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**Authors' Affiliation:**

Department of Microbiology  
and Molecular Genetics,  
University of the Punjab,  
Lahore - Pakistan

**\*Corresponding Author:**

Ejaz Ali  
Email:  
[ejazali067@gmail.com](mailto:ejazali067@gmail.com)

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## Contribution of *GJB2* gene mutations to hearing loss in Pakistani population – A Narrative Review

Ejaz Ali\*, Nageen Hussain

## Abstract

Pakistan has a unique population for the study of recessive genetic diseases due to a higher consanguinity rate. Hearing impairment is the loss of hearing normal sounds, and it is a common sensory disorder that affects more than 466 million people worldwide. Immuno-genetic and other environmental factors like loud noises, drug usage, and viral infections are the causes of hearing loss. Hearing loss is categorized into a syndromic hearing loss (70%) and non-syndromic hearing loss (30%). *GJB2* mutations are one of the main causes of hearing loss in different populations, including Pakistan. The *GJB2* gene encodes a gap junction protein involved in the homeostasis of the inner ear through the recycling of potassium ions. The prevalence of *GJB2* mutation in the Pakistani population varies from 6.1 to 9.2%. The most common mutations found in the Pakistani population are 71G>A (p.(Trp24\*), 231G > A (p. Trp77\*), c.35delG (p. Gly11Leufs24\*), c.355G>T (p. Glu119\*) 457G > A (p.Val153Ile), 598G > A (p.Gly200Arg), 439G > A (p.Glu147Lys), c.377\_378insATGCGGA (p.Arg127Cysfs\*85), c.1055C>T (p. Pro352Leu), c.6202A>C p.(Thr2068Pro), c.2496\_2496delC p.(Tyr832\*) and c.355G>T p.(Glu119\*).



## Introduction

Hearing loss (HL) or hearing impairment is the loss of hearing normal sounds [1]. It is one of the most common diseases that affect 466 million people worldwide and 1 in 500-1000 newborns [2]. HL is classified based on different parameters such as onset, severity, and other associated diseases. Thus, HL is caused by environmental (high-intensity sounds, viral infections, and drug usage) and immuno-genetic factors. The genetic contribution to HL is a great challenge. Genetic and immunological factors cause almost 50 % of the HL. [3, 4].

Inheritance of HL can be recessive, dominant, X-linked, and mitochondrial [5]. HL due to genetic factors is classified into two categories, which are syndromic hearing loss (SHL), representing 20-30%, and non-syndromic hearing loss (NSHL), representing 70-80% cases [6]. More than 400 different syndromes are associated with SHL, which is categorized based on the mode of inheritance to the next generation, such as the maternal mode of inheritance due to mitochondrial gene mutations [7]. NSHL may follow an autosomal recessive (ARNSHL) or autosomal dominant (ADNSHL) mode of inheritance [8]. The gene locus for NSHL is known as DFN (DeafNess). The locus for a gene that inherits in an autosomal dominant pattern is DFNA, autosomal recessive pattern as DFNB, and X-linked pattern as DFN [7]. It is estimated that more than 200 genes are responsible for HL; however, only 121 genes have been identified [9]. One of the leading genetic causes is mutations in the *GJB2* gene, which encodes a gap junction connexin 26 protein, involved in the inner ear's homeostasis ear through the recycling of potassium ions [10].

## Methods

### Literature Search Strategy and Selection Criteria

A systematic search was carried out from Google Scholar, NCBI, and Google Web Browsers through key terms *GJB2*, non-syndromic hearing loss, hearing impairment, and deafness. The literature found was further screen by inclusion and exclusion criteria. Recent research papers were selected. Research articles before 2005 were excluded. More than 20 articles were selected.

## Discussion

### Mechanism of hearing loss

The cochlea comprises three fluid-filled compartments known as scala tympani, scala media, and scala vestibule. The scala tympani and scala vestibule contain a fluid (perilymph) with a high concentration of Na<sup>+</sup> and low concentration of K<sup>+</sup>; whereas, scala media is filled with fluid (endolymph) which contain high concentrations of K<sup>+</sup> and low concentration of Na<sup>+</sup>. The endolymph in scala media also includes a high positive endocochlear potential equal to 110 to 120 mV. This potential drives the K<sup>+</sup> ion present in endolymph through the mechano-transduction in the hair's cells. Expelled out of K<sup>+</sup> ions in the extracellular space is necessary to restore the cell polarization. This extra expelled K<sup>+</sup> around hair cells

needs to be removed to avoid K<sup>+</sup> ion toxicity and maintain hair cell function. According to the K<sup>+</sup> recycling hypothesis, these K<sup>+</sup> ions are sunken by neighboring cells and transported back to endolymph through gap junction. [11] During auditory transduction in the cochlea of the inner ear cochlea, *GJB2* (Gap junction beta-2 protein) maintains potassium homeostasis [5]. The six connexins 26 (Cx26) molecules assemble and form a single connexon in each cochlea cell, where Cx26 is mostly expressed. A gap junction between two connexons of the neighboring cochlea cells is formed, which serves as a path to maintain the K<sup>+</sup> ion concentration balance between the different fluid compartments of the inner ear. Mutations in the *GJB2* gene disrupt the communication channels between these cells, cause an imbalance of the potassium ion exchange and affect hearing function [12].

### *GJB2* gene involvement in hearing loss

*GJB2* gene is one of the most common causes of non-syndromic hearing loss, and almost 300 different variants have been reported. The most common hereditary type of hearing impairment is ARNSHL, and more than 700 different causative mutations have been identified in over 80 DFNB loci. DFNB1 locus on chromosome 13q12.11 contains the most common ARNSHL gene (*GJB2*) with a single coding-exon, and more than 50% ARNSHL is linked with *GJB2* mutations. More than 100 *GJB2* mutations responsible for ARNSHL have been documented so far [13].

### Prevalence of *GJB2* gene mutation in Pakistani population

The prevalence of *GJB2* mutations is different in different areas. According to the WHO, 2012, the prevalence rate of HL in Pakistan was 2.4% higher than the world's prevalence of 1.7% [13]. Compared to other populations, it is one of the most common mutations in Pakistan [13]. Consanguineous marriages increase the rate of recessive genetic disorders. High consanguinity in any population may lead to genetic diseases like HL. In Pakistan, consanguineous marriages are high; therefore, the population is unique to study recessive genetic disorders such as HL. The prevalence of profound bilateral HL in Pakistan is 1.6 per 1000 population, and 70% of the disorder arises in consanguineous families [7]. The studies conducted on the Pakistani population revealed a variable prevalence of *GJB2* ranging from 4.2% to 53.33% [14-16].

In the Pakistani population, the contribution of *GJB2* to NSHL is varied from 4.2 to 53.33%. In 2005, Santos *et al.* showed that only 6.1% of the studied families in Pakistan had *GJB2* linked HL [17]. The most common mutations found in this report were p.Trp\* and p.Trp77\*, p.Arg2His, and p.Leu90Pro mutations were also detected. The 70% studied families belonged to the Punjab province, and another 30% belonged to other Pakistan provinces. In 2013, Bukhari *et al.* found a low prevalence (4.28%) of *GJB2* mutation in the Hazara division, KPK province, compared to other provinces. Only three mutations, p.Trp24\*, p.Ile35Ser, and p.Gly11Leufs24\*, were found after sequencing the DNAs of 70 deaf patients (18). However, in 2014, Anjum *et al.*

showed that the frequency of *GJB2* mutation is higher (50%) in deaf patients from different areas of Pakistan [18]. The reported mutations were Trp24\*, Gly12Valfs\*2, Gln124\*, Trp77\*, Val153Ile, and Thr8Met. Similarly, in 2014 Shafique *et al.* revealed that the prevalence of *GJB2* gene mutations in deaf patients of Punjab province was 53% [14]. The most common mutations were p.Trp24\* and p.Trp77\*. Other identified mutations were p.Gly200Arg p.Gly11Leufs24\*, p.Glu147Lys, and p.R127Cfs\*85. In 2017, Wang *et al.* revealed only mutation Gly11Leufs24\* (35 del G). Similarly, in 2017, Shaikh *et al.* studied *GJB2* mutations in a population of Sindh province, and prevalence was 6 % (9/150). The mutations found during the study were c.71G> A (p. Trp24\*), c.231G> A (p.Trp77\*), C35delG (Gly11Leufs24\*), c.233delC (p.Leu79Cysfs3\*), c.310del14 (p.Leu79Cysfs3\*) , c.380G>A (p.Arg127His) as mention in table 01 and table 02. In 2019, mutations found in *GJB2*, were c.1055C>T (p.Pro352Leu), c.6202A>C p.(Thr2068Pro), c.2496\_2496delC p.(Tyr832\*) and c.355G>T p.(Glu119\*) [13].

Gene	Percentage	Disease	Reference
GJB2	6 (9/150)	Non-familial	[15]
	9.52 (8/84)	Familial	[19]
	4.65 (4/86)	Non-familial	[19]
	53.33 (16/30)	Familial	[14]
	4.28 (3/70)	Non-familial	[16]
	6.12 (12/196)	Familial	[17]
	8.33 (1/12)	Familial	[3]
	14.28 (3/21)	Familial	[20]
	16.82 (54/321)	Familial	[21]
	19.04 (4/21)	Familial	[22]
	25 (2/8)	Familial	[23]
	50 (10/20)	Familial	[19]

**Table 1:** Prevalence of *GJB2* mutation in the Pakistani population.

Gene	Nucleotide change	Amino acid change	Reference
GJB2	35 del G	Gly12Valfs*2	[3]
	c.71G> A	p.Trp24*	[13,15]
	c.231G> A	Trp77*	[15]
	c.35delG	Gly11Leufs24*	[15]
	c.233delC	p.Leu79Cysfs3*	[15]
	c.310del14	p.Lys105Argfs2*	[15]
	c.380G>A	p.Arg127His	[15]
	377-378ins ATGCCGA	Arg127Cysfs*85	[14]
	598G > A	Gly200Arg	[14]
	95G > A	Arg32His	[14]
	358-360delGAG	delGlu120	[14]
	269T > C	Leu90Pro	[14]
	439G>A	p. Glu147Lys	[14]
	c.370C>A	p.Gln124*	[18]
	c.231G>A	p.Trp77*	[18]
	c.23C>T	p.Thr8Met	[18]
	c.457G>A	p.Val153Ile	[18]
	c.35delG	p.Gly12Valfs*1	[18]
	104 T>G	p.Ile35Ser	[16]
	c.355G>T	p.(Glu119*)	[13]
	95G > A	p.Arg32His	[17]
	358-360delGAG	p.delGlu120	[17]
	269T > C	p.Leu90Pro	[17]
	457G > A	p.Val153Ile	[17]
	493C > T	p.Arg165trp	[17]
	79G > A	p.Val27Ile	[17]
	341 A > G	p.Glu114Gly	[17]
	c.1055C>	p.Pro352Leu	[13]
T c.2496_2496delC	p.Tyr832*	[13]	
c.6202A>C	p.Thr2068Pro	[13]	

**Table 2:** Reported *GJB2* mutations in the Pakistani population.

## Conclusion

This narrative review concluded that non-syndromic hearing loss NSHL is caused by a mutation in more than

100 genes. The prevalence of hearing loss due to mutation in *GJB2* varies from 4.2% to 53.33%. One of the most common causes of NSHL in the Pakistani population is a mutation in the *GJB2* gene. The prevalence of *GJB2* mutation in Pakistan is higher than the world's prevalence due to a higher rate of consanguinity. The most common mutations were p. Trp24\* and p. Trp77\*. Some recent mutations of *GJB2* found are c.1055C>T (p. Pro352Leu), c.6202A>C p. Thr2068Pro, c.2496\_2496delC p.(Tyr832\*) and c.355G>T p.(Glu119\*). The rate of NSHL can be reduced by avoiding consanguineous marriages. People should be educated about the consequences of consanguinity. This narrative review will be an excellent addition to the literature to understand hearing loss.

## Author Contributions

Both authors have equally contributed to the manuscript. Ejaz Ali wrote the manuscript, and Nageen Hussain edited and reviewed the manuscript.

## Competing Interest

The authors certify that they have no conflict of interest to declare in the subject matter or materials discussed in this manuscript.

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