Expanding the Diagnostic Yield of Sensorineural Hearing Loss Through Whole-Genome Sequencing: A Comprehensive Genomic Approach

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Introduction

Sensorineural hearing loss (SNHL) is a condition caused by damage to the inner ear or auditory nerve, often with a genetic basis. Despite its prevalence, the genetic underpinnings of SNHL remain incompletely understood. In some cases, SNHL may be a symptom of a rare underlying disease, adding complexity to the diagnosis. As with many rare diseases, identifying the genetic components of SNHL can be challenging, often leading to prolonged diagnostic journeys and delayed treatment. Comprehensive genomic analysis is critical to uncover the causes of SNHL in both common and rare disease contexts.

Methods

This study included 394 unrelated patients diagnosed with SNHL, along with their family members. Patients were categorized into non-syndromic SNHL (n=342) and syndromic SNHL (n=52). A structured, multi-step genetic testing approach was used. Initially, all non-syndromic patients underwent RT-PCR with classical deafness genes. Undiagnosed patients (n=294) progressed to targeted panel sequencing (n=99) or whole-exome sequencing (WES) (n=249). Further testing included mtDNA sequencing (n=11) and multiplex ligation-dependent probe amplification (MLPA) (n=54). Finally, whole-genome sequencing (WGS, RareVision, INOCRAS, San Diego, CA) was performed on 120 patients who remained undiagnosed after earlier tests (See Figure 1)

Clinical and Demographic Characteristics of the SNHL Cohort

	N=394 families
Sex (Proband)	
Male	183(46.19)
Age at Genetic Test, Median (range, year)	13(0-76)
0~10	170(43.15)
11~20	61(15.48)
21~30	37(9.39)
31~40	30(7.61)
41~50	31(7.87)
51~60	38(9.64)
61~70	21(5.33)
71~76	6(1.52)
Hearing Loss Onset	
Early Identification (failed NHS)	148(37.56)
Delay Identification (passed NHS, pediatric onset)	163(41.37)
Adult Onset	83(21.06)
Family History	
Positive	87(22.08)
Syndromic Features	
Syndromic	53(13.45)
Type of HL	
Sensorineural HL	374(94.92)
Mixed HL	20(5.08)
Asymmetry of HL[b]	
Symmetric	338(90.37)
Asymmetric	36(9.63)
Interaural asymmetry(≥30dB)	40(10.70)
Interaural asymmetry(15-30dB)	26(6.60)
Severity of HL[b] (Rt / Lt)	
Mild-to-Moderate / Mild-to-Moderate	59(15.78)
Mild-to-Moderate / Moderate-to-Severe	13(3.48)
Mild-to-Moderate / Severe-to-Profound	6(1.60)
Moderate-to-Severe / Mild-to-Moderate	8(2.14)
Moderate-to-Severe / Moderate-to-Severe	147(39.30)
Moderate-to-Severe / Severe-to-Profound	19(5.08)
Severe-to-Profound / Mild-to-Moderate	2(0.53)
Severe-to-Profound / Moderate-to-Severe	15(4.01)
Severe-to-Profound / Severe-to-Profound	105(28.07)
Configuration of HL[b] (Rt / Lt)	
Flat / Flat	238(63.64)
Flat / Down-Sloping	8(2.14)
Flat / Cookie-Bite	3(0.80)
Flat / Up-Sloping	1(0.27)
Down-Sloping / Flat	5(1.34)

Results

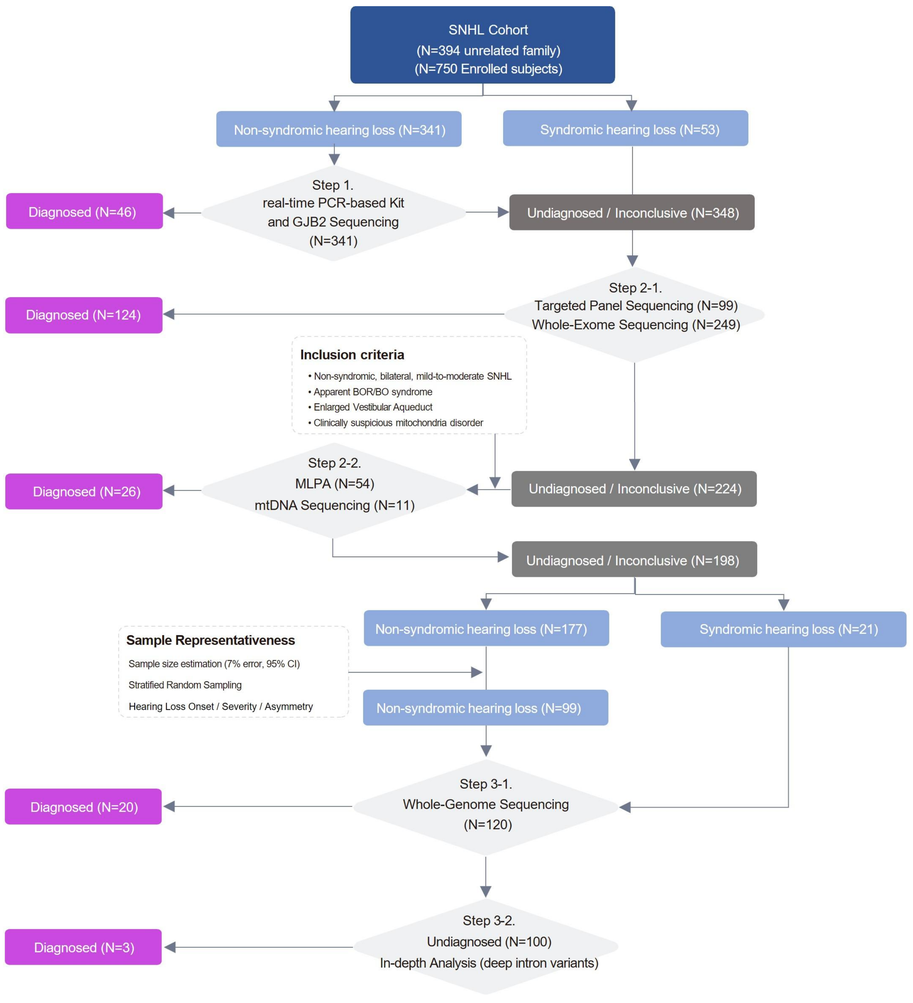

Figure 1. Study Design and Diagnostic Pipeline
Flowchart illustrating the structured genetic diagnostic approach applied to 394 unrelated SNHL families. The pipeline follows a stepwise process: Step 1—PCR screening and *GJB2* sequencing; Step 2-1—targeted panel sequencing or whole-exome sequencing (WES); Step 2-2—MLPA and/or mtDNA panel sequencing; Step 3-1—whole-genome sequencing (WGS); and Step 3-2—deep intronic variant analysis.

Conclusion: WGS potentially improves SNHL diagnostics by uncovering rare variants, increasing detection rates, and allowing for early personalized interventions.

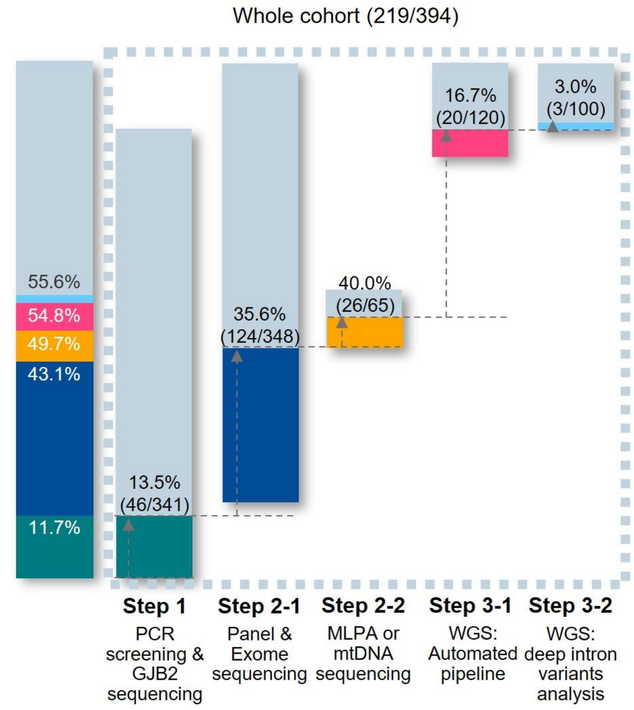

Figure 2. Stepwise Diagnostic Yield in SNHL Patients
Bar graph displaying the cumulative diagnostic yield across sequential genetic testing steps. Each step contributes to the overall diagnostic rate, with WGS and deep intronic analysis further improving detection.

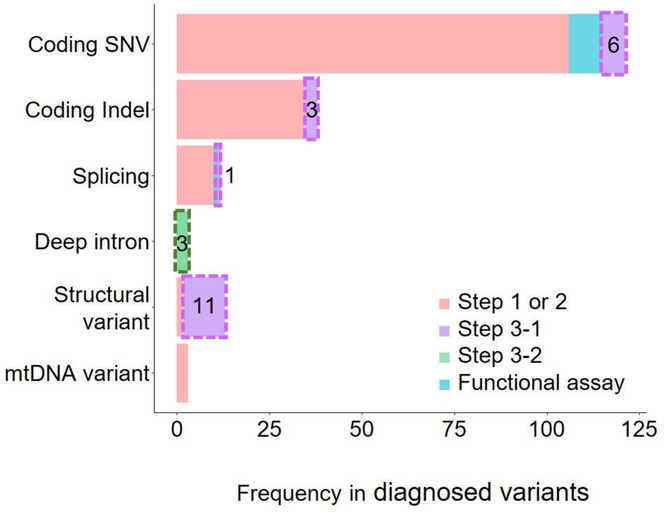

Figure 3. Variant Distribution by Diagnostic Step
Bar graph illustrating the distribution of variant subtypes identified across diagnostic steps. Categories include coding single nucleotide variants (SNVs), indels, splicing variants, deep intronic variants, structural variants, and mtDNA mutations.