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The *SLC26A4* c.706C>G (p.Leu236Val) variant is a frequent cause of hearing impairment in Filipino cochlear implantees

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Abstract

Hypothesis: Variants in *SLC26A4* are an important cause of congenital hearing impairment in the Philippines.

Background: Cochlear implantation is a standard rehabilitation option for congenital hearing impairment worldwide, but places a huge cost burden in lower-income countries. The study of risk factors such as genetic variants that may help determine genetic etiology of hearing loss and also predict cochlear implant outcomes is therefore beneficial.

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Methods: DNA samples from 29 *GJB2*-negative Filipino cochlear implantees were Sanger-sequenced for the coding exons of *SLC26A4*. Exome sequencing was performed to confirm results.

Results: Four cochlear implantees with bilaterally enlarged vestibular aqueducts (EVA) were homozygous for the pathogenic *SLC26A4* c.706C>G (p.Leu236Val) variant, which has a minor allele frequency of 0.0015 in Filipino controls. In patients with the *SLC26A4* variant there was no association between cochlear implant outcome and age at implantation or duration of implant. There was also no association between the occurrence of the *SLC26A4* variant and post-surgical audiometric thresholds and PEACH scores. On the other hand, the *SLC26A4* variant increased pre-surgical median audiometric thresholds ($p=0.01$), particularly at 500–2000 Hz.

Conclusion: The *SLC26A4* c.706C>G (p.Leu236Val) variant is a frequent cause of congenital hearing impairment in Filipinos and is associated with bilateral EVA and increased pre-surgical audiometric thresholds, but does not adversely affect post-implant outcomes.

Keywords

cochlear implant; Filipino; p.Leu236Val; Philippines; *SLC26A4*; enlarged vestibular aqueduct

Introduction

Cochlear implantation is a standard rehabilitation option for congenital hearing impairment worldwide, but places a huge cost burden in lower-income countries. For example, in the Philippines where health insurance is limited in scope, the cost burden for cochlear implantation is largely carried by the patient. The study of risk factors such as genetic variants and temporal bone abnormalities that may help predict cochlear implant outcomes is therefore beneficial.

Congenital hearing impairment occurs in 1–2 per 1000 neonates; this prevalence has been confirmed in various countries including the Philippines (1). In up to 60% of congenitally hearing-impaired infants, the disease etiology is expected to be genetic (2). To date there are ~100 genes identified for nonsyndromic hearing impairment (Hereditary Hearing Loss Homepage). Each population may have specific variants that are prevalent in hearing-impaired individuals, such as: *GJB2* (MIM 121011) c.35delG in European-descent, Latino and Middle Eastern populations (3–6); *GJB2* c.235delC and *SLC26A4* (MIM 605646) p.His723Arg in East Asians (7); *GJB2* c.167delT in Ashkenazi Jews and Palestinians (5); and *SLC26A4* p.Val239Asp and *GJB2* p.Trp24* in South Asians (8–9). In this study, we screened *GJB2*-negative Filipino cochlear implantees for *SLC26A4* variants and found a prevalent mutation. Furthermore the availability of well-phenotyped subjects allowed the study of the potential relationship of carriage of the *SLC26A4* variant and audiologic outcomes post-implantation.

Materials and Methods

Patient ascertainment.

The study was approved by the University of the Philippines Manila Research Ethics Board prior to study initiation. Informed consent was obtained from adult subjects and parents of pediatric cochlear implant recipients. Subject recruitment was performed as previously described (10). In brief, 30 Filipino cochlear implant recipients with bilateral severe-to-profound hearing loss of no definitive etiology from perinatal and maternal history were initially enrolled in the study. One cochlear implant recipient was compound heterozygous for *GJB2* c.35delG/c.235delC (10) and was therefore excluded from further study.

Clinical and audiological evaluation.

All medical records including high-resolution temporal bone CT scan images and serial audiometric test results were reviewed. All patients were tested preoperatively for both aided and unaided pure tone thresholds with behavioral audiometry done in the pediatric patients. Children who were ≤ 5 years old were tested using play audiometry and those >5 years old were tested by conditioning them to raise their hands when they hear a tone. For all patients, frequencies tested include 500 Hz, 1 kHz, 2 kHz, and 4 kHz. Patients fitted with cochlear implants were tested via soundfield in a sound-treated room. Postoperatively, implant-aided pure tone thresholds were obtained as well as Categories of Auditory Performance (CAP) scores (11) for the adults and Parents' Evaluation of Aural/Oral Performance of Children (PEACH) scoring (12) for the children. Cochlear implantation was performed by a single surgeon, and audiometric and speech evaluation was performed at the same institution.

Sanger sequencing.

DNA samples from 29 *GJB2*-negative Filipino cochlear implant recipients were Sanger-sequenced for the 20 coding exons of *SLC26A4* (NM_000441.1). DNA isolation and Sanger sequencing was performed as previously described (10). Sanger sequencing of the *SLC26A4* c.706C>G (p.Leu236Val) variant was performed using 337 unrelated DNA samples from the Cebu Longitudinal Health and Nutrition Survey (CLHNS; 13). The CLHNS DNA samples are from a prospective community-based birth cohort recruited in 1983–1985 from Cebu, Philippines in order to study infant feeding, socio-economic and environmental factors that affect health and nutrition outcomes but not hearing impairment (13).

Exome sequencing and analyses.

In order to rule out the possibility of other variants that are causal of hearing impairment, DNA samples from four *SLC26A4*-positive cochlear implant recipients were submitted for exome sequencing at the University of Washington Northwest Genomics Center. Sequence capture was performed in solution with the Roche NimbleGen SeqCap EZ Human Exome Library v. 2.0 (~37 Mb target). Fastq files were aligned to the hg19 human reference sequence using Burrows Wheeler Aligner (14). Realignment of indel regions and variant detection and calling were performed using the Genome Analysis Toolkit (15). Annotation was performed using ANNOVAR (16). Filtering of exome variants was performed by selecting coding variants within known hearing impairment genes ($n=96$) that have <0.005 minor allele

frequency in any population within the Exome Aggregation Consortium (ExAC) database and in 1000 Genomes. Both homozygous and heterozygous variants were considered. Further selection was performed by choosing rare single nucleotide variants that were considered damaging by at least two bioinformatics tools in dbNSFP (17). For indels, bioinformatics analysis was performed using MutationTaster (18).

Statistical analyses.

The following variables were available for study: carriage of the *SLC26A4* variant; age at implantation and at last audiometric examination; duration of implant use; gender; type of cochlear implant device; pre- and post-implant audiometric thresholds; and PEACH scores. Bivariate analyses were performed using Fisher exact tests for categorical variables and Mann-Whitney-Wilcoxon tests for continuous variables, with a significance threshold of $p < 0.05$. Comparisons were made between carriers and non-carriers of the *SLC26A4* variant. For audiometric thresholds and PEACH scores, a generalized linear model which includes the *SLC26A4* variant, temporal bone abnormalities, and either age at or duration since implantation was used for each PEACH score condition, each audiometric frequency and for the median of audiometric frequencies pre- and post-surgery. All statistical tests were performed using R.

Results

Four cochlear implantees are homozygous for the *SLC26A4* c.706C>G (p.Leu236Val, rs111033242) variant based on Sanger sequencing and exome data. The prevalence of the variant is 13.3% within this cohort of Filipino implantees. The variant is heterozygous in 1 out of 674 chromosomes (minor allele frequency or MAF=0.0015) from unrelated Filipino DNA samples from CLHNS. In the ExAC database, the *SLC26A4* c.706C>G variant is heterozygous in 4 out of 11,578 Latino alleles (Latino MAF=0.0003) but was absent in other ethnic groups. The c.706C>G (p.Leu236Val) is predicted to be damaging by fathmm, MetaLR, MetaSVM, MutationTaster and SIFT, and has a Combined Annotation Dependent Depletion (CADD) scaled score of 19.81, indicating deleteriousness. It is also deemed likely pathogenic in the ClinVar database.

All four cochlear implantees who were homozygous for the *SLC26A4* c.706C>G variant were also homozygous for *SLC26A4* c.200C>G (p.Thr67Ser, rs111033240). The *SLC26A4* variants c.200C>G and c.706C>G are only 11,719 bp apart. The c.200C>G (p.Thr67Ser) variant is rare in ExAC, with only one heterozygous allele among Latinos (Latino MAF=0.00009), and likewise absent in other ethnic groups. However this variant is considered likely benign in ClinVar and is also predicted benign by all bioinformatics tools in dbNSFP, and has a lower CADD score of 11.32. When comparing the exome data from the four *SLC26A4*-positive implantees, no other variants were identified to be homozygous within 1 Mb distal and proximal to the c.706C>G variant. Additionally from the exome data no other heterozygous, compound heterozygous or homozygous variants within known hearing impairment genes were identified to be potentially pathogenic.

All four *SLC26A4*-positive implantees had bilaterally enlarged vestibular aqueducts (EVA; Supplementary Fig. 1, Table 1, Supplementary Table 1). In patients with the *SLC26A4*

variant there was no association between cochlear implant outcome and age at implantation or duration of implant. There was also no association between the occurrence of the *SLC26A4* variant and post-surgical audiometric thresholds and PEACH scores. In the generalized linear model, the significance of age at implantation or duration of implant use varied by pre- or post-surgical audiometric frequency (Table 2). On the other hand, the *SLC26A4* variant increased pre-surgical median audiometric thresholds ($p=0.01$), particularly at 500–2000 Hz (Table 2).

Discussion

While in our previous study we identified *GJB2*-related hearing impairment at 3% prevalence (10), here we show that a *SLC26A4* variant has 13% frequency in a cohort of hearing-impaired patients, which makes it practical to genotype this variant as an initial step in the identification of genetic etiology when screening hearing-impaired patients of Filipino descent. The *SLC26A4* c.706C>G (p.Leu236Val) variant was previously reported in a targeted panel screen (19), a case report (20), and in the Deafness Variation Database (accessed October 26, 2016) as a variant of unknown significance (VUS). Initially when Sanger sequencing revealed four Filipino cochlear implantees who are homozygous for the *SLC26A4* c.706C>G variant, we were doubtful of its pathogenicity because of the low rates of consanguinity in the Philippines. Exome sequencing confirmed that no other coding variants are causal of hearing impairment in these patients. ClinVar currently classifies the p.Leu236Val variant as likely pathogenic due to its occurrence at a residue with a well-known pathogenic variant, i.e. *SLC26A4* p.Leu236Pro, and the report of a single Asian family in which the variant co-segregates with hearing loss. The finding of the *SLC26A4* c.706C>G (p.Leu236Val) in four unrelated cochlear implantees provides strong evidence that the variant is indeed pathogenic, and additional data from controls suggests that this variant is more frequent in the Filipino population compared to other ethnicities. These lines of evidence underscore the importance of screening patients and controls from different populations in order to understand the allelic spectrum of disease.

While our findings support the pathogenicity of the p.Leu236Val variant, the identification of the p.Thr67Ser variant as homozygous in all four patients who are also homozygous for the p.Leu236Val variant support the conclusion that these variants constitute a haplotype, but only the p.Leu236Val variant is pathogenic, in agreement with ClinVar. This two-variant haplotype shared by the four implantees is very short, and the scarcity of data prevents any further study on the origin of the variants. The identification of these two variants in ExAC Latino alleles is interesting given the history of Spanish colonization in the Philippines. Our previous study on otitis media also suggested that rare variants in Latino populations can have a high frequency in the Philippines due to admixture and possibly drift within island populations (21).

We also explored whether the *SLC26A4* variant affects cochlear implant outcomes. In a Taiwanese study using the largest dataset to date of cochlear implantees who were screened for *GJB2* and *SLC26A4* variants ($n=171$), *SLC26A4* variant carriers were shown to have better auditory performance or speech intelligibility scores, however this association was seen only in children who were implanted before 3.5 years of age (22). In contrast, our

previous study in this Filipino cohort showed that age at implantation did not alter implant outcomes, but PEACH scores were significantly associated with duration of implant use irrespective of genotype (10). Although our sample size is small, in the present study we did not find any evidence that the *SLC26A4* p.Leu236Val variant confers any difference in auditory or speech performance post-implantation even after correction for age at implantation. On the other hand, this can also be interpreted as good response to cochlear implantation, with median post-implant thresholds at 37.5 dB across all frequencies for both carriers and non-carriers of the *SLC26A4* variant.

A recent meta-analysis involving ~1,700 patients concluded that two *SLC26A4* variants, c.919–2A>G and p.His723Arg, were associated with hearing loss and EVA (23). The occurrence of bilateral EVA in all four patients with the *SLC26A4* p.Leu236Val variant presents a strong case for an association between the variant and EVA, especially since the variant is rare in non-Filipino populations and only a very small, select Filipino sub-population can afford cochlear implantation and are likely to undergo genetic testing for hearing loss. Additionally we observed worse pre-surgical median thresholds for implantees with the *SLC26A4* variant, further supporting this *SLC26A4* variant as the cause of hearing loss.

In conclusion, the *SLC26A4* c.706C>G (p.Leu236Val) variant is a frequent cause of congenital hearing impairment in Filipinos and is associated with bilateral EVA and increased pre-surgical audiometric thresholds, but does not adversely affect post-implant outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Web Resources

ANNOVAR, <http://annovar.openbioinformatics.org>
Burrows-Wheeler Aligner, <http://bio-bwa.sourceforge.net>
ClinVar, <https://www.ncbi.nlm.nih.gov/clinvar/>
Combined Annotation Dependent Depletion, <http://cadd.gs.washington.edu/>
dbNSFP, <https://sites.google.com/site/jpopgen/dbNSFP>

dbSNP, <https://www.ncbi.nlm.nih.gov/projects/SNP/>
 Deafness Variation Database, <http://deafnessvariationdatabase.org/>
 Exome Aggregation Consortium, <http://exac.broadinstitute.org/>
 fathmm, <http://fathmm.biocompute.org.uk/>
 Genome Analysis Toolkit, <https://software.broadinstitute.org/gatk/>
 Hereditary Hearing Loss Homepage, <http://hereditaryhearingloss.org/>
 MutationTaster, <http://www.mutationtaster.org/>
 OtoSCOPE, <https://www.medicine.uiowa.edu/morl/otoscope/>
 SIFT, <http://sift.jcvi.org/>

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Table 1.*Radiologic findings in 29 Filipino cochlear implantees*

Radiologic findings	n (%)
Large or dilated vestibular aqueduct/EVA/LVAS ¹	10 (34.5)
Malformed cochlea	2 (6.9)
Lateral semicircular canal dysplasia	2 (6.9)
Superior semicircular canal dehiscence (SSCD)	2 (6.9)
High-riding jugular bulb	3 (10.3)
Normal	12 (41.4)

Two patients had both EVA and high-riding jugular bulb. All four *SLC26A4*-positive implantees had bilateral EVA.

Table 2.Generalized linear model^I for audiologic results in patients before and after cochlear implantation (CI)

Audiometric threshold (Hz) or PEACH	SLC26A4 variant, $\beta_{\pm s.e.}$	SLC26A4 variant, p-value	EVA or malformed cochlea, p-value	Age at implant, p-value	Years since implant, p-value
Pre-CI 500	30.9 ± 9.0	0.002	0.02	0.03	--
Pre-CI 1000	23.4 ± 10.5	0.04	0.32	0.06	--
Pre-CI 2000	20.2 ± 7.2	0.01	0.08	0.26	--
Pre-CI 4000	6.6 ± 7.5	0.39	0.24	0.41	--
Pre-CI median	20.2 ± 8.0	0.02	0.08	0.13	--
Pre-CI 500	24.7 ± 9.6	0.02	0.002	--	0.41
Pre-CI 1000	16.9 ± 10.9	0.13	0.08	--	0.34
Pre-CI 2000	17.5 ± 7.2	0.02	0.02	--	0.47
Pre-CI 4000	8.0 ± 7.4	0.29	0.35	--	0.91
Pre-CI median	16.2 ± 8.0	0.06	0.02	--	0.31
Post-CI 500	0.6 ± 8.1	0.94	0.70	--	0.25
Post-CI 1000	-4.3 ± 5.5	0.44	0.21	--	0.65
Post-CI 2000	-1.0 ± 5.7	0.86	0.23	--	0.54
Post-CI 4000	0.08 ± 14.0	0.995	0.27	--	0.04
Post-CI median	0.01 ± 5.9	0.998	0.24	--	0.43
PEACH in quiet	0.1 ± 0.2	0.61	0.85	--	0.03
PEACH in noise	0.1 ± 0.2	0.57	0.72	--	0.14
PEACH overall	0.1 ± 0.2	0.58	0.76	--	0.07

^IBasic model: Audiometric threshold/PEACH ~ *SLC26A4* variant + EVA/malformed cochlea + age at or years since implant. EVA/malformed cochlea was added to the model due to occurrence of these temporal bone abnormalities in non-carriers of the *SLC26A4* variant. Pre-CI thresholds are unaided while post-CI thresholds are aided. P-values for significant independent variables are in bold font. All variables in models including post-CI thresholds or PEACH scores and age at implant were non-significant.