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Research Paper

The Prevalence of *GJB2* Mutation (35delG) in Patients With Non-syndromic Hearing Loss From Northern Iranian Population

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ABSTRACT

Background: Biallelic mutations in *GJB2* are responsible for over half of all autosomal recessive non-syndromic hearing loss (ARNSHL) cases, establishing it as the most critical locus for this disorder globally. Among its many variants, 35delG is one of the most frequently reported.

Objectives: The current study aimed to investigate the prevalence of 35delG and other mutations associated with non-syndromic hearing loss among northern Iranian populations.

Materials & Methods: This study included 313 individuals with non-syndromic hearing loss (age range: 2–84 years; 55.6% female, 44.4% male). Genotyping for the 35delG variant was performed using allele-specific PCR (ARMS). Samples homozygous for 35delG were identified for subsequent analysis, while all other samples underwent bidirectional Sanger sequencing of the entire *GJB2* gene. All statistical analyses were conducted using SPSS software, version 25.

Results: Genetic analysis revealed that 42 individuals (13.4%) were homozygous for the 35delG mutation. An additional 38 subjects (12.14%) were heterozygous for this variant. Other pathogenic mutations were identified in 24 individuals, comprising 4 homozygotes (1.28%) and 20 heterozygotes (6.40%). The specific homozygous mutations other than 35delG were NM_004004.6:c.1+1G>A, NM_004004.6:c.427C>T (p.Arg143Trp), and NM_004004.6:c.290_291insA. Furthermore, 17 individuals (5.43%) were compound heterozygotes. The overall allele frequency for the 35delG variant in the studied population was 21.57%.

Conclusion: This study confirms the high frequency of the 35delG mutation in the *GJB2* gene among northern Iranians over a 7-year period. A consanguineous background was present in half of the 35delG carriers, a notable association that likely explains the high prevalence of this mutation in the studied population.
Keywords: Hearing loss, Sensorineural, Connexin 26, Mutation, Gene frequency

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Highlights

- The 35delG mutation frequency was 21.57% in Northern Iranian ARNSHL patients.
- 45.2% of individuals with a 35delG mutation had a consanguineous background.
- 17 compound heterozygotes carrying 35delG and other *GJB2* mutations were identified.
- 13.4% of the studied cohort were homozygous for the 35delG mutation.

Introduction

Hearing loss is the most prevalent sensorineural condition found in humans. It can be a feature of a syndromic condition in 30% of genetic instances, though the majority of genetic instances of deafness are non-syndromic, where the solely manifest feature is the impairment of hearing [1]. The genetic heterogeneity of this condition is high, as 80% of genetic instances have been found to be due to autosomal recessive inheritance, particularly prelingual deafness. The high incidence of the latter has often been attributed to consanguineous marriages [2].

To date, over 100 genetic loci and more than 60 genes have been implicated in autosomal recessive non-syndromic hearing loss (ARNSHL) [3]. Among these, the *GJB2* gene, which encodes the gap junction protein Connexin 26, is the most significant contributor. Gap junctions, formed by connexin proteins, are critical for intercellular communication and potassium recycling in the inner ear [4]. Biallelic mutations in *GJB2* are responsible for more than half of all ARNSHL cases in many populations, making it the most essential gene for this disorder. The spectrum of *GJB2* mutations includes the NM_004004.6:c.35delG variant, one of the most common pathogenic changes reported globally [5].

In Iran, the frequency of the *GJB2* mutation was also found to be relatively lower than that in Europe initially. Subsequent research showed the geographical gradient [6]. Research conducted in the provinces of Iran indicated that the highest frequency of carriers of the 35delG mutation was in the province of Guilan in the north, suggesting a decreasing gradient from north to south [7]. Based on this, it has been hypothesized that the 35delG mutation may have originated in the northern region of Iran and spread along with migration from the northern to the southern regions of Iran.

To validate this hypothesis, a comprehensive cohort study is necessary in Guilan Province. Accordingly, the objective of this study is to analyze the mutation spectrum, as well as the prevalence, of the *GJB2* gene, particularly the 35delG mutation, among ARNSHL patients in Northern Iran over a period of seven years, from 2016 to 2023*GJB2*.

Materials and Methods

Patient recruitment and selection

This cross-sectional study included 313 unrelated individuals with NSHL from Guilan Province, Iran, recruited over the seven-year period (2016-2023). Participants were selected from multiple sources to ensure a representative sample, including provincial welfare centers, schools for the deaf, and deaf societies. The sampling method was stratified random sampling to cover various age groups and geographic districts within the province. All participants or their legal guardians provided written informed consent. The study protocol was approved by the Ethics Committee for Human Genome/Gene Research at Guilan University of Medical Sciences.

Inclusion and exclusion criteria

The inclusion criterion was a diagnosis of bilateral sensorineural hearing loss. A comprehensive evaluation was conducted to confirm the non-syndromic nature of the hearing loss. This involved a detailed medical history, physical examination, and pedigree analysis up to third-degree relatives to rule out any syndromic features or other health anomalies. Individuals with a history of acquired causes of hearing loss, such as intrauterine infection, meningitis, ototoxic drug exposure, head trauma, or neonatal hyperbilirubinemia requiring transfusion, were excluded from the study.

Sample size justification and laboratory methods

The sample size of 313 was determined to be sufficient to estimate the frequency of *GJB2* mutations with a 95% confidence level and a relative error limit of 10%, based on previous genetic epidemiological studies [8]. Genomic DNA was extracted from 2–5 mL of peripheral blood samples collected from each participant. The 35delG variant was screened using the allele-specific PCR (ARMS) method with specifically designed primers. Samples that were not homozygous for 35delG underwent bidirectional Sanger sequencing of the entire coding region of the *GJB2* gene (exons 1 and 2) to identify other potential mutations. All laboratory procedures were performed at the Cellular and Molecular Research Center of Guilan University of Medical Sciences, and Dr. Keshavarz's Medical Genetics Laboratory.

All cases were sequenced using a 3500 Genetic Analyzer based on the manufacturer's protocols for ExoSAP-IT® PCR cleanup, 5x sequencing buffer, and BigDye® XTerminator. The primers used for the sequencing of exon 1 and exon 2 were as follows:

Exon 1: Forward: 5'-CCCTCCGTAACTTTCCCAGT-3'

Exon 1: Reverse: 5'-AAGGACGTGTGTTGGTCCAG-3'

Exon 2: Forward: 5'-GCTTACCCAGACTCAGAGAAG-3'

Exon 2: Reverse: 5'-CTACAGGGGTTTCAAATGGTTG-3'

Statistical analysis

All statistical analyses were carried out using SPSS software version 25. The χ^2 goodness-of-fit test was used to assess deviations from Hardy-Weinberg equilibrium (HWE).

Results

The present study included 313 unrelated individuals with ARNSHL from Northern Iran (Guilan Province), comprising 174 females (55.6%) and 139 males (44.4%), with an age range of 2 to 84 years (mean: 28 years). Genetic analysis of the *GJB2* gene revealed a spectrum of mutations, with an overall 35delG allele frequency of 21.57% (95% CI, 18.4%, 25.0%).

The distribution of *GJB2* genotypes is summarized in Table 1 and visually presented in Figure 1. Among the cohort, 192 individuals (61.3%) showed no mutations in the *GJB2* gene. Of the remaining 121 individuals with *GJB2* mutations, 42 cases (13.4% of total cohort) were homozygous for the 35delG variant. Additionally, 38 individuals (12.1%) were heterozygous for 35delG, while 20 individuals (6.4%) carried other heterozygous mutations.

A detailed breakdown of all non-35delG mutations identified in heterozygous and compound heterozygous states is provided in Table 2. Notably, 17 individuals (5.4%) were compound heterozygotes, with the majority (7 individuals) carrying the 35delG/c.1+1G>A genotype. The most frequent non-35delG mutation was c.136G>A (p.Ala46Thr), identified in six heterozygous individuals.

Table 1. Summary of *GJB2* genotype distribution in the study cohort (n=313)

Genotype Category	Specific Genotype	No. (%)
No *GJB2* mutations	WT/WT	192(61.34)
Homozygous	35delG/35delG	42(13.42)
Homozygous	Other mutations	4(1.28)
Heterozygous	35delG/WT	38(12.14)
Heterozygous	Other mutation/WT	20(6.39)
Compound heterozygous	35delG/other mutation	17(5.43)
Total		313(100)

Table 2. Spectrum of non-35delG *GJB2* mutations

Mutation / Genotype Combination	Protein Change	Category	Number of Cases
c.1+1G>A	-	Heterozygous	4
c.136G>A	p.Ala46Thr	Heterozygous	6
c.80G>A	p.Cys27Tyr	Heterozygous	1
c.427C>T	p.Arg143Trp	Heterozygous	1
c.176_191del	-	Heterozygous	1
c.326G>A	p.Gly109Asp	Heterozygous	1
c.37G>A	p.Gly13Ser	Heterozygous	1
c.94C>T	p.Arg32Cys	Heterozygous	1
c.109G>A	p.Val37Ile	Heterozygous	1
c.358_360del	p.Glu120del	Heterozygous	1
c.-3404G>A	-	Heterozygous	1
35delG / c.1+1G>A	-	Compound Heterozygous	7
c.109G>A / c.358_360del	p.Val37Ile / p.Glu120del	Compound Heterozygous	2
35delG / c.463_464del	-	Compound Heterozygous	1
35delG / c.290_291insA	-	Compound Heterozygous	1
35delG / c.327_328delinsA	-	Compound Heterozygous	1
35delG / c.551G>C	p.Trp184Ser	Compound Heterozygous	1
35delG / c.176_191del	-	Compound Heterozygous	1
35delG / c.358_360del	p.Glu120del	Compound Heterozygous	1
c.427C>T / 35delG	p.Arg143Trp	Compound Heterozygous	1
c.-3527G>A / c.-3548A>T	-	Compound Heterozygous	1

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Consanguinity was observed in 13.4% of all participants, with a significantly higher prevalence (45.2%) among individuals carrying at least one 35delG allele. Bidirectional Sanger sequencing of both exons 1 and 2 of *GJB2* was performed for individuals who showed no 35delG mutation (Figure 2).

Discussion

The current study screened *GJB2* mutations among Northern Iranians from Guilan Province who suffered from ARNSHL. Our findings demonstrated a high overall frequency of the 35delG mutation, assessed at 21.57% among individuals with ARNSHL over the 7-year period. This result firmly establishes 35delG as the predominant genetic cause of *GJB2*-related hearing loss in this region. A pivotal finding that offers a clear explanation for this high prevalence is the strong association with consanguinity, observed in almost half of the 35delG carriers (45.2%).

Prior studies have reported mutations in the *GJB2* gene and documented that the main disease-causing mutation is 35delG [9]. When placed in a global context, the frequency we report is notably higher than that found in many other populations. A study of 77 Brazilian individuals with NSHLscreened for a panel of common mutations, including *GJB2*-35delG, 167delT, 235delC, and W24X, as well as the GJB6 deletions D13S1830 and D13S1854. The majority of subjects (88.3%) had

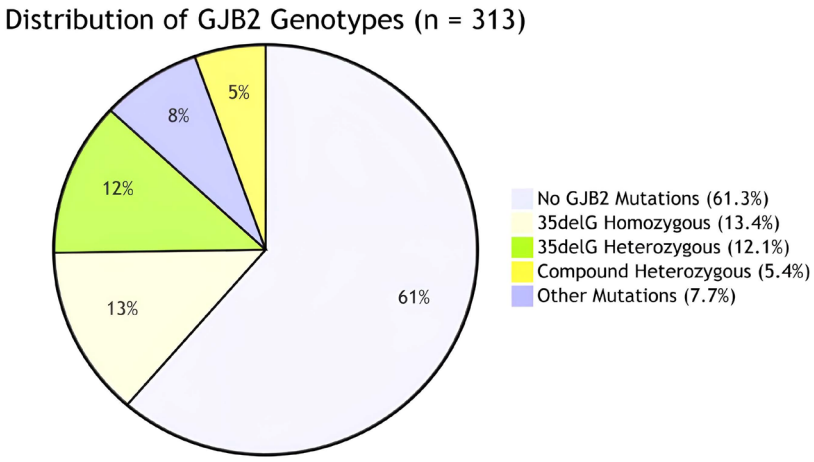

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Figure 1. Distribution of *GJB2* genotypes in a northern Iranian cohort with autosomal recessive non-syndromic hearing loss

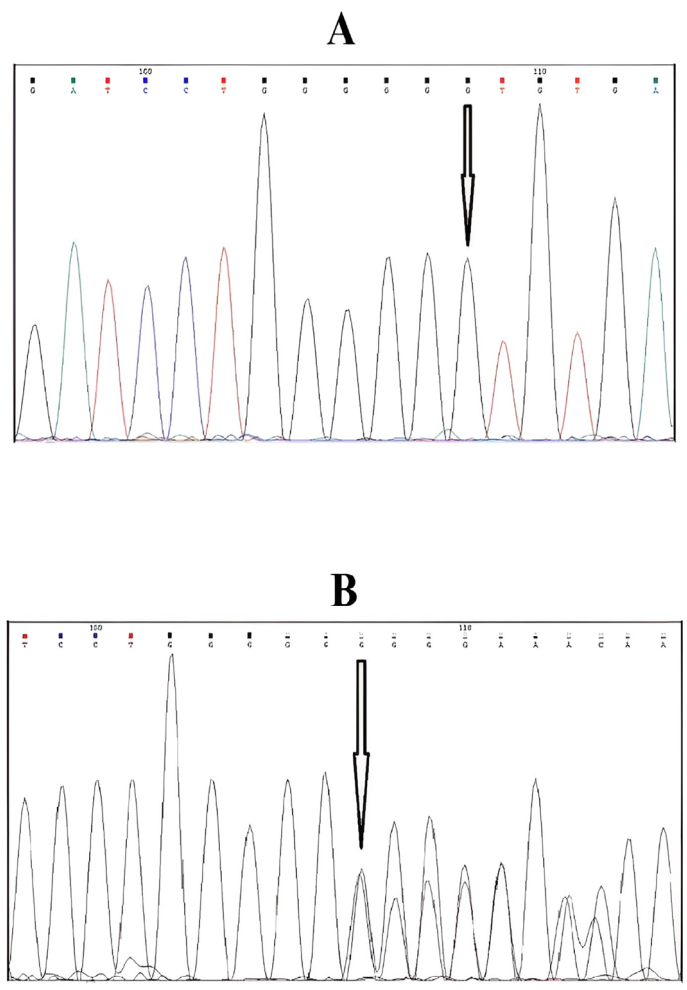

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Figure 2. Results of Sanger sequencing in a normal individual without the 35delG mutation (A), a carrier of 35deG (heterozygote genotype) (B), and a deaf person with a 35delG homozygote genotype (C)

a normal genotype for all mutations tested. Among the mutant genotypes identified, the 35delG variant was the most prevalent. The results showed that 3.9% of individuals were homozygous for 35delG, 5.2% were heterozygous for 35delG, and 1.3% were compound heterozygotes for the 35delG and GJB6-D13S1854 mutations. No other mutations from the panel were detected in this cohort [10].

A study of the Turkish ARNSHL population found that *GJB2* mutations underlie about 30% of cases, and this genetic cause was consistent across different regions of Turkey. The mutation spectrum included not only 35delG but also the W24X and delE120 variants, each of which was found in approximately 5% of patients [11]. This stark contrast highlights the unique genetic architecture of Northern Iran.

Our data provide strong, empirical confirmation for the geographical gradient hypothesis previously proposed for Iran. Research into the 35delG carrier frequency in Iran revealed an overall rate of 1.25%, a figure comparable to other Middle Eastern populations but substantially lower than in Europe [12]. The study, which covered four provinces, identified a regional hotspot in Guilan, where the carrier frequency was found to be 2.8% [7]. An updated genetic analysis of 332 unrelated families assessed the occurrence and spectrum of *GJB2* mutations in Iran. The findings revealed a significant regional variation, with homozygous mutations accounting for 22.5% and 20% of cases in Isfahan and Hamedan provinces, respectively. Overall, the incidence of *GJB2* mutations was 16% in the central provinces, a rate substantially higher than that observed in southern Iranian populations [13]. Analysis of 5,200 controls from 15 Middle Eastern populations established a total NM_004004.6:c.35delG carrier rate of 1.38%, a figure far below European levels. This thorough assessment of 14 studies also identified a potential west-to-east decline in frequency across the region [14]. In a review of six studies involving 812 families from eastern Iran, 19 different *GJB2* mutations were documented, and the mutation frequency was determined to be 8.8%. The most common mutation was c.35delG, which was found in 48.5% of the investigated populations [15]. The marked disparity in prevalence between the north and south, combined with genetic data suggesting a northern origin and subsequent spread of the 35delG mutation, supports the existence of a north-to-south and west-to-east frequency gradient across Iran [16, 17]. Our seven-year cohort from the suspected region of origin provides the most robust local dataset to date, confirming this pattern.

The high frequency of the 35delG mutation in our population is critically linked to the custom of consanguineous marriage. The finding that 45.2% of individuals with a 35delG allele had a consanguineous background provides a clear mechanistic explanation for the persistence and high homozygosity of this recessive allele [18, 19]. This practice significantly increases the likelihood of offspring inheriting identical pathogenic variants from a common ancestor, a well-established driver of autosomal recessive disorders [20]. This association underscores the profound impact of social structure on the genetic landscape of disease.

Beyond 35delG, our study delineated a broader spectrum of *GJB2* mutations. We identified 17 individuals (5.43%) who were compound heterozygotes, with the most common combination being 35delG and the c.1+1G>A splice-site mutation. This finding is crucial for clinical diagnostics, as it demonstrates that a significant portion of *GJB2*-related hearing loss in this population is attributable to complex genotypes that would be missed by targeted 35delG screening alone. Furthermore, the identification of other recurring variants, such as c.136G>A (p.Ala46Thr) in six heterozygous individuals, adds further detail to the mutational profile of the Iranian population. This genetic heterogeneity indicates that comprehensive sequencing of the *GJB2* gene is essential for a complete molecular diagnosis.

A limitation of our study is its primary focus on the *GJB2* gene. Given that 192 individuals (61.3%) in our cohort had no mutations detected in this gene, the genetic etiology of their hearing loss remains unexplained and likely involves other known or novel genetic loci. Future research utilizing whole-exome or whole-genome sequencing will be necessary to uncover the full spectrum of genetic causes of ARNSHL in this population [21].

This study highlights the high prevalence of the 35delG mutation in *GJB2* among northern Iranians with ARNSHL and establishes a clear and significant association with consanguinity. Our findings contribute to the growing body of evidence on the genetic basis of ARNSHL and provide a compelling rationale for the implementation of targeted genetic counseling and carrier screening programs in this region. Such initiatives are vital for reducing the incidence of this disorder and advancing personalized medicine approaches in auditory healthcare.

Conclusion

This study confirms the 35delG mutation as the predominant cause of *GJB2*-related ARNSHL in Guilan (a

northern province of Iran), with a high allele frequency of 21.57%. This prevalence results from a combination of demographic factors, notably consanguinity and genetic mechanisms, likely a founder effect, as evidenced by the distinct north-south gradient within Iran. While the focused sampling on one province limits broader generalizability, our findings strongly support implementing targeted genetic counseling and carrier screening in this high-risk population to reduce disease incidence.

Ethical Considerations

Compliance with ethical guidelines

This study was performed in line with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Guilan University of Medical Sciences, Rasht, Iran (Code: IR.GUMS.REC.1396.452). Informed Consents were obtained from all participants and their legal guardians included in this study.

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Authors contributions

Conceptualization and supervision: Shadman Nemati and Parvaneh Keshavarz; Methodology, design, and data analysis: Shadman Nemati, Alireza Sharafshah, and Ali Albonaim; Experiments: Masoumeh Khani and Alireza Sharafshah; Statistical analysis, interpreting the results: Alireza Sharafshah; Patient recruitment and clinical data collection: Ali Faghih Habibi and Masoumeh Khani; Investigations and writing the original draft: Samin Abed, Shadman Nemati, and Alireza Sharafshah; Review and editing: Samin Abed and Ali Albonaim; Project administration and final approval: Parvaneh Keshavarz.

Conflict of interest

The authors declared no conflict of interests.

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