REVIEW
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# Genetics of Hearing Loss in North Iran Population: An Update of Spectrum and Frequency of *GJB2* Mutations

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Diagnosis of pre-lingual hearing loss (HL) is difficult owing to the high number of genes responsible. The most frequent cause of HL is DFNB1 due to mutations in the *GJB2* gene. It represents up to 40% of HL cases in some populations. In Iran, it has previously been shown that DFNB1 accounts for 16−18% of cases but varies among different ethnic groups. Here, we reviewed results from our three previous publications and data from other published mutation reports to provide a comprehensive collection of data for *GJB2* mutations and HL in northern Iran. In total, 903 unrelated families from six different provinces, viz., Gilan, Mazandaran, Golestan, Ghazvin, Semnan, and Tehran, were included and analyzed for the type and prevalence of *GJB2* mutations. A total of 23 different genetic variants were detected from which 18 *GJB2* mutations were identified. *GJB2* mutations were 20.7% in the studied northern provinces, which was significantly higher than that reported in southern populations of Iran. Moreover, a gradient in the frequency of *GJB2* mutations from north to south Iran was observed. c.35delG was the most common mutation, accounting for 58.4% of the cases studied. This study suggests that c.35delG mutation in *GJB2* is the most important cause of HL in northern Iran.

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**KEY WORDS:** Genetic counseling · Gap junction protein beta 2 · Hearing loss · *GJB2* insertion.

## Introduction

Hearing loss (HL) is a sensory impairment that affects millions of people worldwide, with the probability of approximately 1 in 1000 live births (http://hearing.screening.nhs.uk/nationalprog). Approximately, two-third of individuals with hearing impairment reside in developing countries, wherein more than 60% cases are attributed to genetic factors [1]. The genetic forms of HL are syndromic, which is accompanied by other specific abnormalities, and non-syndromic HL (NSHL), in which no additional abnormalities are observed. Autosomal recessive mode of inheritance (ARNSHL) comprises 80% of NSHL cases. ARNSHL is highly heterogeneous, with over 100 associated loci and >60 identified causative genes (http://hereditaryhearingloss.org/). *GJB2* at the DFNB1 locus is responsible for 60% of all deafness cases, and over 100 *GJB2* pathogenic variants have been reported with variable frequency among disparate world populations [2-11]. c.35delG accounts for >50% of *GJB2*-related NSHL in many western populations [12]. Other mutations are more origin specific. In the Japanese population, 235delC is more prevalent [3] and c.167delT is common in Ashkenazi Jews [2]. In individuals of Indian and Pakistani ancestry, c.71G>A is the common *GJB2* variant [3]. Over the last decade, several studies have been conducted on the Iranian population to identify the mutation spectrum and prevalence of *GJB2* mutations [13-23]. The different ethnicities coupled with the high frequency of familial marriages (38% on an average) [24] tend to change mutation frequencies among the ethnic groups [25]. Therefore, for accurate genetic counseling, studying certain ethnic groups is of high importance. In this study, we have summarized the published data on the frequency and

profile of *GJB2* mutations in 903 unrelated families from six different provinces, viz., Gilan, Mazandaran, Golestan, Ghazvin, Semnan, and Tehran, in north Iran compared to those in other parts of the country.

## Methods

This study included results from our three previous publications on *GJB2*-related HL in Iran [19-36]. We also performed a PubMed, Web of Science, and Google Scholar search using the search terms "*GJB2* mutations", "connexin 26", and "Iran". In the search results, we limited the search to humans with available information on molecular genetics of HL. Studies were included when the following three criteria were fulfilled: 1) inclusion of NSHL subjects, 2) known ethnicity of the tested subjects, and 3) detection of all *GJB2* variants. Studies were excluded if HL was a result of environmental factors, such as infection, trauma, rubella, meningitis, mumps, ototoxic drugs, and premature birth. Research data, including data of 903 unrelated deaf families, from the north provinces were collected. The frequency and mutation type of 903 deaf families were extracted from relevant studies and categorized corresponding to the geographical boundaries. In silico analyses were also performed using the available software tools (Mutation Taster and SIFT; http://www.mutationtaster.org, https://sift.bii.a-star.edu.sg/) to predict the pathogenicity of the mutations.

## Results

Data from 903 unrelated families from six provinces were analyzed (Table 1). The groups studied consisted of 429 families from Tehran (47.5%), 156 families from Gilan (17.3%), 111 families from Semnan (12.3%), 100 families from Mazandaran (11.1%), 85 families from Golestan (9.4%), and 22 families from Ghazvin (2.4%). Among these families, 66.5% reported parental consanguinity, whereas close consanguinity was denied in 33.5% cases (Table 2). *GJB2* mutation allele frequencies of each studied group were 32%, 31.3%, 20.9%, 19.75%, 11.5%, and 9% in the total studied families (n=903) of Mazandaran, Gilan, Golestan, Tehran, Semnan, and Ghazvin, respectively (Fig. 1). When moving from the west to east and north to south of the studied provinces, a gradual decrease in *GJB2* HL was observed.

In total, 30 different variants were identified, 22 of which were reported as pathogenic. These included c.-23+1G>A, c.35delG, c.71G>A, c.95G>A, c.136G>A, c.139G>T, c.167delT, c.224G>A, c.229T>C, c.230G>A, c.235delC, K102Q, c.313-326del, c.327-328delGG, c.358-360delGAG, c.326G>A, c.334-36delAA, c.427C>T, 463-464delTA, c.487A>G, c.511G>A, and c.551G>C. The allele variants identified in various Iranian ARSNSHL families are summarized in Table 3. In the studied populations, c.35delG was the most frequent mutation, accounting for 58.4% cases in the populations studied. The highest rate of c.35delG mutation was detected in the Gilan province with an allele frequency of 27.6%, whereas this rate was 6.3% in Semnan (Table 1). A

**Table 1.** Characteristics of included studies

| Number | First author | Year | Province | Detection method | Case | Hearing loss type | Reference |
|---|---|---|---|---|---|---|---|
| 1 | Chaleshtori | 2002 | Gilan | ARMS-PCR and sanger sequencing | 87 | ARNSHL | [35] |
| 2 | Bazazzadegan | 2012 | Gilan | Sanger sequencing | 69 | NSHL | [30] |
| 3 | Bazazzadegan | 2012 | Ghazvin | Sanger sequencing | 22 | NSHL | [30] |
| 4 | Hosseinipour | 2005 | Golestan | ARMS-PCR and sanger sequencing | 55 | ARNSHL | [19] |
| 5 | Bazazzadegan | 2012 | Golestan | Sanger sequencing | 30 | NSHL | [30] |
| 6 | Bazazzadegan | 2012 | Tehran | Sanger sequencing | 173 | NSHL | [30] |
| 7 | Chaleshtori | 2005 | Tehran | ARMS-PCR and sanger sequencing | 256 | ARNSHL | [36] |
| 8 | Chaleshtori | 2007 | Semnan | Sanger sequencing | 111 | NSHL | [27] |
| 9 | Bazazzadegan | 2012 | Mazandaran | Sanger sequencing | 100 | NSHL | [30] |

ARMS-PCR: amplification-refractory mutation system PCR, ARNSHL: autosomal recessive non-syndromic hearing loss, NSHL: non-syndromic hearing loss

**Table 2.** The frequency of consanguinity among different provinces of north Iran

| Province | Gilan | Mazandaran | Golestan | Tehran | Semnan | Ghazvin |
|---|---|---|---|---|---|---|
| Consanguinity | 85 | 57 | 58 | 307 | 76 | 18 |
| Non-consanguinity | 71 | 43 | 27 | 122 | 35 | 4 |
| Total* | 156 | 100 | 85 | 429 | 111 | 22 |

*Total case number


**Fig. 1.** The prevalence of *GJB2*-related mutations in different regions of Iran (south 0–4% [27,44], northwest 22–27% [27,44], and central 13–15% [30,44]). Six north provinces (Gilan, Mazandaran, Golestan, Ghazvin, Semnan, and Tehran) are shown in the map.

specific combination of *GJB2* mutation types and frequencies were observed in the different studied provinces (Table 3). A higher *GJB2* mutation diversity (17 types) was identified in Tehran, whereas the lowest diversity was observed in Ghazvin (two types).

## Discussion

In this study, we reviewed the prevalence and type of *GJB2* mutations in 903 deaf families from six provinces in northern Iran. *GJB2* mutations accounted for 20.7% of HL cases. The genetic epidemiology of HL is very different in a country even in neighboring provinces because of subtle variations in their ethnic composition and founder effects [26]. The Iranian population is composed of many different ethnic groups; therefore, it is significant to discuss ethnicity-specific data. Accepting the northwest to southeast *GJB2* HL gradient throughout Iran, our data showed a north to south gradient among Iranian populations with a *GJB2* mutations frequency of 32% in Mazandaran and 9% in Ghazvin. A study performed by Chaleshtori, et al. [27] on 890 ARNSHL families showed that *GJB2* mutations account for 14.6% HL cases in the Iranian population, and c.35delG mutation was the most frequent mutation (~75% of the reported *GJB2* mutations).

Our results showed that the contribution of *GJB2* mutations to ARNSHL was 32% in Mazandaran (north Iran), which is similar to the data from the Azer Turkish population in northwest Iran [28]. Bonyadi, et al. [28] screened 209 HL families from the Azerbijan and Ardebil provinces in northwest Iran for *GJB2* mutations. They reported that *GJB2* mutations were detected in 28% of the HL families studied and c.35delG was the most prevalent mutation, accounting for 64.5% of mutations, which is similar to the results reported for the Turkish population [29].

In the study performed by Bazazzadegan, et al. [30] on 111 deaf families, *GJB2* mutations accounted for 11.5% HL cases in the Semnan province, which is approximately one-third of the frequency of *GJB2* mutations in the Mazandaran province. In a previous study, we showed that *GJB2* mutations explain the etiology of HL in 3.7% patients from the Hormozgan province in south of Iran [31]. On the basis of these results, it can be concluded that the incidence of *GJB2* mutations decreases gradually in both west to east and north to south directions (Fig. 1), drawing the migration pathway of the initial founders.

Another finding of this study was the mutation rate of c.35delG in the Gilan province, which was different from that of Iranian population regions. Chaleshtori, et al. [27] screened 87 deaf families from the Gilan province in north Iran for DFNB1 mutations and reported that *GJB2* mutations were found in 27.6% of the deaf families studied. Interestingly, c.35delG mutation was identified in 95.9% of *GJB2* mutations in the Gilan province, whereas this mutation was absent in the Baluchi population (southeast Iran) [32]. According to our knowledge, this is the highest rate of c.35delG mutation reported from Iran so far. Results obtained for the carrier frequency of c.35delG mutation was 2.8% in the Gilan province, whereas it was 1% in the remaining Iranian groups [33]. However, this population is bounded in the north by the Caspian Sea and remains relatively isolated by mountains from other parts of Iran.

In our studied populations, the most frequent mutation was c.35delG, accounting for 58.4% of *GJB2* mutations. c.35delG (deletion of guanine in position 30–35; rs80338939) is the most common mutation worldwide as well as in many countries in the Middle East, such as Turkey and north and northwest Iran [34]. The study of the geographical distribution of *GJB2* mutations showed more allelic heterogeneity in the north compared to that in the south of Iran [31,35,36]. The four most frequent mutations of *GJB2* in the north of Iran were c.35delG, c.71G>A, c.-23+1G>A, and c.551G>C and are responsible for ~66.3% of all pathogenic alleles in north Iran (Table 3). c.35delG mutation, which is rare among southern regions, accounts for 58.4% of *GJB2* mutations in the northern populations. c.71G>A, c.-23+1G>A, and c.551G>C are the second, third, and fourth common mutations, with an occurrence of 2.9%, 2.45%, and 2.45%, respectively, of all pathogenic alleles.

**Table 3.** *GJB2* mutations, their frequencies and in silico analyses in six provinces of Iran

| Mutations | Gilan [30] | Gilan [35] | Mazandaran [30] | Golestan [30] | Golestan [19] | Ghazvin [30] | Tehran [36] | Tehran [30] | Semnan [27] | Mutation type | Classification | Functional effect | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | Mutation taster | SIFT |
| c.35delG | 39 (28.3) | 47 (27) | 47 (23.5) | 17 (28.3) | 10 (9.1) | 2 (4.5) | 48 (9.4) | 38 (10.1) | 14 (6.3) | Frameshift | T | Disease causing | NA |
| c.71G>A | - | - | 2 (1) | - | - | - | 2 (0.4) | 4 (1.16) | 5 (2.25) | Missense | T | Disease causing | Damaging |
| c.95G>A | - | - | 5 (2.5) | - | - | - | 2 (0.4) | 2 (0.58) | 1 (0.45) | Missense | NT | Disease causing | Damaging |
| c.136G>A | 2 (1.44) | - | - | - | - | - | - | - | - | Missense | NT | Disease causing | NA |
| c.139G>T | - | - | - | - | - | - | 1 (0.2) | - | - | Missense | NT | Disease causing | NA |
| c.167delT | - | - | - | - | 1 (0.9) | - | 1 (0.2) | - | - | Frameshift | T | Disease causing | NA |
| c.224G>A | - | - | 1 (0.5) | - | - | - | - | 1 (0.29) | - | Missense | NT | Disease causing | Damaging |
| c.229T>C | - | - | - | - | - | - | - | - | - | Missense | NT | Disease causing | Damaging |
| c.230G>A | - | - | 1 (0.5) | - | - | - | - | - | 2 (0.9) | Missense | NT | Disease causing | NA |
| c.235delC | 1 (0.72) | - | - | - | - | - | 6 (1.18) | - | - | Frameshift | T | Disease causing | NA |
| c.257C>A | - | - | - | - | - | - | 1 (0.2) | - | - | Missense | NT | Disease causing | NA |
| c.313-326del | - | - | - | - | - | - | - | 2 (0.58) | - | Frameshift | T | Disease causing | NA |
| c.326G>A | - | - | - | - | - | - | - | - | 1 (0.45) | Missense | NT | Disease causing | NA |
| c.327-328delGG | 1 (0.72) | 2 (1.15) | - | - | - | - | 1 (0.2) | - | - | Frameshift | T | Disease causing | NA |
| c.334-336delAA | - | - | - | - | - | - | - | 1 (0.29) | - | Frameshift | T | Disease causing | NA |
| c.358-360delGAG | - | - | 1 (0.5) | - | - | - | - | 7 (2.02) | - | Inframe deletion | NT | Disease causing | NA |
| c.427C>T | - | - | - | - | - | - | 3 (0.6) | 4 (1.16) | - | Missense | NT | Disease causing | Damaging |
| c.463-464delTA | - | - | - | - | - | - | - | 2 (0.58) | - | Frameshift | T | Disease causing | NA |
| c.487A>G | - | - | - | - | - | - | 2 (0.4) | - | - | Missense | NT | Disease causing | NA |
| c.511G>A | - | - | - | - | - | - | - | - | - | Missense | NT | Disease causing | Damaging |
| c.551G>C | 1 (0.72) | - | 1 (0.5) | - | - | 2 (4.5) | 4 (0.8) | 3 (0.87) | - | Missense | NT | Disease causing | Damaging |
| c.-23+1G>A | 2 (1.44) | - | 3 (1.5) | 1 (1.6) | - | - | - | 4 (1.16) | 1 (0.45) | Splice site | T | Disease causing | NA |
| c.79G>A | 1 (0.72) | 2 (1.15) | - | - | 2 (1.8) | - | - | 2 (0.58) | 2 (0.9) | Missense | NT | polymorphism | Tolerated |
| c.186C>T | - | - | - | - | - | - | - | - | - | Missense | NT | polymorphism | Benign |
| c.341A>G | - | 2 (1.15) | 1 (0.5) | - | 1 (0.9) | - | - | 1 (0.29) | 1 (0.45) | Missense | NT | polymorphism | Benign |
| c.380G>A | - | - | - | - | - | - | - | - | - | Missense | NT | polymorphism | Benign |
| c.457G>A | 3 (2.17) | 4 (2.3) | 5 (2.5) | 1 (1.6) | 2 (1.8) | - | 30 (5.9) | 4 (1.16) | 7 (3.15) | Missense | NT | polymorphism | Benign |
| c.478G>A | - | - | - | - | - | - | 1 (0.2) | 1 (0.29) | - | Missense | NT | polymorphism | Benign |
| c.608T>C | - | - | - | - | - | - | - | 1 (0.29) | - | Missense | NT | polymorphism | Benign |
| c.-3558C>T | - | - | - | - | - | - | 21 (4.1) | - | - | Missense | NT | polymorphism | Benign |
| Normal | 88 | 117 | 133 | 41 | 94 | 40 | 389 | 269 | 187 | - | - | - | - |
| Total | 138 | 174 | 200 | 60 | 110 | 44 | 512 | 346 | 222 | - | - | - | - |

Values are presented as n (%) unless otherwise indicated. SIFT: Sorting Intolerant from Tolerant, T: truncated protein, NA: not available, NT: non-truncated protein

p.Trp24*, a nonsense mutation, is because of c.71G>A transition, which changes TGG codon for tryptophan residue to a stop codon, leading to a truncated protein with probably no functional properties. c.71G>A is the most common mutation in Slovak Romany, Pakistan, and Indian populations [37-39]. The rate of carriers of c.71G>A mutation is 4.08% in the Pakistan population [8]. This mutation is observed at a high frequency in the Baluchi group (southeast Iran) and accounts for 80% of the mutant alleles in this ethnicity, whereas this rate was only 2.9% in our study population [40].

p.Arg184Pro, a missense variant, is the result of c.551G>C transition, which changes CGC codon for arginine residue to a CCC codon for proline, probably leading to a non-functional protein. This mutation has been reported in an Australian family for the first time [41]. In silico analyses are consistent with the pathogenicity of the mutation (Table 3). p.Arg184Pro is not the common mutation in Iranian populations, but this mutation is observed at a high frequency in north and northwest Iran because of founder effects [25].

The present data showed a particular combination of *GJB2* mutation diversity in different provinces of north Iran. A higher *GJB2* mutation diversity (17 types) was identified in the Tehran province, showing the co-existence of several different ethnic groups and marked immigration to the metropolitan during the last century. In contrast with high diversity in Tehran, we found a very low rate of diversity in some populations, such as Ghazvini who are probably isolated owing to cultural and geographical barriers.

Chaleshtori, et al. [27] reported that more than 40% of patients were heterozygous carriers for *GJB2* mutations in the Gilan province. Hence, these patients are subjected to analysis to investigate *GJB6* mutations [42-44].

## Conclusion

The critical and specific position of Iran and the existence of various ethnic groups of different cultures suggest high heterogeneity throughout Iran, but specific intra-ethnic traditions, such as intragroup marriages, may result in high homogeneity in some loci and mutations within groups. *GJB2* mutations are responsible for 20.7% cases of deaf families in the north, which is more than that in central Iran (13−15%), suggesting the migration pathway from the north to central Iran through the silk route. Regarding *GJB2* mutations, c.35delG was the most common mutation first tested. In the studied populations, some mutations were frequent, which were detected in each group, e.g., the frequency of c.35delG mutation showed a high rate in the Gilan province (north Iran) accounting for 90.2% of the mutant alleles studied. In addition, the causes of HL in some populations, such as Golestani, are likely more homogenous than those in other parts of north Iran. The present study will help in improving genetic diagnosis, cascade screening, genetic counseling, and molecular epidemiology of HL in Irani populations, particularly of northern origin.

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**Conflicts of interest**

The authors have no financial conflicts of interest.

**Author Contributions**

Data curation: Farideh Koohian. Methodology: Farideh Koohian. Project administration: Morteza Hashemzadeh-Chaleshtori. Validation: Fatemeh Azadegan-Dehkordi. Writing—original draft: Mahbobeh Koohiyan. Writing—review & editing: Mahbobeh Koohiyan.

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