

## REVIEW

# Study of common mitochondrial mutations in patients with nonsyndromic hearing loss

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## ABSTRACT

**INTRODUCTION:** Hearing loss is the most common sensorineural disorder involving one out of 1000 people. Around 50% of hearing losses occur due to genetic causes. Three mitochondrial mutations, A1555G in MTRNR1, A3243G in MTTL1, and A7445G in MTTS1, are the most important non-syndromic sensorineural causes of hearing loss in some populations. The aim of this review was to study common mitochondrial mutations in people with hearing loss in Iran.

**EVIDENCE ACQUISITION:** Directory of Open Access Journals (DOAJ), Google Scholar, PubMed (NLM), LISTA (EBSCO) and Web of Science were searched.

**EVIDENCE SYNTHESIS:** Studies have indicated that the mitochondrial mutations A3243G, A1555G, and A7445G play no significant part in the development of hearing loss in Iran. Different variants of A7445C and G3316A have been identified in Iran.

**CONCLUSIONS:** Further studies on other ethnicities and with a larger sample size are necessary to elucidate the role of these genes in hearing loss development in Iran.

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**Key words:** Hearing loss - Mutation - Disease susceptibility.

## Introduction

The prevalence of congenital hearing loss is about 1/1000 live births, over half of which occur due to genetic causes.<sup>1,2</sup> To date, over 30 different genetic loci have been reported to cause hearing loss, 70% of which cause non-syndromic hearing loss and the rest do syndromic hearing loss. Non-syndromic hearing loss is divided into four types, autosomal dominant DFNA, autosomal recessive DFNB, X-linked DFN, and mito-

chondrial. Meanwhile, 75-80% of hearing losses are autosomal recessive, 10-20% autosomal dominant, 1-5% X-linked, and 2% mitochondrial (Figure 1).

Hearing loss can be classified by age at incidence, the location of defect in the ear, and associated physical symptoms. Based on age, hearing loss is divided into prelingual or congenital hearing loss and post-lingual or late hearing loss, according to the location of defect in ear, into conductive hearing loss (involvement of otitis media or outer ear), sensorineural hearing loss (in-

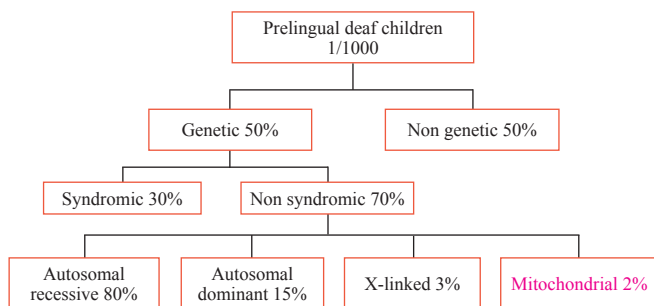


Figure 1.—Frequency of different types of hearing loss.

involvement of inner ear or auditory nerve), and mixed hearing loss (concurrent involvement of different parts of the ear), and according to physical symptoms, into syndromic hearing loss (accompanied by other physical symptoms) and non-syndromic hearing loss (without other physical symptoms).<sup>3</sup> In different populations, different mutations are considered to cause or be generically predisposing to hearing loss. For example, according to the available evidence, GJB2 mutations account for 14.6% of non-syndromic hearing losses with recessive inheritance pattern.<sup>4</sup> Connexin 26 is the first genetic locus known to cause non-syndromic hearing loss. The connexin 26 gene that localizes in this site codes the protein connexin 26. The mutation delG35 at connexin 26 accounts for half of congenital hearing losses worldwide.<sup>5</sup>

### Evidence synthesis

#### *Mutations in mitochondrial genes*

Approximately 25,000-35,000 nuclear genes and 37 mitochondrial genes have been identified in humans. An estimate of about 1% of all human genes had been reported to cause hearing loss. In general, each mitochondria contains 3-10 mitochondrial chromosomes in its matrix, and each chromosome in human has 16569 bp. Hearing loss is a heterogeneous disease from etiological, clinical, and genetic perspectives.<sup>6,7</sup> 12S rRNA and tRANSer(UCN) are two mitochondrial genes that cause non-syndromic hearing loss. It is noteworthy that all types of hearing losses due to mutations in mitochondrial genes are inherited from the mother and affect both genes equally.<sup>8</sup> There are different types of hearing loss that are due to mutation in the mitochondrial gene.

Hearing loss after use of antibiotics (aminoglycosides) and due to diabetes, or sensorineural (non-syndromic) and neuromuscular disease-associated hearing loss are the most common types of this hearing loss.<sup>9,10</sup> Studies on deaf people of all ages in Finland and Japan demonstrated that mitochondrial mutations were seen in 6.8% and 8.5% of people with non-syndromic sensorineural hearing loss, respectively.<sup>11,12</sup> It appears that the mitochondrial mutations occur in less than 1% of children with non-syndromic (prelingual) hearing loss.<sup>3</sup> In Caucasian population, at least 5% of hearing loss has been demonstrated to develop after starting talking (postlingually) because of pathogenic mitochondrial mutations.<sup>13</sup> The mutations in the mitochondrial genome are likely to occur in around 20% of people with postlingual hereditary hearing loss; however, this figure can vary due to racial differences.<sup>14</sup> Since 1988 and identification of the first case of hearing loss due to mutation in mitochondrial gene, over 70 point mutations, deletion, and DNA replication that are associated with a variety of genetic diseases in humans had been identified. Different mutations in 12S RNA-coding MTRNR1 can cause non-syndromic hearing loss with maternal inheritance whose pattern can be similar to autosomal recessive for different reasons. The A1555G mutation that occurs in 12S rRNA-coding MTRNR1 is the first mitochondrial mutation associated with non-syndromic hearing loss.<sup>15</sup> Several mutations in tRANSer(UCN)-coding MTTSL1 have been identified to be associated with sensorineural hearing loss, including T7511C, T7510C, A7445G, and 7412insC.<sup>16</sup> Three mutations, *i.e.* T3271C, A3243G, and T4216C, have been detected in tRANLeu(UUR) (MTTL1), and A3243G was identified in 0.0314% of the population with hearing loss in Japan. Moreover, A3243G has been identified in people with diabetes mellitus.<sup>17</sup>

#### *A1555G mutation*

The study by Dachun *et al.* on the mitochondrial genes 12S rRNA and tRANSer(UCN) culminated in the identification of the A1555G mutation in 12S rRNA which is an approximately homoplasmic mutation. This finding reflects that biochemical defects due to this mutation may become more likely with an increase in age, and this mutation is associated with different types of auditory anomalies.<sup>18</sup> The A1555G mutation

in MTRNR1 as well as the delG35 mutation in GJB2 is potentially the most common hearing loss-associated mutation. Besides that, the A1555G is the most common mitochondrial mutation such that it has been reported to occur in 0.5-1% of the Caucasian population and comparably more frequently in Spaniards and Asian populations as well.<sup>19</sup> Patients with the A1555G mutation are at increased risk of hearing loss after treatment with aminoglycoside. The carriers of this mutation are likely to develop hearing loss without undergoing pharmacotherapy.<sup>20, 21</sup> The A1555G mutation was studied for the first time in a Korean population with non-syndromic hearing loss. In this study, 227 unrelated people were studied, two of whom were found to carry A1555G.<sup>22</sup> A study reported that 2% of people with prelingual hearing loss carried the A1555G mutation.<sup>23</sup> The incidence rate of the A1555G mutation is high in Asian populations for example, 2.9% in China,<sup>24</sup> 3% in Japan,<sup>16</sup> and 5.3% in Indonesia.<sup>25</sup> Although the A1555G is a homoplasmic mutation, a number of families have been reported to carry this mutation as heteroplasmic.<sup>20, 26</sup> The frequency of the A1555G has been reported to be about 1% in people with hereditary hearing loss in Tunisia,<sup>27</sup> about 1.8% in people with prelingual hereditary non-syndromic hearing loss in Turkey,<sup>28</sup> and around 3.2% in people with non-syndromic hearing loss in Taiwan.<sup>29</sup> The phenotypic incidence rate of the A1555G varies in a wide spectrum of the carriers ranging from those with normal hearing to those with absolute deafness.<sup>30</sup> The variability of the A1555G phenotype implies that other factors can be effective in the phenotypic incidence of mtDNA mutations, which affects the age at development and progression of hearing loss.

In a molecular investigation, the mitochondrial mutations A7445G, A1555G, and A3243G in people with non-syndromic hearing loss in Fars province (Iran) were investigated, and none of the A1555G, A3243G and A7445G mutations were detected in this study. The evidence indicated that the mitochondrial A1555G, A3243 and A7445G mutations had no role in auditory deficits in the studied patients. It is recommended to study different mitochondrial mutations in a larger population in Fars province to further elucidate the role of the mitochondrial mutations in development of hearing loss in this province.<sup>31</sup> A study reported the frequency of the A1555G in the population of Chaharmahal va Bakhtiari Province, southwest Iran to be 0%, which is lower than

those reported in other populations. However, because most of the studied cases of hearing loss were children of prelingual age, this frequency is similar to those in the populations at younger and prelingual age with hearing loss. The frequency of the A1555G mutation in population with post lingual hearing loss in Boushehr Province (south Iran) was derived 4.35%, which is similar to those in the corresponding populations in Italy and England.<sup>13, 32</sup> The A1555G mutation had a variable frequency among subpopulations of different ethnicities in Iran: Azeri Turkish (4.16%), Lurs (0.0%), Fars (0.0%) and Bushehris (2.86%).<sup>33</sup>

#### *A3243G mutation*

The A3243G mutation in the tRNA<sup>Leu</sup> (UUR) gene represents one common cause of non-syndromic hearing loss and diabetes.<sup>15</sup> The age at incidence and intensity of the hearing loss varied in the affected people. A number of cases are deaf at birth while some cases develop a slowly progressing hearing loss at puberty. In the tRNA<sup>Leu</sup>-coding MTTL1, three mutations, *i.e.* T3271C, A3243G, and T4216C, have been detected, of which the A3243G has been detected in people with diabetes mellitus. Therefore, the A3253G mutation in people with diabetes mellitus should be taken into account because of hearing loss in these patients.<sup>16</sup>

In the provinces of Fars, Hormozgan, and Khuzestan, this mutation has not been found,<sup>31, 34, 35</sup> but in Sistan va Balouchestan, its frequency was reported to be 0.9%.<sup>36</sup>

#### *A7445G mutation*

The A7445G is one of the known mutations reported to be associated with non-syndromic hearing loss.<sup>37-39</sup> The A7445G in the tRNA<sup>Ser</sup> (UCN)-coding MTT51 was first detected in a Scottish family, and then in families from New Zealand, Japan, France, Ukraine, Portugal, and Hungary.<sup>16, 40</sup> According to a study, the frequency of this mutation was derived 0.33% in a number of Mongolian students.<sup>41</sup>

In a study in Iran, a mutation was reported to occur at the same gene locus but as A7445C with 1.61% frequency. This study demonstrated that the mitochondrial mutation A7445C is the cause of a small number of prelingual hearing losses, and the A7445G had no role in development of hearing loss in the population

of Khouzestan Province, Iran. In this study, a different variant was found that was confirmed to be G3316A.<sup>35</sup> According to the conducted studies, the change in G3316A associated with amino acid alanine conversion to treonin has been reported to occur in patients with diabetes mellitus.<sup>18, 42</sup> A study was conducted to screen for three mitochondrial mutations A1555G, A3243G, and A3243G in people with hearing loss in Sistan va Balouchestan, Iran. In this study, people with autosomal recessive non-syndromic hearing loss were found to carry a different variant that was confirmed to be G3316A.<sup>36</sup> Moreover, it seems that this variant is involved in LHON and hypertrophic cardiomyopathy as well. However, its association with hearing loss remains to be confirmed and needs to be investigated further.<sup>18, 42, 43</sup>

### Discussion

A number of principal and purposeful studies on non-syndromic hearing with recessive inheritance have been conducted in Iran. Most studies have been conducted on a specific locus, especially DFNB1 that contains the gene connexin-26. Surprisingly heterogeneous nature of hearing loss alongside Iran's population diversity highlighted the necessity of conducting systematic population-based studies in this disorder so that purposeful structural studies are conducted according to the type of ethnicity and population. Therefore, study of different involved genes, especially the mitochondrial genes, in non-syndromic hearing loss with recessive inheritance as well as in people with acquired hearing loss with genetic predisposition seems necessary to elucidate the etiology, potential pathogenic mechanisms, and subsequent treatment interactions. In general, in the conducted studies in different regions of the world, the association of three common mitochondrial mutations with hearing loss has been investigated, consisting of A1555G in 12S rRNA-coding MTRNR1, three mutations, *i.e.* 7472insC, A7445G, and T7511C, in Set(UCNtRNA)-coding MTTS1, and A3243G, T3271C, and T4216C in tRNA<sup>Leu</sup> (UUR)(MTTL1).<sup>16</sup> Some of the mitochondrial genes including above mentioned ones play a part in hearing loss. However, their role in hearing loss with non-syndromic autosomal recessive pattern is less significant, but in some populations such as ones from China and Spain, the role of the mutations in mitochondrial

genes has been found to be more significant. Many mitochondrial mutations have been found to be associated with prelingual and postlingual hearing loss. In certain populations such as ones from Spain and China, up to 20% of postlingual hearing losses were found to be due to mitochondrial mutations.<sup>21</sup> A study conducted in England demonstrated that the mitochondrial mutations were seen in around 30% of people with hearing loss with maternal inheritance.<sup>44</sup> In the Far East populations, the frequency of the mitochondrial mutations is likely to be higher, especially 12S rRNA-coding MTRNA1 and tRNA genes that were found to be associated with hearing loss. Studies have indicated that the mitochondrial mutations A3243G, A1555G, and A7445G play no significant part in development of hearing loss in Iran (Table I). Different variants of A7445C and G3316A have been identified in Iran. In the recent years, a large number of new mitochondrial mutations have been reported to cause non-syndromic hearing loss.<sup>45</sup> A study conducted in Iran found a different mutation which was confirmed to be G3316A. According to the conducted studies, the change in G3316A associated with amino acid alanine conversion to treonin has been reported to occur in patients with diabetes mellitus, but its association with hearing loss has not yet been confirmed and should be further investigated.<sup>36, 42</sup>

### Conclusions

It is necessary to take into account the role of the mutations in the mitochondrial genes in hearing loss in the genetic counseling concerned with hearing loss in Iranian populations so that this role can be specified. Because of relatively high rate of consanguineous marriage in most regions of Iran, Iranian populations can be considered a very rich source for studies on genetic diseases with autosomal recessive inheritance, including hearing loss. Obviously, the findings of such studies can help screen for hearing loss in populations and consequently, appropriate genetic counseling as well as Preimplantation genetic diagnosis (PGD). Extensive studies on newborns can contribute greatly to determine the frequency of mitochondrial mutations more precisely. Because of specific complexity of phenotypic incidence, pattern of inheritance, and involvement of other factors in incidence and severity of the phenotypes in the mitochondrial mutations, special attention should be

TABLE I.—Frequencies of mtDNA A1555G, A3243G and A7445G mutations in the previous studies in Iranian populations.

Title of study	Types of hearing loss	Number of participants and location	Method	Main results	Ref
mtDNA A1555G, A3243G and A7445G mutations	NSHL	72 Fars	PCR-RFLP	None of the A1555G, A3243G and A7445G mutations were detected in this study. The evidence indicated that the mitochondrial A1555G, A3243 and A7445G mutations had no role in auditory deficits in the studied patients.	(31)
Mitochondrial gene mutation screening	NSHL	110 Hormozgan	PCR-RFLP	None of the 110 subjects were found to carry A1555G, A3243G and A7445G mutations. The association of A1555G, A3243G and A7445G mutations with hearing loss in Hormozgan province is negligible.	(34)
Common mitochondrial mutations in Arab patients	ARNSHL	62 Khuzestan	PCR-RFLP	None of the investigated mutations, A1555G, A3243G and A7445G, were detected in this study. This study showed that mtDNA mutations consisting of G3316A and A7445C are responsible for ARNSHL in a few number of cases in the studied sample and none of the A1555G, A3243G and A7445G mutations were found to be responsible for ARNSHL in this population.	(35)
Frequency of the common mitochondrial DNA (mtDNA) mutations	NSHL	150 southwest subpopulations	PCR-RFLP	None of these mutations were found in subjects with acquired and prelingual autosomal recessive NSHL from Chaharmahal va Bakhtiari province, but the A1555G mutation with frequency of 4.35% was found in postlingual NSHL patients in Boushehr province.	(32)
Screening of three common mtDNA mutations, A1555G, A3243G and A7445G	NSHL	110 Sistan va Baluchestan	PCR-RFLP	None of the A1555G and A7445G mutations were detected in this study. However, found one sample to carry A3243G mutation (0.9%). This study showed that mtDNA mutations are responsible for less than 1% of pre-lingual ARNSHL associated subjects.	(37)
Frequency of the mitochondrial A1555G mutation	NSHL	152 unrelated Iranian populations	PCR-RFLP	Totally, two patients carrying the homoplasmic A1555G mutation were identified with a total frequency of 1.3% in Iran. The A1555G mutation had a variable frequency among subpopulations of different ethnicities in Iran: Azeri Turkish (4.16%), Lurs (0.0%), Fars (0.0%) and Bushehris (2.86%).	(33)
Novel human mitochondrial tRNA <sup>phe</sup> mutation in a patient with hearing impairment: A case study	NSHL	A 7-year-old boy	PCR- direct sequencing	Mitochondrial genes analysis revealed a novel heteroplasmic nucleotide substitution, m.628C. T, in the phenylalanine transfer RNA gene as a novel mitochondrial nucleotide change which may be important in mitochondrial deafness.	(46)
Large-scale screening of mitochondrial DNA mutations among Iranian patients with prelingual nonsyndromic hearing impairment	NSHI	1000 unrelated probands individuals in 13 different provinces throughout Iran.	PCR-RFLP	Two of the studied mutations, namely A3243G and A7445G, were each found in a single family (a frequency of 0.1% for each). DNA sequencing led to the identification of G3316A substitution, with no prior link to HI. screening for A3243G in the studied population identified 6 cases (0.6%) in probands and 10 (1%) in normal subjects. A1555G, the most common mtDNA mutation associated with deafness in other populations, was not found in the studied samples.	(47)

NSHL: non-syndromic hearing loss; PCR-RFLP: PCR-restriction fragment length polymorphism; NSHI: nonsyndromic hearing impairment; ARNSHL: autosomal recessive non-syndromic hearing loss.

paid to genetic counseling for families of people with hearing loss carrying the mitochondrial mutations. Accordingly, the mitochondrial mutations can cause hearing loss. This argument should be investigated in populations with hearing loss. Based on the evidence, the mutations in the mtDNA and their role in development of hearing loss in populations are significant and further studies on other ethnicities and with larger sample size are necessary to elucidate the role of these genes in hearing loss development in Iran (Table I).

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