The Contribution of Common Variants in Deafness-Associated Genes to Age-Related Hearing Loss

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INTRODUCTION

Age-related hearing loss (ARHL) is a broadly impacting complex disease, with both environmental and genetic factors implicated in its pathophysiology. To identify potential common genetic contributions, we tested the hypothesis that select common variants in deafness-associated genes are deleterious over a lifetime and contribute to ARHL.

METHODS

1. **Variant selection**: Common variants most likely to contribute to ARHL were identified using a targeted filtering approach.
2. **Cohort definition**: Participants from the *All of Us* Research Program were divided into two cohorts—one with documented use of hearing devices (cochlear implants or hearing aids) and one without.
3. **Association testing**: A logistic regression model was used to test for associations between the variants and hearing device usage.
4. **Effect visualization**: For significantly associated variants, the incidence of hearing devices across age groups was plotted and compared by genotype.

VARIANT SELECTION

Three genes—*CDH23*, *TRIOBP*, and *WHRN*—were targeted based on prior reports of associations with ARHL[1,2] or noise-induced hearing loss (NIHL)[3], and unpublished data.

Filtering

Missense variants in Deafness Variation Database[4] v9.2

↓

Targeted genes: *CDH23*, *TRIOBP*, *WHRN*

↓

Common variants: Allele frequency (AF) ≥5% in gnomAD[5] v4.1.0 non-Finnish European population

↓

Predicted deleteriousness: Combined Annotation Dependent Depletion (CADD)[6] Phred score ≥10

↓

Top variants: Top three in each gene by CADD Phred score

Figure 1. Filtering steps used to select variants. The Deafness Variation Database was accessed at https://deafnessvariationdatabase.org/ on January 21, 2026.

Gene	HGVS	CADD Phred	AF
CDH23	NP_071407.4:p.Pro2380Leu	26.7	27.8%
CDH23	NP_071407.4:p.Arg1804Gln	25.4	17.9%
CDH23	NP_071407.4:p.Glu2044Lys	24.9	27.8%
TRIOBP	NP_001034230.1:p.Ser217Asn	17.5	57.2%
TRIOBP	NP_001034230.1:p.Phe1187Leu	16.2	45.0%
WHRN	NP_056219.3:p.Pro562Ala	19.5	12.4%
WHRN	NP_056219.3:p.Ala440Thr	16.1	22.5%

Table 1. Selected variants.

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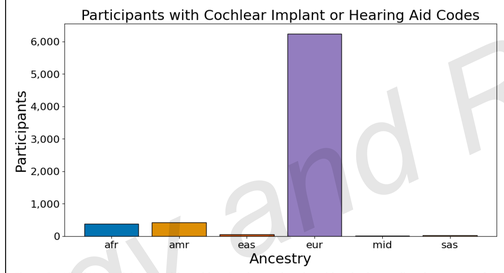
COHORT DEFINITION

- Accessed *All of Us* Curated Data Repository (CDR) v8.
- Identified 79 concepts that indicate a participant has cochlear implants or hearing aids.
- 8,571 of 414,830 participants (2.1%) with whole-genome sequencing data had at least one of these concepts.

Population Stratification



Cochlear implant and hearing aid codes are relatively infrequent in non-European ancestry participants.

So, to increase statistical power, the cohorts were limited to European ancestry participants.

Figure 2. *All of Us* participants with cochlear implant or hearing aid codes by predicted ancestry. afr = African ancestry; amr = admixed American ancestry; eas = East Asian ancestry; eur = European ancestry; mid = Middle Eastern ancestry; sas = South Asian ancestry.

Cohorts

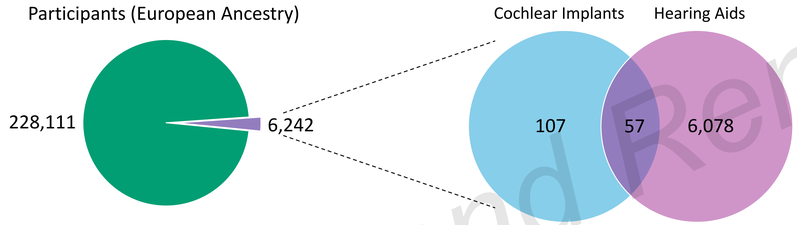


Figure 3. Participant counts for two cohorts.

Figure 4. Participant count breakdown of cases cohort by hearing device type.

ASSOCIATION TESTING

For each of the seven variants, a logistic regression model was fit as follows:

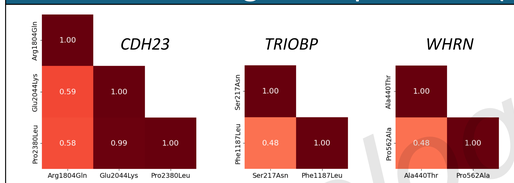
$$\mathbf{hearing\_devices} \sim \mathbf{genotype} + \mathbf{age} + \mathbf{sex} + \mathbf{PC_1} - \mathbf{PC_{10}}$$

where:

- **hearing_devices** = 1 if the patient has cochlear implants or hearing aids; 0 if none
- **genotype** = biallelic genotype coded according to specified disease model
- **PCs 1-10** = the first ten principal components (PCs) from the *All of Us* principal component analysis

For each variant, the disease model (additive, dominant, or recessive) yielding the lowest Bayesian Information Criterion (BIC) was selected as the best-fitting model. The PCs were included to model population substructure within the European ancestry cohort.

Linkage Disequilibrium (LD) Analysis



All variants within each gene show moderate-to-high LD (r^2 ≥0.48).

So, the SNP in each gene with the lowest *p* value was taken as the lead SNP, to represent the signal and avoid overcorrection for multiple testing.

Figure 5. Pairwise LD (r^2) for variants in each gene. Calculated using LDlink (https://ldlink.nih.gov/) for (EUR) European population.

RESULTS

Gene	Variant	Model	P	P_{adj}	OR [95% CI]
CDH23	p.Pro2380Leu	recessive	0.024	0.035	1.12 [1.02-1.23]
~~*CDH23*~~	~~p.Arg1804Gln~~	~~recessive~~	~~0.061~~	~~n/a~~	~~1.15 [0.99-1.33]~~
~~*CDH23*~~	~~p.Glu2044Lys~~	~~recessive~~	~~0.032~~	~~n/a~~	~~1.11 [1.01-1.23]~~
~~*TRIOBP*~~	~~p.Ser217Asn~~	~~dominant~~	~~0.030~~	~~n/a~~	~~1.08 [1.01-1.17]~~
TRIOBP	p.Phe1187Leu	dominant	3.9E-06	1.2E-05	1.15 [1.08-1.21]
WHRN	p.Pro562Ala	recessive	0.083	0.083	1.19 [0.98-1.44]
~~*WHRN*~~	~~p.Ala440Thr~~	~~additive~~	~~0.68~~	~~n/a~~	~~1.01 [0.97-1.05]~~

Table 2. Association of variants with hearing device usage. Only lead SNPs are tested for significance; other SNPs are struck through. *P* values adjusted via Benjamini–Hochberg procedure. Significant values (P_{adj} < 0.05) are highlighted.

Hearing Device Incidence by Age

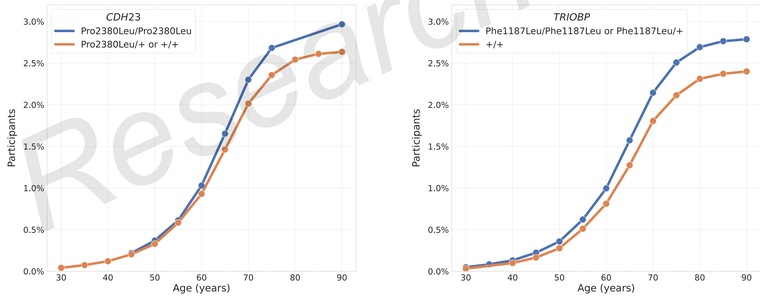


Figure 6. Cumulative percentage of European ancestry participants with hearing devices (cochlear implants or hearing aids). Reference alleles indicated by '+'. Some points omitted to comply with *All of Us* Data and Statistics Dissemination Policy.

- *CDH23* Pro2380Leu homozygotes show a higher rate of cochlear implant or hearing aid use than non-homozygotes.
- *TRIOBP* Phe1187Leu carriers show a higher rate of cochlear implant or hearing aid use than non-carriers.

CONCLUSIONS

A targeted association study of United States European-ancestry persons identified two significant associations between ARHL (measured by the proxy of hearing device usage) and common variants:

1. A highly significant (P_{adj} = 1.2E-05) association with *TRIOBP* Phe1187Leu
   - Previously implicated in ARHL[2]
   - Modest effect in this study (OR = 1.15)
2. A nominally significant (P_{adj} = 0.035) association with *CDH23* Pro2380Leu
   - No previous reports found
   - Modest effect in this study (OR = 1.12)

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