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## GJB2 GENE; ITS CONTRIBUTION TO GENETIC DEAFNESS? : A REVIEW

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**ABSTRACT...** This article reviews the most prevalent sensory illness of mammals especially humans – Genetic Deafness or hearing loss (HL). For genetic hearing loss more than 100 candidate genes have been discovered. The most common candidate gene of these all that is found all around the world is GJB2 gene. Different types of mutations are found in GJB2 gene. Some of these mutations are non-sense while some are sense mutations. This study is focus on mutation in GJB2 gene and its prevalence in different region of the world.

**Key words:** Genetic Deafness, GJB2 gene, Mutations.

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### INTRODUCTION

Hearing loss (HL) is the most common sensory defect in human beings. It is affecting 1.86 among 1000 newborns around the world<sup>1</sup>. More than 50% of deafness cases are due to genetic factors<sup>2</sup>. It is estimated that the prevalence of profound bilateral hearing loss is 1.6 per 1000 in Pakistan and 70% of hearing loss arises in consanguineous families. Hereditary hearing loss may be syndromic or non-syndromic. About 30% of deafness cases are syndromic, while 70% is non-syndromic. The main pattern of inheritance of deafness in Pakistani population is autosomal recessive. The common deafness syndromes are Usher, Pandred and Warrenburg syndromes. The non-syndromic deafness may be Autosomal Dominant, Autosomal Recessive, X-linked, Y-linked and Mitochondrial. Approximately 75% cases of inherited deafness are autosomal recessive, 12-24% autosomal dominant and 1-3% is X-linked<sup>3</sup>. To date more than 67 loci and 21 genes have been identified for non-syndromic recessive deafness<sup>4-6</sup>.

Deafness may occur at any stage of life depending upon the age of onset. Hearing loss has three types. In the Prelingual stage, loss of hearing occurs before speech is acquired. If a child has a congenital hearing impairment, he or she would

not be able to speak normally. In Postlingual stage loss of hearing occurs after speech is developed while Presbycusis or age-related HL (ARHL) started as the person is going old. Epidemiologic studies showed that nearly 25 % of 60 years old and more than 50 % of 80 year ages undergo ARHL<sup>7</sup>.

### GJB3 Gene in genetic hearing impairment

GJB2 gene is located on DFNB1 locus, initially identified by linkage analysis using the markers D13S143, D13S175, D13S292 in a large Tunisian family. It was mapped to chromosome 13q12-q13 in two consanguineous families<sup>8</sup>. After three years, it was shown that Cx26 gene mutations are responsible for HL<sup>9</sup>. Approximately, 90 different GJB2 variants have been identified. These include insertion, large and small deletions, substitution, miss sense mutation, splice site and frame shift mutations<sup>10</sup>. It has been reported that autosomal recessive non-syndromic hearing loss (ARNSHL) results from GJB2 gene mutations in many cases<sup>11-13</sup>. It causes 50% HL in children in some populations<sup>13</sup>. GJB2 gene mutation is responsible for 50% of profound HL cases, 30% severe HL cases, 20% moderate HL and 1-2% of mild HL<sup>14</sup>. In addition, a high frequency of this gene mutation has been observed in some of the ethnic groups<sup>15</sup>. Similarly, 50% of autosomal recessive

non-syndromic deafness in the Caucasians is due to GJB2 mutations<sup>16</sup>.

At position 30-35 coding regions of GJB2 gene, there is a small repeated sequence of six G residues. If there is deletion of one G residue in codon 10, then this mutation is referred as 30delG or 35delG<sup>17</sup>. It was identified by method proposed by Storm<sup>18</sup>. 35delG, the most frequent mutation in the Caucasians, is responsible for 70% of GJB2 mutations. The most prevalent nonsense mutation W24X truncating Cx26 protein (24 amino acids), was first reported in a Pakistani family<sup>5</sup>. The GJB2 mutations which cause syndromic HL include delE42<sup>19</sup>, G12R, D50N, R75W, S17F<sup>20</sup>, G59A<sup>21</sup>, N54K<sup>22</sup>, R75Q<sup>23</sup>, D66H and G130V<sup>24</sup>. While autosomal dominant non-syndromic HL is caused by C202F<sup>25</sup>, R143Q, W44C, R184Q<sup>26</sup>, D179N and G21R gene mutations<sup>27</sup>. It lies in the first intracellular domain. C202F mutation is located in the M4 transmembrane domain of the GJB2 protein. This domain functions in the oligomerisation of connexins. Heterozygous W44C mutation is present in the extracellular loop E1, which allows the interactions between adjacent cells connexins of the protein. Other known GJB2 mutations are E47X, I20T, R184P, L90P, delE120 and V95M<sup>4</sup>.

The 35delG mutation is more common in non-European ethnic groups<sup>28</sup>. In contrast with 35delG in whites and 167delT in Ashkenazi Jewish populations, the 235delC mutation is most common among Japanese and Korean patients with childhood hearing loss<sup>28</sup>. In some families a missense mutation (Val95Met) was found simultaneously with other novel missense mutations. The second missense mutation was Val84Met, 250GrC. The valine at this position is invariant in all known alpha and beta connexin genes. This mutation was inherited from the maternal grandfather, through the mother. The third missense mutations were Ser113Arg and 339TrG. Although this mutation does not change a conserved residue yes it causes a radical change from a small polar group to a bulky charged group<sup>5</sup>.

Another mutation in GJB2 gene mutation called del(GJB6-D13S1854) mutation accounts for 25.5% of the affected GJB2 heterozygotes which remained unresolved after screening for del(GJB6-D13S1830) in Spain, 22.2% in the UK, 6.3% in Brazil, and 1.9% in Northern Italy<sup>29</sup>. It was not found in affected GJB2 heterozygotes from France, Belgium, Israel, the Palestinian Authority, USA, or Australia<sup>30</sup>. In Turkey 35delG and 120delE mutations are the commonest in GJB2 gene that causes non-syndromic HL<sup>30</sup>. In Lebanon one third of non-syndromic HL is caused by 30delG mutation in GJB2 gene. Analysis of the different genes concerned in hearing loss in the Lebanese population will improve the performance of clinical providing genetic counseling, especially in consanguineous Lebanese families<sup>31</sup>.

More than 50% of autosomal recessive non-syndromic hearing loss in Pakistan is due to GJB2 mutation<sup>32</sup>. Unlike other regions of the world, the 35delG mutation and p135S mutations are very rare in Pakistan and were discovered for the first time in 2013 by Ikhtisham Bukhari and coworkers in two Pakistani families<sup>33</sup>. The spectrum of GJB2 sequence variants in Pakistan may reflect shared origins of hearing impairment alleles within the Indian subcontinent. The high degree of consanguinity within Pakistan may have maintained the GJB2 prevalence at a much lower rate than within India and other populations in the subcontinent<sup>34</sup>.

## CONCLUSIONS

Mostly GJB2 gene mutation is causing non syndromic hearing loss in humans. It is observed that in most areas of the world GJB2 mutation was 30delG mutation. In some areas the high frequency of GJB2 mutation was shown to be consanguineous. While in other areas despite consanguinity GJB2 mutation frequency was much lower than the areas where consanguinity is not common. This is a puzzle for researchers that need to be resolved which requires continuous efforts of exploration.

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