochlear implantation outcome prognosis in 174 cochlear implant cases. The strongest predictor influencing the outcome was the age at cochlear implant surgery. The outcome for the *GJB2* patients was equivalent to that for other cochlear implant patients.
Davcheva-Chakar M	Speech perception outcomes after cochlear implantation in children with *GJB2*/DFNB1 associated deafness.	Balkan Med J 2014;31:60–3	18	Genetic analysis was conducted on 18 cochlear implant patients, and found seven cases with *GJB2* gene mutations. Results of speech perception testing conducted after the cochlear implantation did not differ significantly.
Popov TM	Auditory outcome after cochlear implantation in patients with congenital non-syndromic hearing loss: influence of the *GJB2* status.	Otol Neurotol 2014;35:1361–5	30	Authors compared 30 cochlear implant patients with *GJB2* mutations to 30 cochlear implant patients without *GJB2* gene mutations. As a result, the *GJB2* mutation group performed significantly better at many kinds of tests including the speech discrimination test.
Yan YJ	The effect of *GJB2* and *SLC26A4* gene mutations on rehabilitative outcomes in pediatric cochlear implant patients.	Eur Arch Otorhinolaryngol 2013;270:2865–70	15	Genetic analysis was conducted on 41 cochlear implant patients, and identified 15 patients with *GJB2* gene mutations and 10 cases of *SLC26A4* gene mutation. The results of Meaningful Auditory Integration Scale (MAIS), CAP and Speech Intelligibility Rating (SIR) for the *GJB2* group were the most favorable, followed by the *SLC26A4* group and unknown group.
Yoshida H	Long-term speech perception after cochlear implant in pediatric patients with *GJB2* mutations.	Auris Nasus Larynx 2013;40:435–9	10	Genetic analysis was conducted on 29 cases of cochlear implant, and 10 cases with *GJB2* gene mutations were found. The results of Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS), monosyllable, and word discrimination for the *GJB2* group were better than those for the others.
Riahi Z	A novel frameshift mutation (c.405delC) in the *GJB2* gene associated with autosomal recessive hearing loss in two Tunisian families.	Int J Pediatr Otorhinolaryngol 2013;77:1485–8	2	Two cases with a novel *GJB2* gene mutation are reported. Outcomes of the cochlear implantation were good.
Riahi Z	Compound heterozygosity for dominant and recessive *GJB2* mutations in a Tunisian family and association with successful cochlear implant outcome.	Int J Pediatr Otorhinolaryngol 2013;77:1481–4	1	Case reports of compound heterozygous *GJB2* autosomal dominant and autosomal recessive mutations. Outcomes of the cochlear implantation were good.
da Motta LH	Prevalence of the 35delG mutation in deaf South Brazilian infants submitted to cochlear implantation.	Int J Pediatr Otorhinolaryngol 2012;76:287–90	3	Genetic analysis was conducted on 37 cases of cochlear implant, and three cases with *GJB2* gene mutations were found. The SIR score of the *GJB2* group was better than that of the others.

(*continued*)

Table 1. Continued

First author	Title	Journal	Number of patients	Summary
Matsui T	Outcome of cochlear implantation in children with congenital cytomegalovirus infection or *GJB2* mutation.	Acta Otolaryngol 2012;132:597–602	7	Authors compared five cCMV infection hearing loss patients to seven patients with *GJB2* gene mutations. MAIS and Meaningful Use of Speech Scale (MUSS) scores did not significantly differ between the groups.
Black J	Defining and evaluating success in paediatric cochlear implantation—an exploratory study.	Int J Pediatr Otorhinolaryngol 2012;76:1317–26	6	Authors conducted an analysis of the factors affecting cochlear implant outcomes for 25 cases of cochlear implant. As a result, *GJB2* was found to have a small impact on outcome, whereas delay in cochlear implantation had a major impact.
Wu CC	Genetic characteristics in children with cochlear implants and the corresponding auditory performance.	Laryngoscope 2011;121:1287–93	9	Genetic analysis was conducted for 110 cochlear implant patients, and nine cases with *GJB2* mutations, 18 cases with *SLC26A4*, and one case with *OTOF* mutation were identified. The CAP score for the genetic etiology group was better than that for the others.
Motasaddi Zarandy M	Clinical application of screening for *GJB2* mutations before cochlear implantation in a heterogeneous population with high rate of autosomal recessive non-syndromic hearing loss.	Genet Res Int 2011;2011:787026	46	Genetic analysis was conducted for 201 cases of cochlear implant, and 46 cases with *GJB2* gene mutations were identified. Results of the Speech Reception Threshold (SRT) conducted after cochlear implantation showed the improvement in the *GJB2* group was the same level as in the other groups.
Peyvandi A	Detection of the *GJB2* mutation in Iranian children with hearing loss treated with cochlear implantation.	Balkan J Med Genet 2011;14:19–24	6	Genetic analysis was conducted for 42 cases of cochlear implant, and identified six cases with *GJB2* gene mutations. Speech perception scores of the *GJB2* group were significantly better than those of the others.
Karamert R	Association of *GJB2* gene mutation with cochlear implant performance in genetic non-syndromic hearing loss.	Int J Pediatr Otorhinolaryngol 2011;75:1572–5	22	Genetic analysis was conducted for 65 cochlear implant patients, and identified 22 cases with *GJB2* gene mutations. MAIS and MUSS scores for the *GJB2* patients were better but not significantly so.
Weegerink NJ	Phenotypes of two Dutch DFNA3 families with mutations in *GJB2*.	Ann Otol Rhinol Laryngol 2011;120:191–7	3	Relatively rare autosomal dominant inherited *GJB2* gene mutations were identified in one case. The cochlear implant outcome was favorable.
Daneshi A	Prevalence of *GJB2*-associated deafness and outcomes of cochlear implantation in Iran.	J Laryngol Otol 2011;125:455–9	33	Genetic analysis was conducted on 166 cochlear implant patients, and 33 cases with *GJB2* gene mutations were identified. CI outcomes of 33 *GJB2* mutations cases and 36 other cases were favorable in both groups.
Chora JR	DFNB1-associated deafness in Portuguese cochlear implant users: prevalence and impact on oral outcome.	Int J Pediatr Otorhinolaryngol 2010;74:1135–9	41	Genetic analysis was conducted for 117 cases of cochlear implant, and identified 41 cases with *GJB2* gene mutations. The *GJB2* gene mutation group showed more favorable results for various tests.
Reinert J	High homogeneity in auditory outcome of pediatric CI-patients with mutations in Gap-Junction-Protein Beta2.	Int J Pediatr Otorhinolaryngol 2010;74:791–5	13	Genetic analysis was conducted for 44 cochlear implant patients. Authors compared the cochlear implant outcome of 13 *GJB2* gene mutation cases, 15 *GJB2*-negative cases with other affected family members, and 16 sporadic cases without *GJB2* mutations. As a result, some of the tests revealed the *GJB2* group outcomes were the most favorable among the groups.
Lalwani AK	Predictability of cochlear implant outcome in families.	Laryngoscope 2009;119:131–6	9	Genetic analysis was conducted on 71 cochlear implant patients from 35 families, and identified nine cases with *GJB2* gene mutations. The results of various evaluations showed that the outcomes in the *GJB2* gene mutation group were poorer than the others.
Dalamón V	Performance of speech perception after cochlear implantation in DFNB1 patients.	Acta Otolaryngol 2009;129:395–8	11	Genetic analysis was conducted for 24 cases of cochlear implant, and identified 11 cases with *GJB2* gene mutations. The Speech Perception testing was conducted after cochlear implantation and the *GJB2* group showed the same level of improvement as the other group.
Wu CC	Predominance of genetic diagnosis and imaging results as predictors in determining the speech	Arch Pediatr Adolesc Med. 2008 Mar;162(3):269-76.	4	Genetic analysis was conducted for 67 cochlear implant children, and identified four cases with *GJB2* gene mutations, and 18 cases with *SLC26A4* gene mutations. The Speech

(*continued*)

Table 1. Continued

First author	Title	Journal	Number of patients	Summary
	perception performance outcome after cochlear implantation in children.			Perception results of the *GJB2* group were better than those of the *SLC26A4* group and the other cases.
Connell SS	Performance after cochlear implantation in DFNB1 patients.	Otolaryngol Head Neck Surg 2007;137:596–602	12	The cochlear implantation outcome measured by Reynell language tests for 32 cases with *GJB2* gene mutations was better than that for the non-*GJB2* group.
Taitelbaum-Swead R	Connexin-associated deafness and speech perception outcome of cochlear implantation.	Arch Otolaryngol Head Neck Surg 2006;132:495–500	30	Authors compared the cochlear implantation outcomes for 30 patients with *GJB2* gene mutations with those for 30 cases without *GJB2* mutations. Results showed that the CI outcomes did not differ significantly between groups.
Propst EJ	Auditory responses in cochlear implant users with and without *GJB2* deafness.	Laryngoscope 2006;116:317–27	39	Authors compared the Electrically Evoked Compound Action Potential (e-CAP) of the cochlear implantation for 39 patients with *GJB2* gene mutations to 58 cases without *GJB2* mutations. Results showed that the e-CAP of the basal turn and apical turn region did not differ in the *GJB2* group. On the other hand, a reduction in basal region response was observed in the non-*GJB2* group.
Lustig LR	*GJB2* gene mutations in cochlear implant recipients: prevalence and impact on outcome.	Arch Otolaryngol Head Neck Surg 2004;130:541–6	3	Genetic analysis was conducted for 77 cochlear implant cases, and three cases with *GJB2* gene mutations were identified. The cochlear implantation outcome of the *GJB2* group was same as that of the other group.
Cullen RD	Cochlear implantation for children with *GJB2*-related deafness.	Laryngoscope 2004;114:1415–9	20	Genetic analysis was conducted for 47 cochlear implant patients, and 20 patients with *GJB2* gene mutations were identified. Speech perception scores for the *GJB2* group were better than those for the others, but not significantly so.
Sinnathuray AR	Connexin 26 (*GJB2*) gene-related deafness and speech intelligibility after cochlear implantation.	Otol Neurotol 2004;25:935–42	14	Genetic analysis was conducted for 39 cochlear implant patients, and 14 patients with *GJB2* gene mutations were identified. Results of the speech intelligibility test for the *GJB2* group were significantly better than those for the others.
Sinnathuray AR	Auditory perception and speech discrimination after cochlear implantation in patients with connexin 26 (*GJB2*) gene-related deafness.	Otol Neurotol 2004;25:930–4	11	Genetic analysis was conducted for 31 cochlear implant patients, and 11 patients with *GJB2* gene mutations were identified. The results of a sentence perception test for the *GJB2* group were significantly better than those for the others.
Bauer PW	The effect of *GJB2* allele variants on performance after cochlear implantation.	Laryngoscope 2003;113:2135–40	22	Genetic analysis was conducted for 55 cases of cochlear implantation, and 22 cases with *GJB2* gene mutations were identified. Reading and cognitive skills for the *GJB2* gene mutation group were favorable.
Matsushiro N	Successful cochlear implantation in pre-lingual profound deafness resulting from the common 233delC mutation of the *GJB2* gene in the Japanese.	Laryngoscope 2002;112:255–61	4	Genetic analysis was conducted for 15 cochlear implant patients, and four patients with *GJB2* gene mutations were identified. The speech discrimination score of the *GJB2* group was better than that of the others.
Fukushima K	Better speech performance in cochlear implant patients with *GJB2*-related deafness.	Int J Pediatr Otorhinolaryngol 2002;62:151–7	3	Genetic analysis was conducted for seven cochlear implant patients, and three patients with *GJB2* gene mutations were identified. The language developmental index of the *GJB2* group was better than that of the others.
Green GE	Performance of cochlear implant recipients with *GJB2*-related deafness.	Am J Med Genet 2002;109:167–70	8	Genetic analysis was conducted for 20 cochlear implant patients, and eight cases with *GJB2* gene mutations were identified. The reading skills of the *GJB2* group were better than those of the others.

Table 2. Cochlear implantation outcomes in patients with *SLC26A4* mutations.

First author	Title	Journal	Number of patients	Summary
Wu CM	Long-term cochlear implant outcomes in children with *GJB2* and *SLC26A4* mutations.	PLoS One. 2015;10:e0138575.	25	Genetic analysis was conducted on 222 cochlear implant patients, and identified 25 patients with *GJB2* gene mutations, and 23 cases of *SLC26A4* gene mutation. Auditory performance of the *GJB2* and *SLC26A4* mutation groups were favorable.
Gratacap M	Pediatric cochlear implantation in residual hearing candidates.	Ann Otol Rhinol Laryngol 2015;124:443–51	21	Authors analyzed cochlear implantation outcomes of 53 cochlear implanted children by the type of hearing. The *SLC26A4* gene mutations did not significantly affect the outcomes.
Yamazaki H	*SLC26A4* p.Thr410Met homozygous mutation in a patient with a cystic cochlea and an enlarged vestibular aqueduct showing characteristic features of incomplete partition type I and II.	Int J Pediatr Otorhinolaryngol 2014;78:2322–6	1	Case reports for patients with *SLC26A4* gene mutations with incomplete partition type II (IP-II) and enlarged vestibular aqueduct (EVA). For these cases, it is necessary to consider the possibility of a gusher during cochlear implant surgery.
Yan YJ	The effect of *GJB2* and *SLC26A4* gene mutations on rehabilitative outcomes in pediatric cochlear implant patients.	Eur Arch Otorhinolaryngol 2013;270:2865–70	10	Genetic analysis was conducted on 41 cochlear implant patients, and 15 patients with *GJB2* gene mutations and 10 cases of *SLC26A4* gene mutation were identified. The results of the Meaningful Auditory Integration Scale (MAIS), CAP, and Speech Intelligibility Rating (SIR) for the *GJB2* group were the most favorable, followed by the *SLC26A4* group and unknown group.
Kim BG	Enlarged cochlear aqueducts: a potential route for CSF gushers in patients with enlarged vestibular aqueducts.	Otol Neurotol 2013;34:1660–5	35	To investigate the possibility of a gusher in cochlear implant surgery in EVA patients, authors performed high-resolution CT imaging of 35 cochlear implanted patients with *SLC26A4* mutations. Regarding the average EVA width, that of the intra-operative gusher group was significantly wider (3.65 ± 1.12 mm) than the non-gusher group (2.03 ± 0.66 mm).
Lai R	Genetic diagnosis and cochlear implantation for patients with non-syndromic hearing loss and enlarged vestibular aqueduct.	J Laryngol Otol 2012;126:349–55	12	Genetic analysis was conducted for 21 cochlear implant children with EVA, and 12 kinds of *SLC26A4* gene mutations were identified. The cochlear implantation outcomes were favorable.
Wu CC	Genetic characteristics in children with cochlear implants and the corresponding auditory performance.	Laryngoscope 2011;121:1287–93	18	Genetic analysis was conducted for 110 cochlear implant patients, and nine cases with *GJB2* mutations, 18 cases with *SLC26A4*, and one case with an *OTOF* mutation were identified. The CAP score of the genetic etiology group was better than those of the other.
de Wolf MJ	Two siblings with progressive, fluctuating hearing loss after head trauma, treated with cochlear implantation.	J Laryngol Otol 2010;124:86–9	2	Case reports of twin cochlear implant patients with *SLC26A4* gene mutations. The cochlear implantation outcomes of these cases were favorable, even in the patient with an inner ear malformation.
Wu CC	Predominance of genetic diagnosis and imaging results as predictors in determining the speech perception performance outcome after cochlear implantation in children.	Arch Pediatr Adolesc Med 2008;162:269–76.	18	Genetic analysis was conducted for 67 cochlear implants children, and four cases with *GJB2* gene mutations, and 18 cases with *SLC26A4* gene mutations were identified. The Speech Perception results for the *GJB2* group were better than those for the *SLC26A4* group and the other cases.

Table 3. Cochlear implantation outcomes in patients with *CDH23* mutations.

First author	Title	Journal	Number of patients	Summary
Usami S	Patients with CDH23 mutations and the 1555A > G mitochondrial mutation are good candidates for electric acoustic stimulation (EAS).	Acta Otolaryngol 2012;132:377–84	3	Genetic analysis was conducted for 18 patients with EAS, and three cases with *CDH23* mutations and one case with mitochondrial m.1555A > G mutation were identified. All cases showed favorable EAS outcomes.

Table 4. Cochlear implantation outcomes in patients with *OTOF* mutations.

First author	Title	Journal	Number of patients	Summary
Zhang LP	Identification of novel *OTOF* compound heterozygous mutations by targeted next-generation sequencing in a Chinese patient with auditory neuropathy spectrum disorder.	Int J Pediatr Otorhinolaryngol 2013;77:1749–52	1	Next-generation sequencing analysis was conducted for cochlear implant patients with auditory neuropathy and *OTOF* gene mutations were identified. The cochlear implant outcome was favorable in this case.
Runge CL	A novel otoferlin splice-site mutation in siblings with auditory neuropathy spectrum disorder.	Audiol Neurootol 2013;18:374–82	2	Case reports of twins with *OTOF* gene mutations. The language performance and the e-CAP differed even between the twins. The children with good e-CAP responses showed relatively good cochlear implant performance.
Wu CC	Genetic characteristics in children with cochlear implants and the corresponding auditory performance.	Laryngoscope 2011;121:1287–93	1	Genetic analysis was conducted for 110 cochlear implant patients, and nine cases with *GJB2* mutations, 18 cases with *SLC26A4*, and one case with *OTOF* mutations were identified. The CAP scores of the genetic etiology group were better than those of the others.
Santarelli R	Information from cochlear potentials and genetic mutations helps localize the lesion site in auditory neuropathy.	Genome Med 2010;2:91	NA	The e-CAP reaction in cochlear implantation patients with *OTOF* gene mutations was positive and considered to be similar in pattern to the hearing loss caused by intracochlear etiology.
Rouillon I	Results of cochlear implantation in two children with mutations in the *OTOF* gene.	Int J Pediatr Otorhinolaryngol 2006;70:689–96	2	Case reports of two cochlear implant patients with *OTOF* mutations. The Neural Response Telemetry (NRT) and speech discrimination scores were favorable.
Loundon N	Auditory neuropathy or endocochlear hearing loss?	Otol Neurotol 2005;26:748–54	1	Case reports of cochlear implant patients with *OTOF* mutations.
Rodríguez-Ballesteros M	Auditory neuropathy in patients carrying mutations in the otoferlin gene (*OTOF*).	Hum Mutat 2003;22:451–6	11	Authors identified 37 cases with *OTOF* gene mutations and 11 cases received cochlear implants. The cochlear implantation outcomes for these patients were favorable.

spectrum disorder (ANSD) [12,13]. ANSD due to *OTOF* gene mutations can be characterized by the presence of OAEs in the first 2 years of life, but OAEs later disappear and the hearing loss then resembles other types of non-syndromic hearing loss. Otoferlin (encoded by *OTOF*) is expressed in the inner hair cells and plays an important role in the calcium-dependent exocytosis process for auditory signal transmission. Based on this mechanism of hearing loss, *OTOF* mutations are expected to be a good outcome marker for CI in patients with ANSD [14].

In the database search, we identified 9 articles including the selected keywords, with seven of them mentioning CI outcomes (Table 4). The reports consisted of a systematic review, retrospective analysis, and case reports of CI patients, and patients with *OTOF* mutations showed adequate CI performance in comparison with those in other groups.

Cochlear implantation outcomes in patients with mitochondrial mutations

Mitochondrial mutations are the cause of maternally inherited hearing loss, and generally cause progressive hearing loss. Among the mitochondrial mutations, m.1555A > G mutations in mitochondrial 12S rRNA are frequently found (0.6–5.3%, depending on the ethnic group) in aminoglycoside-induced and late-onset non-syndromic hearing loss [15]. On the other hand, m.3243A > G mutations in tRNA^{Leu}?down>(UUR) are associated with maternally inherited diabetes combined with deafness (MIDD) [16], and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), which frequently present with hearing loss.

In the database search, we identified 39 articles including the selected keywords, with five of them mentioning CI

Table 5. Cochlear implantation outcomes in patients with mitochondrial mutations.

First author	Title	Journal	Number of patients	Summary
Usami S	Patients with CDH23 mutations and the 1555A > G mitochondrial mutation are good candidates for electric acoustic stimulation (EAS).	Acta Otolaryngol 2012;132:377–84	1	Genetic analysis was conducted for 18 patients with EAS, and three cases with *CDH23* mutations and one case with mitochondrial m.1555A > G mutation were identified. All cases showed favorable EAS outcomes.
Sudo A	Successful cochlear implantation in a patient with mitochondrial hearing loss and m.625G > A transition.	J Laryngol Otol 2011;125:1282–5	1	Case report of a cochlear implant patient with a mitochondrial m.625G > A mutation. Cochlear implantation was greatly beneficial for this patient.
Howes T	Role of mitochondrial variation in maternally inherited diabetes and deafness syndrome.	J Laryngol Otol 2008;122:1249–52	1	Case report of bilateral cochlear implantation patients caused by mitochondrial m.3243A > G mutation. The bilateral cochlear implantation outcome was favorable in this case.
Mancuso M	A non-syndromic hearing loss caused by very low levels of the mtDNA A3243G mutation.	Acta Neurol Scand 2004;110:72–4	1	Case report of non-syndromic hearing loss cochlear implantation patients caused by mitochondrial m.3243A > G mutation. The bilateral cochlear implantation outcome was favorable in this case.
Tono T	Cochlear implantation in a patient with profound hearing loss with the A1555G mitochondrial mutation.	Am J Otol 1998;19:754–7	1	Case report of a cochlear implant patient caused by the mitochondrial m.1555A > G mutation. Cochlear implantation was greatly beneficial in this case.

outcomes (Table 5). Two of them were case reports of patients with m.1555A > G mutations, and another two were case reports of patients with m.3243A > G mutations. All reports suggested that CI/EAS is a good treatment option for patients with mitochondrial mutations.

Cochlear implantation outcomes in patients with COCH *mutations*

Hearing loss associated with *COCH* mutations is characterized by late-onset progressive hearing loss complicated with vertigo. The *COCH*-encoded protein cochlin is the most abundant protein in the inner ear; however, its function remains unclear. Histological analysis of the temporal bone in patients with *COCH* mutations revealed the presence of eosinophilic deposits in the spiral ligament, limbus, and osseous spiral lamina [17].

In the database search, we identified six articles including the selected keywords, with only one of them mentioning CI outcomes (Table 6). In this report, the authors compared the CI outcomes of 11 patients with *COCH* mutations to those of 39 other CI patients, and found that patients with *COCH* mutations showed an identical level of CI performance to those in the other group.

Cochlear implantation outcomes in patients with ACTG1 *mutations*

ACTG1 encodes γ-actin, the predominant actin isoform in auditory hair cells and particularly in the cuticular plate, adherens junctions, and stereocilia [18]. Patients with *ACTG1* mutations are characterized by progressive high frequency-associated severe-to-profound hearing loss with residual hearing at low frequencies. From this audiogram type, patients with *ACTG1* mutations are speculated to be a good candidate for EAS.

In the database search, we identified two articles including the selected keywords, with both of them mentioning EAS outcomes (Table 7). The patients with *ACTG1* mutations showed good EAS performance in comparison to those in other groups.

Cochlear implantation outcomes in patients with TMPRSS3 *mutations*

TMPRSS3 is the gene responsible for autosomal recessive hearing loss. Interestingly, *TMPRSS3* causes both DFNB10 (congenital severe-to-profound deafness) and DFNB8 (postlingual onset, high frequency hearing loss with residual hearing at low frequencies) phenotypes [19]. *TMPRSS3* is a type-II transmembrane serine protease proposed to be involved in the processing of the epithelial sodium channel (ENaC) and potassium ion channel (KCNMA1).

In the database search, we identified six articles including the selected keywords, with five of them mentioning CI/EAS outcomes (Table 8). Most reports were retrospective analyses or case reports of CI patients. The CI outcomes of patients with *TMPRSS3* mutations were not consistent. So, further study is required to confirm the outcomes for these patients.

Table 6. Cochlear implantation outcomes in patients with *COCH* mutations.

First author	Title	Journal	Number of patients	Summary
Vermeire K	Good speech recognition and quality-of-life scores after cochlear implantation in patients with DFNA9.	Otol Neurotol 2006;27:44–9	11	Authors compared the cochlear implantation outcome between 11 patients with *COCH* gene mutations to 39 control cases. As a result, speech discrimination and QoL improvements in the cochlear implant patients with *COCH* mutations were equivalent to those of the controls.

Table 7. Cochlear implantation outcomes in patients with *ACTG1* mutations.

First author	Title	Journal	Number of patients	Summary
Miyagawa M	Mutational spectrum and clinical features of patients with ACTG1 mutations identified by massively parallel DNA sequencing.	Ann Otol Rhinol Laryngol 2015;124(Suppl 1): 84S–93S	1	Authors performed next-generation sequencing analysis for 1120 sensorineural hearing loss patients, and five cases with *ACTG1* mutations were identified. One of the five cases wore an EAS and its performance was favorable.
Miyagawa M	Massively parallel DNA sequencing successfully identifies new causative mutations in deafness genes in patients with cochlear implantation and EAS.	PLoS One 2013;8:e75793	1	Genetic analysis was conducted for eight cochlear implants and EAS patients without *GJB2* or *SLC26A4* gene mutations, and causative mutations in *MYO15A*, *TECTA*, *TMPRSS3*, and *ACTG1* were identified. Cochlear implant or EAS performance in these cases was favorable.

Table 8. Cochlear implantation outcomes in patients with *TMPRSS3* mutations.

First author	Title	Journal	Number of patients	Summary
Battelino S	*TMPRSS3* mutations in autosomal recessive non-syndromic hearing loss.	Eur Arch Otorhinolaryngol 2016;273:1151–4	2	Genetic analysis was conducted for 35 autosomal recessive inherited hearing loss families, and one family with a *TMPRSS3* mutation was identified. The cochlear implantation outcome of this patient was favorable.
Miyagawa M	The patients associated with *TMPRSS3* mutations are good candidates for electric acoustic stimulation.	Ann Otol Rhinol Laryngol 2015;124(Suppl 1):193S–204S	3	Authors performed next-generation sequencing analysis for 1120 sensorineural hearing loss patients, and five cases with *TMPRSS3* mutations were identified. Three of the five cases wore an EAS and performance was favorable.
Miyagawa M	Massively parallel DNA sequencing successfully identifies new causative mutations in deafness genes in patients with cochlear implantation and EAS.	PLoS One 2013;8:e75793	1	Genetic analysis was conducted for eight cochlear implants and EAS patients without *GJB2* or *SLC26A4* gene mutations, and causative mutations in *MYO15A*, *TECTA*, *TMPRSS3*, and *ACTG1* were identified. Cochlear implant or EAS performance in these cases was favorable.
Eppsteiner RW	Prediction of cochlear implant performance by genetic mutation: the spiral ganglion hypothesis.	Hear Res 2012;292:51–8	2	Authors performed next-generation sequencing analysis for 29 cochlear implant cases, and two patients with *TMPRSS3* gene mutations, and one patient with a *LOXHD1* mutation were identified. The cochlear implantation outcomes for *TMPRSS3* patients were poor while that for the *LOXHD1* patient was favorable.
Weegerink NJ	Genotype-phenotype correlation in DFNB8/10 families with *TMPRSS3* mutations.	J Assoc Res Otolaryngol 2011;12:753–66	9	Authors performed linkage analysis and direct sequencing analysis for autosomal recessive non-syndromic hearing loss families, and eight families with *TMPRSS3* gene mutations were identified. The cochlear implantation outcome in nine patients with *TMPRSS3* was varied: seven cases showed a favorable outcome, but hearing deteriorated in two cases.

Cochlear implantation outcomes in Usher syndrome patients

Usher syndrome is an autosomal recessive disorder characterized by sensorineural hearing loss, retinitis pigmentosa, and vestibular dysfunction. To date, 10 genes (*MYO7A*, *USH1C*, *CDH23*, *PCDH15*, *SANS*, *CIB2*, *USH2A*, *VLGR1*, *WHRN*, and *CLRN1*) have been reported to be responsible for Usher syndrome.

In the database search, we identified 22 articles including the selected keywords, with 7 of them mentioning CI outcomes (Table 9). The CI outcomes of the Usher syndrome patients varied. However, as the retinitis pigmentosa associated with Usher syndrome is late onset and progressive in nature, it is recommended to provide Usher syndrome children with the best available hearing amplification or CI, if applicable, accompanied with intensive training and/or habilitation prior to the development of retinitis pigmentosa.

Cochlear implantation outcomes in Waardenburg syndrome patients

Waardenburg syndrome is characterized by pigmentary abnormalities of the hair, skin, and eyes, congenital sensorineural hearing loss, and lateral displacement of the inner canthus of each eye. However, the phenotypes of Waardenburg syndrome are heterogeneous [20]. To date, six genes (*PAX3*, *MITF*, *SNAI2*, *EDNRB*, *EDN3*, and *SOX10*) have been reported to be responsible for Waardenburg syndrome.

In the database search, we identified 27 articles including the selected keywords, with 14 of them mentioning CI outcomes (Table 10). The CI outcomes of the Waardenburg syndrome patients varied. In many reports, Waardenburg syndrome CI patients with pervasive developmental or cognitive disorders showed poor outcomes. However, most of the cases demonstrated CI outcomes similar to those for non-syndromic hearing loss patients.

Another difficulty related to CI for Waardenburg syndrome patients is the presence of inner ear malformation. Oysu et al. reported that cochlear hypoplasia was observed in 8% of Waardenburg syndrome patients, which is the same level as that for non-syndromic hearing loss patients [21]. Kontorinis et al. also reported inner ear malformation in Waardenburg syndrome patients at the same level as that for non-syndromic hearing loss cases [22].

In this review article, we summarized the CI outcomes for patients with hearing loss of various genetic causes. Most of

Table 9. Cochlear implantation outcomes in Usher syndrome patients.

First author	Title	Journal	Number of patients	Summary
Broomfield SJ	Cochlear implantation in children with syndromic deafness.	Int J Pediatr Otorhinolaryngol 2013;77:1312–6	9	Among 38 syndromic hearing loss cochlear implanted patients, nine were Usher syndrome patients. The cochlear implantation outcome for cases without cognitive delay was relatively favorable.
Jatana KR	Usher syndrome: characteristics and outcomes of pediatric cochlear implant recipients.	Otol Neurotol 2013;34:484–9	26	Among 712 cochlear implant patients, 26 cases were diagnosed with Usher syndrome by the electro retinogram (ERG) or genetic analysis. 90% of cases had sufficient speech discrimination.
Pietola L	Speech recognition and communication outcomes with cochlear implantation in Usher syndrome type 3.	Otol Neurotol 2012;33:38–41	19	Case series of 19 cochlear implanted Usher syndrome type 3 patients. The cochlear implantation outcomes were favorable and word recognition scores were significantly improved.
Liu XZ	Cochlear implantation in individuals with Usher type 1 syndrome.	Int J Pediatr Otorhinolaryngol 2008;72:841–7	9	Case series of nine cochlear implanted Usher syndrome type 1 patients. The cochlear implantation outcomes measured by word perception test of the patients under 3 years old were significantly improved. On the other hand, the cochlear implant outcome of the children wearing a CI after 3 years old was worse and they used lip reading or total communication.
Damen GW	Quality-of-life and cochlear implantation in Usher syndrome type I.	Laryngoscope 2006;116:723–8	28	Authors compared the QoL of 14 cochlear implanted Usher syndrome type 1 patients and 14 Usher syndrome type 1 patients not receiving a cochlear implant. The QoL of the cochlear implant group was significantly improved in comparison with the patients without cochlear implant.
Pennings RJ	Audiologic performance and benefit of cochlear implantation in Usher syndrome type I.	Laryngoscope 2006;116:717–22	14	Case series of 14 cochlear implanted Usher syndrome type 1 patients. Among 14 cases, 13 showed good performance and word discrimination also significantly improved.
Loundon N	Usher syndrome and cochlear implantation.	Otol Neurotol 2003;24:216–21	13	Among 185 cochlear implant patients, there were 13 Usher type 1 patients. Word recognition and oral expression scores significantly improved in nine of 13 cases that received cochlear implants under age 9.

Table 10. Cochlear implantation outcomes in Waardenburg syndrome patients.

First author	Title	Journal	Number of patients	Summary
van Nierop JW	Paediatric cochlear implantation in patients with Waardenburg syndrome.	Audiol Neurootol 2016;21:187–94	14	Authors compared the cochlear implantation outcome including speech perception and language comprehension of 14 Waardenburg syndrome cases to 48 reference cases. Children with WS performed similarly to the reference group in the study.
Koyama H	The hearing outcomes of cochlear implantation in Waardenburg syndrome.	Biomed Res Int 2016;2016:2854736.	5	Case series of 5 cochlear implanted Waardenburg syndrome patients. Their auditory performance measured by MAIS, MUSS, and monosyllable and word perception developed. Authors concluded that cochlear implantation could be a good treatment option for Waardenburg syndrome.
Kontorinis G	Inner ear anatomy in Waardenburg syndrome: radiological assessment and comparison with normative data.	Int J Pediatr Otorhinolaryngol 2014;78:1320–6	20	Authors compared the rate of inner ear malformations in 20 Waardenburg syndrome cases to 50 normal hearing controls, but did not find significant differences between the groups.
Broomfield SJ	Cochlear implantation in children with syndromic deafness.	Int J Pediatr Otorhinolaryngol 2013;77:1312–6	10	Case series of 10 cochlear implanted Waardenburg syndrome patients. Cochlear implantation was also effective for the Waardenburg syndrome patients without a cognitive delay.
Magalhães AT	Audiological outcomes of cochlear implantation in Waardenburg Syndrome.	Int Arch Otorhinolaryngol 2013;17:285–90	10	Among 806 cochlear implant cases, 10 had Waardenburg syndrome. Six of the 10 cases showed favorable cochlear implantation outcomes, whereas four cases were worse than the others.
de Sousa Andrade SM	Cochlear implant rehabilitation outcomes in Waardenburg syndrome children.	Int J Pediatr Otorhinolaryngol 2012;76:1375–8	7	Among 261 cochlear implantation cases, seven had Waardenburg syndrome. The cochlear implantation outcomes assessed by MAIS, MUSS, CAP, and SIR were the same as normal cochlear implant children.
Amirsalari S	Cochlear implantation outcomes in children with Waardenburg syndrome.	Eur Arch Otorhinolaryngol 2012;269:2179–83	6	Authors compared the cochlear implantation outcomes of 75 non-syndromic hearing loss cases to six Waardenburg syndrome cases. The CAP and SIR scores were slightly worse than those of normal cochlear implant children, but not significantly.
Kontorinis G	Outcomes and special considerations of cochlear implantation in Waardenburg syndrome.	Otol Neurotol 2011;32:951–5	25	Case series of 25 cochlear implanted Waardenburg syndrome patients. In 21 cases, speech discrimination scores after cochlear implantation were sufficient.
Deka RC	Cochlear implantation in Waardenburg syndrome: The Indian scenario.	Acta Otolaryngol 2010;130:1097–100	4	Case series of four cochlear implanted Waardenburg syndrome patients. The cochlear implantation outcomes measured by MAIS, CAP, and SIR were the same as those in normal cochlear implant children. However, the results for cases with developmental disorders were significantly worse than those for the others.
Kaufmann L	Dysplasia of the cerebellum in Waardenburg syndrome: outcomes following cochlear implantation.	Int J Pediatr Otorhinolaryngol 2010;74:93–6	1	Case reports of Waardenburg syndrome patients with cerebellar dysplasia. Despite the cerebellar dysplasia, cochlear implantation was effective to some extent.
Cullen RD	Cochlear implants in Waardenburg syndrome.	Laryngoscope 2006;116:1273–5	7	Among 500 cochlear implants children, seven (1.4%) were diagnosed with Waardenburg syndrome. Also, in cases without developmental disorders, comparable outcomes for cochlear implantation were observed.
Migirov L	Cochlear implantation in Waardenburg's syndrome.	Acta Otolaryngol 2005;125:713–7	5	Case report on five cochlear implant cases of Waardenburg syndrome. These cases didn't have inner ear malformations, and the cochlear implant outcome of four out of 5 cases was favorable.
Daneshi A	Cochlear implantation in children with Waardenburg syndrome.	J Laryngol Otol 2005;119:719–23	6	Case series of six cochlear implanted Waardenburg syndrome patients. Auditory perception test and SIR scores improved with cochlear implantation.

(*continued*)

Table 10. Continued

First author	Title	Journal	Number of patients	Summary
Oysu C	Temporal bone imaging findings in Waardenburg's syndrome.	Int J Pediatr Otorhinolaryngol 2001;58:215–21	36	Among 1166 cochlear implantation cases, 12 had Waardenburg syndrome. Including the family members of these 12 cases, cochlear hypoplasia was observed in three of 36 cases (8%). This ratio was the same as the occurrence in general non-syndromic hearing loss cases, and cochlear implantation might be a good treatment option, even in Waardenburg syndrome cases, after confirmation of inner ear malformation by high-resolution CT imaging.

the cases were suspected of an intra-cochlear etiology, such as those with *GJB2*, *SLC26A4*, and *OTOF* mutations, showing relatively good CI outcomes. However, there have only been a limited number of reports on patients with other gene mutations. To progress toward more solid evidence-based CI intervention, a greater number of reports including CI outcomes for specific gene mutations are desired.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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