Elina Kari, MD*
Isabelle Schrauwen, PhD*
Lorida Llaci, BS
Laurel M. Fisher, PhD
John L. Go, MD
Marcus Naymik, MS
James A. Knowles, MD, PhD
Matthew J. Huentelman, PhD
Rick A. Friedman, MD, PhD

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## COMPOUND HETEROZYGOUS MUTATIONS IN *MASP1* IN A DEAF CHILD WITH ABSENT COCHLEAR NERVES

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Abnormal cochleovestibular nerves (i.e., as absent, aplastic, or deficient) are a rare congenital malformation that have a devastating impact on hearing and language development. To date, there have been no genes identified associated with this abnormality.

**Case description.** A healthy male child was born with profound sensorineural hearing loss (SNHL) and was referred for cochlear implantation (CI). Auditory brainstem response thresholds were absent or profound across all frequencies. His facial nerve function was normal on examination, and he did not have any motor delays. Vestibular testing was not performed. His evaluation included high-resolution CT and MRI of the temporal bones. CT revealed bony cochlear modioli, normal cochlear partitioning, narrow or absent cochlear apertures, enlarged vestibules, dysplastic semicircular canals, and bifid internal auditory canals (IACs). MRI revealed only 1 nerve in the lateral IAC. On the left, the IAC was too narrow in caliber to determine the contents, but findings suggested a single nerve in the lateral IAC (figure). Findings were consistent with abnormal cochleovestibular nerves bilaterally with likely absent cochlear nerves.

The child underwent a single cochlear implant and demonstrated no benefit. He ultimately underwent an auditory brainstem implant (ABI) at age 3. His postoperative hearing and language outcomes are evolving, and the data are unavailable at this time.

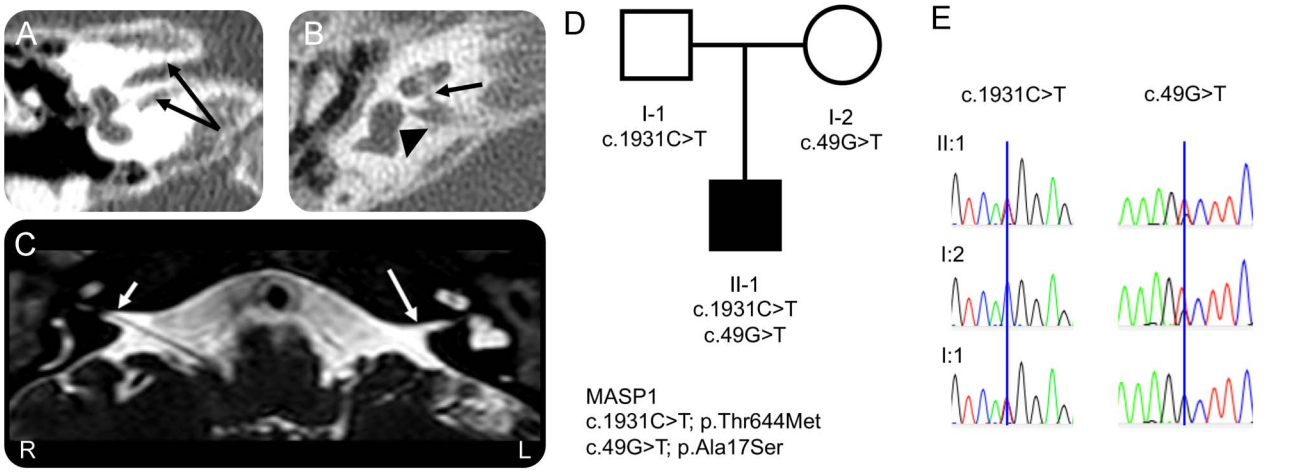
**Methods.** Institutional review board approval was obtained. Exome sequencing was performed in the proband and parents using the TruSeq Exome Library Prep Kit followed by 100 bp paired-end sequencing on a HiSeq 2500 instrument. We identified a compound heterozygote mutation in *MASP1* in the propositus (c.1931C>T[p.Thr644Met] and c.49G>T[p.Ala17Ser]), each inherited from one parent, which was confirmed by Sanger sequencing. Both variants are rare in the ExAC Browser database of 60,706 unrelated individuals (3.049e-4 and 2.481e-05 allele frequencies, respectively), and the gnomAD beta browser of 126,216 exome sequenced and 15,136 whole-genome sequenced individuals, with no homozygotes reported. Both variants were predicted damaging when assessed with 2 separate integrative pathogenicity prediction tools that implement diverse annotations into a single overall prediction, i.e., Combined Annotation Dependent Depletion (CADD) score (33 and 22.7, respectively) and a random forest analysis with Integrating Molecular Heuristics and Other Tools for Effect Prediction (IMHOTEP; based on ENST00000296280 and ENST00000337774, respectively). Both variants are also conserved among species based on the genomic evolutionary rate profiling method. Last, p.Thr644Met and p.Ala17Ser are located within important protein domains in MASP1: p.Thr644Met affects a very conserved trypsin-like serine protease domain, likely affecting catalytic-proteolytic enzyme activity and p.Ala17Ser affects the CUB domain, which is often involved in oligomerization and/or recognition of substrates and binding partners. All of the preceding suggest these to be function-altering, deleterious, and disease-causal variants.

Mutations of this gene have been associated previously with 3MC syndrome (Carnevale, Mingarelli, Malpuech and Michels, or craniofacial-ulnar-renal syndrome).[1] Affected individuals present with a range of anomalies that lead to abnormal facial/limb/vesicorenal development, cleft lip and/or palate, cognitive dysfunction, and craniosynostosis.[2] Patients exhibit variable hearing and vestibular dysfunction. However, our patient does not have any other clinical features consistent with 3MC syndrome other than his SNHL and vestibular anomalies, expanding the clinical spectrum of *MASP1* mutations.

**Discussion.** Nearly 2–3 per 1,000 newborns suffer from hearing loss ranging from mild to profound in the United States each year.[3] Children with profound SNHL are potentially considered for a CI or an ABI.[4] However, current clinical imaging protocols are unable to consistently predict cochlear nerve status to guide surgeons' choice of auditory prosthesis.[5] Improving preoperative imaging characterization is a subject of widespread research but has not yet reached clinical use.

**Figure** **Imaging, pedigree, and anger sequencing of a child with absent cochlear nerve**




(A) Coronal high-resolution CT of a bifid and narrow internal auditory canal (IAC). (B) Axial high-resolution CT showing a pinpoint cochlear aperture (arrow) and an enlarged vestibule (arrowhead). Cochlear partitioning was normal, but the modiolus was bony and semicircular canals were dysplastic (not shown). (C) Axial high-resolution heavily T2-weighted (constructive interference in steady state [CISS]/fast imaging employing steady-state acquisition [FIESTA]) MRI of IACs bilaterally showing narrow IACs, one nerve in right IAC (short arrow) and nothing seen in left IAC (long arrow). Oblique cross-sectional imaging confirmed findings (not shown). (D) Family pedigree showing the mutations in *MASP1*. (E) Sanger sequencing traces showing the mutations inherited in the pedigree.

The variability of hearing outcomes in children with abnormal cochleovestibular nerves receiving CIs/ABIs coupled with the current inability to predict their outcomes[4–7] leads to children enduring multiple assessments and interventions. The length of time to determine which treatment will provide benefit often exceeds the sensitive periods for auditory development, delaying spoken language.

*MASP1* encodes mannan-binding lectin serine protease 1 that is involved in complement activation. Previous studies show that MASP1 is involved to direct the migration of neural crest cells during embryonic development,[2] and mutations cause a spectrum of human malformation syndromes as previously described, which demonstrate the involvement of MASP1 in facial, umbilical, and ear development during the embryonic period. Zebrafish morphants also develop pigmentary defects and severe craniofacial abnormalities.[2]

In this report, we expand the spectrum of phenotypic variability caused by *MASP1* mutations and suggest that *MASP1* screening should be considered in patients with nonsyndromic profound SNHL and abnormal cochleovestibular nerves.


* *These authors contributed equally to this work as co–first authors.*

*From the Tina and Rick Caruso Department of Otolaryngology–Head and Neck Surgery (E.K., L.M.F., J.L.G., J.A.K., R.A.F.), Keck University of Southern California School of Medicine, Los Angeles; and TGen (I.S., L.L., M.N., M.J.H.), Translational Genomics Research Institute, Phoenix, AZ.*


*Author contributions: Elina Kari: collection of data, interpretation of data, writing of the manuscript, and the corresponding author. Isabelle Schrauwen: collection of data, DNA sequencing, analysis of data, and writing of the manuscript. Lorida Llaci: DNA sequencing and sample preparation. Laurel M. Fisher: collection of data and interpretation of data. Marcus Naymik: bioinformatics. John L. Go: collection of data and interpretation of data. James A. Knowles: interpretation of data. Matthew J. Huentelman: interpretation of data. Rick A. Friedman: interpretation of data and final manuscript preparation.*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*Correspondence to Dr. Kari: Elina.kari@med.usc.edu*



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# Compound heterozygous mutations in *MASP1* in a deaf child with absent cochlear nerves

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