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Exome sequencing reveals novel variants and unique allelic spectrum for hearing impairment in Filipino cochlear implantees

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Graphical Abstract

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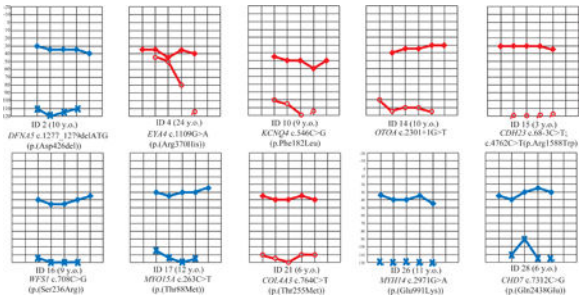
Web URLs
Cebu Longitudinal Health and Nutrition Survey (CLHNS), www.cpc.unc.edu/projects/cebu
ClinVar, www.ncbi.nlm.nih.gov/clinvar/
dbNSFP, sites.google.com/site/jpopgen/dbNSFP
Genetic Variant Interpretation Tool, www.medschool.umaryland.edu/Genetic_Variant_Interpretation_Tool1.html/
Genome Aggregation Database, gnomad.broadinstitute.org
Hereditary Hearing Loss Homepage, hereditaryhearingloss.org
Integrative Genomics Viewer, software.broadinstitute.org/software/igv/
Leiden Open Variation Database, http://www.lovd.nl/3.0/home
MutationTaster, www.mutationtaster.org
Online Mendelian Inheritance of Man, www.omim.org
UCSC Genome Browser, genome.ucsc.edu



To the Editor:

Genetic hearing impairment is mostly nonsyndromic (80%), and >6,000 causal variants in >100 genes have been identified. Generally in hearing-impaired patients of Asian descent, *GJB2* variants are most common (36%), followed by variants in *SLC26A4* (MIM 605646), *MYO15A* (MIM 602666) and *CDH23* (MIM 605516).[1] Here we report seven novel variants in Filipino cochlear implantees, suggesting that the allelic spectrum for non-/syndromic hearing impairment in Filipinos is unique.

The UP Manila Research Ethics Board approved the study. Adult subjects and parents of pediatric patients provided informed consent. DNA samples and clinical data were obtained from 30 cochlear implantees with bilateral, severe-to-profound, congenital, non-progressive hearing loss as previously described.[2–3] After excluding one patient with *GJB2* c.[35delG];[235delC],[2] twenty-nine DNA samples were submitted for exome sequencing, of which four are homozygous for *SLC26A4* c.706C>G (p.(Leu236Val)).[3] For the twenty-five *GJB2-/SLC26A4*-negative patients, homozygous/heterozygous coding variants within 132 non-/syndromic hearing impairment genes were selected if with MAF<0.005 in any gnomAD population. Rare variants were selected further if considered damaging by MutationTaster and/or ≥2 dbNSFP tools. Eleven Filipino-descent US families with no history of hearing impairment were ascertained for MAF estimation for speech delay (SDFIL) and were Sanger-sequenced for selected exome variants. Variants with zero MAF in the SDFIL cohort were then screened using samples from ≥88 unrelated Filipinos from the Cebu Longitudinal Health and Nutrition Survey, a cohort examined for various health outcomes. Screened exome variants were excluded due to increased MAF, lack of a second rare variant in an autosomal recessive gene and/or poor clinical correlation.

Of 30 Filipino cochlear implantees, we identified a genetic cause in sixteen (53%). Seven novel hearing loss variants were discovered (Table 1): *CHD7* (MIM 608892) c.7312C>G (p.(Gln2438Glu)); *COL4A3* (MIM 120070) c.764C>T (p.(Thr255Met)); *DFNA5* (MIM 600994) c.1277_1279delATG (p.(Asp426del)); *EYA4* (MIM 603550) c.1109G>A (p.(Arg370His)); *MYH14* (MIM 608568) c.2971G>A (p.(Glu991Lys)); *MYO15A* c.263C>T (p.(Thr88Met)); and *OTOA* (MIM 607038) c.2301+1G>T. Patient #28 with the *CHD7* variant has microcephaly and seizures, both known features of CHARGE syndrome (MIM 214800). Additionally he has left superior semicircular canal dehiscence (SSCD)[3] but no vertigo or dizziness. Both *DFNA5* c.1277_1279delATG and *EYA4* c.1109G>A were previously identified through systematic clinical genetic screening and are annotated in

ClinVar as variants of unknown significance. Patient #4 with the *EYA4* variant complains of dizziness and balance problems; temporal bone findings include right enlarged vestibular aqueduct and a left jugular bulb diverticulum that impinges onto the ipsilateral vestibular aqueduct.[3] *COL4A3* c.764C>T was previously reported for familial kidney disease[4] but not hearing impairment. *MYH14* c.2971G>A is cited in LOVD as likely benign but was not clarified for nonsyndromic DFNA4A (MIM 600652) or peripheral neuropathy, myopathy, hoarseness and hearing loss (PNMHH; MIM 614369). This *MYH14* variant is the only rare, damaging variant identified in patient #26, who has developmental delay and left foot inversion.

Variants *CDH23* c.68–3C>T and c.4762C>T (p.(Arg1588Trp)), *KCNQ4* (MIM 603537) c. 546C>G (p.(Phe182Leu)), and *WFS1* (MIM 606201) c.708C>G (p.(Ser236Arg)) have been previously reported for hearing impairment. Patient #10 with the *KCNQ4* variant has SSCD on the left[3] but no vestibular symptoms. *WFS1* c.708C>G was reported in a patient with compound heterozygous *WFS1* variants and autosomal recessive Wolfram syndrome (MIM 222300).[5] Patient #16 has no second *WFS1* coding variant but has birth history of cord coil, white matter disease and mild motor delay.

Clinical data helped identify the correct gene when multiple potentially causal variants were present. Patients with pathogenic variants had higher pre-surgical audiometric thresholds at ≥1kHz (Wilcoxon $p<0.05$). However there was no significant difference in post-surgical thresholds, suggesting that carriage of the genetic variants reported here does not determine the outcome of cochlear implantation, with average implant-aided hearing at 38dB across frequencies. Therefore for carriers of these variants, cochlear implantation remains an excellent option for rehabilitation.

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Table 1.

Pathogenic/likely pathogenic variants in Filipino cochlear implantees identified in this study[†]

ID	Geno-type	Gene	Expected MOI	RefSeq NM_	cDNA Variant	Amino Acid Variant	Damaging Prediction	CADD	gnomAD MAF Overall	gnomAD MAF NFE	gnomAD MAF EAS
2[‡]	Het	***DFNA5***	DFNA5	004403	**c.1277_1279delATG**	**p.(Asp426del)**	MT	--	0.0006	0	0.0005
4[§]	Het	***EYA4***	DFNA10	004100	**c.1109G>A**	**p.(Arg370His)**	Fa,LRT,mLR, mSVM,MA,MT, PP2_HD/HV, PR,SI	35	0.00004	0.00006	0
10[‡]	Het	*KCNQ4*	DFNA2A	004700	c.546C>G	p.(Phe182Leu)	MT	22	0.0003	0	0.004
14[¶]	Hom	***OTOA***	DFNB22	144672	**c.2301+1G>T**	NA	MT	27.1	0	0	0
15[‡]	Cpd het	*CDH23*	DFNB12; AR USH1D	022124	c.68–3C>T	NA	MT	--	0.0005	0.000008	0.008
15[‡]	Cpd het	*CDH23*	DFNB12; AR USH1D	022124	c.4762C>T	p.(Arg1588Trp)	LRT,MA,MT, PP2_HD/HV, PR,SI	23.3	0.0002	0.00007	0.001
16	Het	*WFS1*	DFNA6/14/38; AD/AR Wolfram	006005	c.708C>G	p.(Ser236Arg)	Fa,LRT,mLR,MT	12.9	0	0	0
17[‡]	Hom	***MYO15A***	DFNB3	016239	**c.263C>T**	**p.(Thr88Met)**	Fa, PP2_HD	18.6	0.00007	0	0
21	Het	***COL4A3***	AD/AR Alport	000091	**c.764C>T**	**p.(Thr255Met)**	Fa,mLR,mSVM, MT,PP2_HD/HV,SI	33	0.00009	0.000009	0.00006
26	Het	***MYH14***	DFNA4A; AD PNMHH	001145809	**c.2971G>A**	**p.(Glu991Lys)**	Fa,mLR,mSVM,MA,MT,PP2_HD/HV,PR,SI	28.9	0.00001	0	0.00007
28	Het	***CHD7***	AD CHARGE	017780	**c.7312C>G**	**p.(Gln2438Glu)**	LRT,MT, PP2_HD/HV	25.3	0	0	0

[†]All variants listed were not found in Filipino controls from SDFIL and CLHNS. Novel variants are in bold font.

[‡]Confirmed to have nonsyndromic hearing impairment (if including *GJB2-/SLC26A4*-positive patients, total 9 of 15 or 60% of those with genetic variants).

[§]Prior to surgery, patient #4 had a steeply sloping audiogram with 45–50 dB hearing at 500–1000 kHz and profound loss at 4000 Hz. All other patients listed in Table 1 had flat audiograms with severe-to-profound hearing loss. Additional clinical information on these patients were previously provided in reference #3.

[¶]Patient #14 has global developmental delay and a history of maternal rubella, low birth weight, exchange transfusion for jaundice, antibiotic treatment and mechanical ventilation for neonatal pneumonia, and intraventricular hemorrhage.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CADD, Combined Annotation-Dependent Depletion; Cpd het, compound heterozygous; DFNA#, nonsyndromic autosomal dominant hearing loss; DFNB#, nonsyndromic autosomal recessive hearing loss; EAS, East Asian; Fa, FATHMM; gnomAD, Genome Aggregation Database; HD, HumDiv; Het, heterozygous; Hom, homozygous; HV, HumVar; LRT, Likelihood Ratio Test; MA, MutationAssessor; MAF, minor allele frequency; mLR, MetaLR; MT, MutationTaster; mSVM, MetaSVM; NFE, non-Finnish European; PNMHH, peripheral neuropathy, myopathy, hoarseness and hearing loss; PP2, PolyPhen2; PR, PROVEAN; RefSeq, Reference Sequence; SI, SIFT; USH1D, Usher syndrome Type I