**Supplemental Methods**

*Genetic testing and Variant Classification*

The hearing-loss gene panel (GeneDx) encompassed 146 nuclear genes and 6 variants in 3 mitochondrial genes accounting primarily for NSHL and select genetic syndromes that present with HL. Sequencing of coding regions and splice junctions with selected deletion/duplication analysis and copy-number variant detection was performed.20 Each variant was classified on the genetic testing report as Benign, Likely Benign (LBV), Variant of Unknown Significance (VUS), Likely Pathogenic (LPV) or Pathogenic based on the ACMG 2015 Guidelines.21,22  We further classified Uncertain VUSs as Benign or Deleterious VUSs based on ClinVar designation and PROVEAN (Protein Variation Effect Analyzer) score (<= -2.5: predicted deleterious; > -2.5: predicted benign) when ClinVar report was unavailable. Variants that lacked a categorization in the clinical report, ClinVar designation, or PROVEAN prediction were ultimately categorized as Uncertain VUSs.

Variants were given a Variant Molecular Diagnosis (Variant MD) between 0-6 in order of pathogenicity (Supplemental Figure 1), and each gene was assigned a number between 0-4 (Gene MD) reflecting the likelihood that a variant contributed to hearing loss based upon the Variant MD and inheritance pattern (Supplemental Figure 2). If a patient had a negative result on their genetic test report (no variants reported), the Gene MD was zero.

Inheritance was reported by GeneDx for most variants. In some instances, inheritance was reported as autosomal dominant or autosomal recessive. In these cases, inheritance pattern was determined using ClinVar/OMIM designation if available, if not, clinical history was used to determine inheritance pattern (Supplemental Figure 3). Several genes with a digenic inheritance pattern were identified and treated as autosomal recessive variants of the same gene (Supplemental Figure 4). In cases where conflict existed in primary data, these conflicts were resolved on discussion between the primary and senior authors (MF, SLR, DKC).

Using the highest Gene MD among all the genes identified for a patient, each patient was assigned a genetic diagnosis score (Patient MD) between 0-4, a value representing the likelihood of a genetic cause of hearing loss. Patient MD was then dichotomized to reflect current standard of care, in which a patient received a “definite genetic diagnosis” if their Patient MD was 4 and did not receive a definite genetic diagnosis if their Patient MD was less than 4. In a subsequent analysis, subjects with a Patient MD of 3, indicating a combination of predicted deleterious VUSs that would, if confirmed pathogenic, indicate involvement of that gene in hearing loss, were designated as having a “possible genetic diagnosis.”

**Supplemental Tables**

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|  | N = 939 |
| **Variant MD** |  |
| No. (%) 0-No variant foun | 10 (1.0) |
| No. (%) 1- Benign/Likely Benign  | 1 (0.1) |
| **No. (%) 2-4 - VUS** | 768 (81.8) |
|  No. (%) 2- Benign VUS | 347 (45.2) |
|  No. (%) 3- Unknown VUS | 170 (22.1) |
|  No. (%) 4- Deleterious VUS | 251 (32.7) |
| **No. (%) 5-6 - Variant Known** | 171 (18.2) |
|  No. (%) 5- Likely Pathogenic  | 43 (4.6) |
|  No. (%) 6- Pathogenic  | 127 (13.5) |
|  |  |
| **Gene MD**  | N=856 |
| No. (%) 0                      | 10 (1.2) |
| No. (%) 1  | 492 (57.5) |
| No. (%) 2  | 183 (21.4) |
| No. (%) 3  | 112 (13.1) |
| No. (%) 4  | 59 (6.9) |
| **Patient MD** | N = 240 |
| No. (%) 0  | 10 (4.2) |
| No. (%) 1  | 42 (17.5) |
| No. (%) 2  | 65 (27.1) |
| No. (%) 3  | 69 (28.8) |
| No. (%) 4  | 54 (22.5) |
| **No. (%)** **Definite Genetic Diagnosis****No. (%)** **Possible** **Genetic Diagnosis** | 54 (22.5)69 (37.1) |

**Supplemental Table 1.** Descriptive analysis of genetic data (number(percentage)).

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| --- | --- |
|  | **Definite Genetic Diagnosis** |
| **Dichotomized race/ethnicity** | 0.177 (95% CI: 0.084-0.372, p<0.001) |
| **Primary home language** | 0.854 (95% CI: 0.592-1.231, p=0.40)  |
| **Hearing loss laterality** | 0.240 (95% CI: 0.075-0.770, p=0.02) |
| **Hearing loss onset** | 1.002 (95% CI: 0.992-1.009, p=0.96) |
| **Baseline hearing loss level** | 0.878 (95% CI: 0.642-1.201, p=0.42) |
|  |   |
|  | **Possible Genetic Diagnosis** |
| **Dichotomized race/ethnicity** | 0.799 (95% CI: 0.411-1.552, p=0.51) |
| **Primary home language** | 1.189 (95% CI: 0.823-1.716, p=0.36) |
| **Hearing loss laterality** | 0.603 (95% CI: 0.262-1.390, p=0.24) |
| **Hearing loss onset** | 1.00 (95% CI: 0.991-1.007, p=0.85) |
| **Baseline hearing loss level** | 0.844 (95% CI: 0.629-1.131, p=0.26) |

**Supplemental Table 2**. Logistic regression analysis of definite patient MD and new patient MD with demographic covariates that were significant on univariate analysis, including dichotomized race/ethnicity and primary home language as well as definite clinical covariates including hearing loss laterality, hearing loss onset, and baseline hearing loss level. Results include the regression coefficient, 95% confidence interval, and p-values.

**Supplemental Figure Legends**

**Supplemental Figure 1. Variant classification.** Algorithm for variant categorization into Variant Molecular Diagnoses (Variant MDs) of 1-6 based on clinical report classifications, *in silico* analysis, ClinVar and PROVEAN with number of variants included for each step.

**Supplemental Figure 2. Gene classification.** Algorithm for gene categorization into Gene Molecular Diagnoses (Gene MDs) of 1-4 based on Variant MDs and inheritance pattern with number of variants included for each step.

**Supplemental Figure 3. Inheritance classification.** Algorithm for inheritance pattern determination for hearing-loss genes.

**Supplemental Figure 4. Complex Inheritance classification.** Algorithm for inheritance pattern for non-simple autosomal recessive/dominant genes.