GJB2 p.V37I Mutation Variant Associated with Hearing Loss Under 40 in an Adult Taiwanese Population

Ting-Ting Yen [1], Ting-Gang Chang [2], Yi-Ming Chen [3]

1 Department of Otolaryngology, Taichung Veterans General Hospital, Taichung , Taiwan
2 Department of psychiatry, Taichung Veterans General Hospital, Taichung, Taiwan
3 Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan

Introduction

- A global rise in sensorineural hearing loss (SNHL), highlights the need for better screening and intervention.
- Genetic factors, especially the common GJB2 p.V37I variant in East Asian populations, contribute significantly to SNHL.
- This study employs a genotype-first approach to resolve previous inconsistencies and test the hypothesis that p.V37I carriers (especially males) show earlier, high-frequency SNHL.

Aim of this study was to establish p.V37I as a clinically actionable biomarker for progressive SNHL in adults.

Methods

Study Design and Setting

This genotype-first case-control study, embedded within the Taiwan Precision Medicine Initiative(TPMI) biobank (32,728 Taiwanese participants), recalled 96 GJB2 p.V37I homozygous carriers and 95 non-carrier controls between November 2022 and July 2024 at Taichung Veterans General Hospital. All participants underwent audiological and clinical evaluations to assess the variant's effect. (Figure 1)

Inclusion Criteria

Cases were homozygous for the GJB2 p.V37I variant and free of other hearing-loss mutations. Controls were selected from the same cohort lacked relevant genotypes.

Exclusion Criteria

Excluded subjects with other hearing-related gene variants, ear trauma, or ototoxic exposures.

Clinical and Demographic Data

Participants underwent standardized interviews and physical exams to collect data on demographics, lifestyle, noise exposure, medical history, and physical measurements.

Audiometric Assessment

Audiologists performed standardized pure-tone audiometry. Consistent with World Health Organization (WHO) recommendations, abnormal hearing was defined as >20 dB HL or greater at any measured frequency.

Chinese-Mandarin version of the Tinnitus Handicap Inventory (THI-CM)

Tinnitus severity was measured using the THI-CM. Significant tinnitus was THI score ≥18.

Statistical Analysis

Chi-square/Fisher's, t/Mann–Whitney U tests, and multivariable logistic regression were used; p<0.05 defined significance. Analyses used SPSS and R.

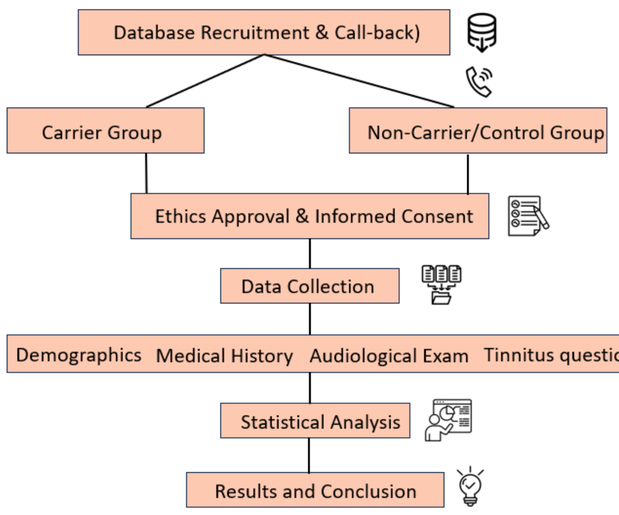

Figure 1. Research flowchart

Result

Baseline Characteristics Differ by GJB2 p.V37I Genotype

GJB2 p.V37I carriers, compared to non-carriers, were older and had a lower proportion of females. They also had significantly higher weight, BMI, blood pressure, and a greater prevalence of cardiometabolic comorbidities, smoking, and noise exposure. (Table 1)

	Total (n=191)	GJB2 (n=96)	Control (n=95)	p value
Age of first audiogram, mean±SD	49.3±13.6	58.4±11.0	40.1±9.0	<0.001
Gender, n (%)				<0.001
Male	50 (26.2%)	37 (38.5%)	13 (13.7%)	
Body weight (kg), mean±SD	62.6±13.9	65.6±14.9	59.6±12.2	0.003
BMI (kg/m2), mean±SD	24.2±4.1	25.3±4.3	23.0±3.6	<0.001
Systolic blood pressure (mm Hg)	120.9±13.9	126.3±14.2	115.3±11.4	<0.001
Diastolic blood pressure	74.0±9.1	76.2±9.1	71.8±8.7	0.002
Comorbidity, n (%)				
Hypertension	54 (28.3%)	50 (52.1%)	4 (4.2%)	<0.001
Diabetes Mellitus	28 (14.7%)	27 (28.1%)	1(1.1%)	<0.001
Hyperlipidemia	42 (22.0%)	35 (36.5%)	7(7.4%)	<0.001
Behavior, n (%)				
Smoker	26 (13.6%)	22 (22.9%)	4 (4.2%)	<0.001
Noise, n (%)				
Noise (year), mean±SD	15.4±12.9	16.6±12.7	1.5±0.0	0.006

Table 1. Baseline Demographics and Clinical Characteristics

Tinnitus Severity and Cochleovestibular Symptoms in GJB2 Carriers

GJB2 carriers had significantly higher PTA thresholds (34 dB) and abnormal hearing (>80%) than controls. GJB2 p.V37I carriers had a higher burden of tinnitus, with elevated THI-CM scores and greater prevalence of clinically significant tinnitus. They also showed significant bilateral high-frequency hearing loss, and higher rates of self-reported symptoms. (Table 2)

	Total (n=191)	GJB2 (n=96)	Control (n=95)	p value
THI-CM, mean±SD	6.3±15.2	10.3±19.5	2.2±7.0	<0.001
THI-CM_Abnormal, n (%)	22 (11.5%)	17 (17.7%)	5 (5.3%)	0.007
Pure-tone average, mean±SD				
Right ear	22.7±18.1	34.2±19.0	11.1±5.3	<0.001
Left ear	22.3±18.2	33.6±19.2	10.8±5.7	<0.001
Hearing loss, n(%)				
Right ear	97 (50.8%)	81 (84.4%)	16 (16.8%)	<0.001
Left ear	93 (48.7%)	77 (80.2%)	16 (16.8%)	<0.001
Binaural hearing impairment (%), mean±SD	-5.7±26.1	11.0±27.2	-22.5±7.4	<0.001
Unilateral hearing impairment (%),				
Right ear (%)	-3.6±26.9	13.6±28.0	-20.9±8.0	<0.001
Left ear (%)	-4.2±26.9	12.8±28.1	-21.3±8.6	<0.001
Self-reported symptoms				
Hearing loss, n (%)	63 (33.0%)	59 (61.5%)	4 (4.2%)	<0.001
Dizziness, n (%)	33 (17.3%)	25 (26.0%)	8 (8.4%)	0.001
Tinnitus, n (%)	33 (17.3%)	31 (32.3%)	2 (2.1%)	<0.001

Table 2. Tinnitus Handicap, Hearing Impairment, and Symptoms

Audiometric Thresholds Stratified by Age and Sex

Audiometric thresholds progressively increased with age, especially in males and at high frequencies. While univariate analysis showed GJB2 p.V37I carrier status was associated with abnormal THI-CM scores, this association was not significant in multivariate analysis. (Figure 2)

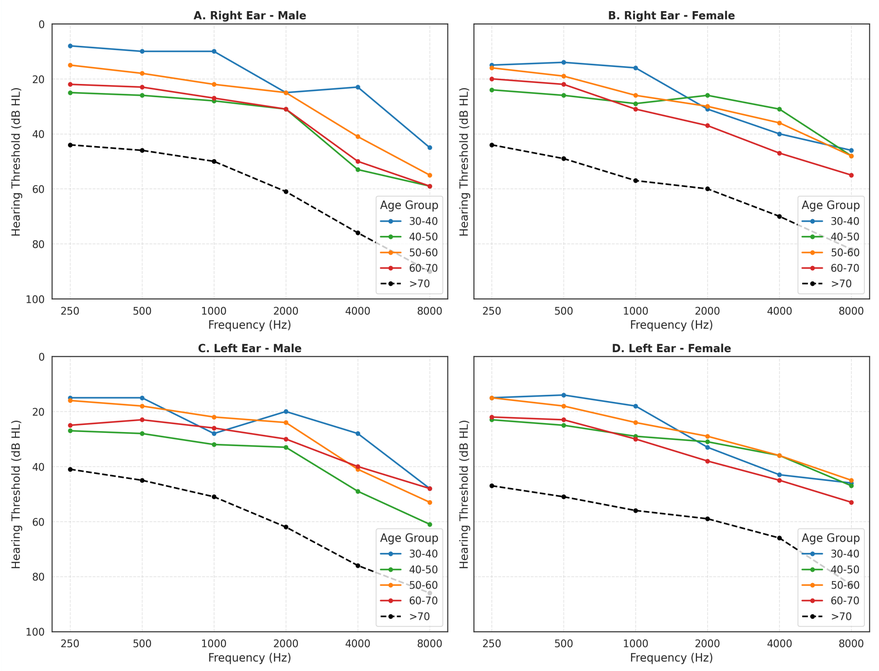

Figure 2. Audiometric Threshold by Age , Sex and Ear

Risk Factors for Abnormal Hearing Thresholds

GJB2 homozygosity (OR = 6.52; 95% CI: 2.52–16.86; $p < 0.001$) and age(OR = 1.05; p = 0.014) were independent risk factors for abnormal hearing.

Discussion

- This genotype-first study shows that GJB2 p.V37I homozygosity is significantly linked to progressive high-frequency hearing loss, tinnitus, and vestibular issues in East Asian adults.
- This evidence challenges the view of the variant as minimally penetrant and supports its reclassification as a clinically actionable, likely pathogenic marker.
- The findings underscore the importance of integrating genetic screening with perceptual and physiological assessments for personalized care.

Limitations

- Cross-sectional design and reliance on self-reported data limit the ability to draw causal inferences.
- Single-ethnicity focus restricts the generalizability of findings to other populations.

Conclusion

- GJB2 p.V37I homozygosity confers a substantial risk of progressive, multidimensional adult-onset auditory dysfunction.
- These findings challenge prior benign or hypomorphic variant status.
- Implementation of targeted genomic screening and perceptual assessment is recommended for earlier detection and individualized intervention.
- Validation in diverse and longitudinal cohorts is recommended.

Contact

Ting-Ting Yen
Department of Otolaryngology, Taichung Veterans General Hospital , Taichung , Taiwan
1650 Taiwan Boulevard Sect. 4, Taichung, Taiwan 407219, ROC
tingting@vghtc.gov.tw

Reference

1. Chen, P.Y., et al. (2020). Ear and Hearing, 41(1), 143–149.
2. Chen, Y., et al. (2022). Genetics in Medicine, 24(4), 915–923.
3. Chiang, Y.-T., et al. (2023). The Journal of Molecular Diagnostics, 25(11), 827-837
4. Yen, T. T., et al. (2023). Ear and hearing, 44(6), 1423–1429.