International Journal of Epidemiologic Research, 2017; 4(2): 166-172.

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Hearing loss: A review on molecular genetics and epidemiologic aspects

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Received: 8/Dec/2016 Accepted: 21/Jan/2017

ABSTRACT

Background and aims: Hearing loss (HL) happens due to the genetic or environmental causes or both. Risk factors include congenital infections and congenital deformities of auricle and ear duct. The present study was performed to briefly explain the genetics, molecular biology and epidemiology of HL in Middle East especially in Iran.
Methods: An intense an comprehensive literature search was prformed through heading journals in the field. All data was organized using Mendeley software and incorporated to the text as required.
Results: While the etiology of 25% of HL cases remains indistinct, it is estimated that at least 50% of pre lingual HL cases have a genetic cause. About 70% of genetic HL cases are non Syndromic (NSHL) without anomaly, whereas the remaining 30% are Syndromic. Autosomal recessive non-syndromic hearing loss forms (ARNSHL) are the severest forms of congenital HL with defect in cochlea. In addition to X-linked (DFNX), autosomal dominant (DFNA), autosomal recessive (DFNB) and Y-linked (DFNY) inheritance patterns, HL can be inherited through mitochondrial genes including MT-RNR1 and MT-TS. At least 120 genes have been reported to be associated with HL. Among them, mutations in connexin 26 (GJB2) have been shown to play a very important role in developing ARSNSHL in many populations depending on geographical location and ethnicity. In Caucasians and Spainish/Italian populations, 50% and 79% of HL cases have respectively been reported to be occurred due to mutations in GJB2 gene.
Conclusion: In the Middle East, the prevalence seems different as an average of 14-20% of the HL in several region of Iran is due to mutation in GJB2 gene. Alternatively similar studies showed the prevalence of GJB2 mutations around 25% and 6.1% in Turkey and Pakistani populations respectively.

Keywords: Hearing loss, Iranian population, GJB2.

Review article

INTRODUCTION

Neuronal cell damage and death is mediated through a spectrum of genetic and biological processes. In addition to Genetic causes, excessive amounts of toxic reagents

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and free radicals have detrimental effects on neurons.[1,2]

According to WHO global estimates on prevalence of hearing loss, disabling hearing refers to hearing loss greater than 40 dB in the better hearing ear in adults (15 years or older) and greater than 30 dB in the better hearing ear in children (0 to 14 years). Hearing loss (HL) is one the most common sensory disorders that affect about 4% of people under 45 years. HL is a highly heterogeneous disorder containing a broad spectrum of clinical presentations including conductive or sensory neural, congenital or late onset, and syndromic or non-syndromic.[3] In addition to the great economic burden on families, this disorder also has many psychological and emotional effects and the main problem in the distinction of deafness is heterogeneity.[4]

The normal hearing threshold is 15 dB (decibel) and the level of a regular conversation is 45 to 60 dB.[5] Based on different criteria HL can be divided to various types including severity (mild: 20-39 dB, moderate: 40-69 dB, severe: 70-89 dB, or profound: ≥90 dB), age of onset (pre or post lingual, Presbycusis or age-related HL (ARHL) types), origin (sensorineural, conductive or mixed) and attendance or absence of associated features (non-syndromic or syndromic).[6] Among them, Syndromic HL correlates with physical problems and non-syndromic genetic HL is without ever complexity.[5]

Conductive HL generally occurs by the external and middle ear congenital abnormalities like atrophy and dysplasia, duct blockage, impacted cerumen, otitis and middle ear and Tympanic membrane deficiency.[7] However, congenital causes and infections like measles, cytomegalovirus and bacterial meningitis are the most common causes of Sensorineural HL.[5]

It is known that HL happens due to the genetic or environmental causes or both.[8] Based on the cause of sensorineural deafness, HL is classified into three major forms including acquired, genetic and unknown:

1. Acquired HL: In addition to genetic background that has an important role on HL occurrence, infectious and pharmaceutical agents (e.g. teratogens) could influence the sense of hearing. Risk factors may include congenital infections (e.g. smallpox, toxoplasmosis, syphilis, measles, herpes virus orcytomegalovirus) and congenital deformities of auricle and ear duct.[5,9] Prematurity and low birth weight (less than 1500 g) and high blood bilirubin during birth are other important threats.[5] Moreover, the HL may pathologically originate postnatal and may be due to infections and bacterial meningitis, mumps, otitis media, blood infection, autotoxic drugs such as aminoglycosides and head injury or skull fracture that result to anesthesia;[5]
2. Mixed HL: In which the conductive and sensorineural problems are seen simultaneously;[5] 3. Genetic HL: In the early 18th century, William Wild, the Irish physician, discovered the inheritance of HL. He discriminated between dominant and recessive forms and also described HL in men with X-linked transmission.[5]

While the etiology of 25% of HL cases remains indistinct, it is estimated that at least 50% of pre-lingual HLs have a genetic cause. Also, about 70% of genetic HL cases are non-syndromic (NSHL) without anomaly, whereas the remaining (30%) are Syndromic. To date, over 400 Syndromic forms of HL have been introduced as Usher syndrome and Pendred syndrome which together are the most common instants.[10] Therefore, the genetic study of HL has noteworthy benefits for patients that are as follows:

A. Determining a treatment strategy including medical and nonmedical decisions (eg.cochlear implant); B. Carrier and prenatal diagnosing; C. Performing genetic counseling before marriage, especially when there is heterogeneity that freight different mutated genes; D. Eliminating unnecessary

experiments and investigations; E. Forecasting for the going state of the disease.

Genetic evaluation should be carried out for children with newly recognized HL especially if no specific cause is determined. For example, although genetic evaluation of the family of a child with HLof meningitis is unnecessary, they may need to assure not transmitting the disease to the next birth. Various steps of Genetic evaluation include:[4]
1. Revising the complete medical history of prenatal, neonatal and growth and development; 2. Completing physical test of patients and other family members; 3. Assessing the genetics, cellular and molecular diagnosis.

HL is one of the concerns about public health in developing countries as two thirds of HL patients live in these countries.[11] The worldwide incidence of genetic HL ranges from 1 in 2000 up to 1 in 650 live births.[12] Generally 1.06 in 1000 cases suffers from pre-lingual hearing loss disorder.[13] About 80% of the hereditary deafness cases are non-syndromic and predominantly inherited as autosomal recessive.[14]

Middle East and North Africa region are known to have the lowest prevalence (5.9%, 3.0%-11.5%) of hearing problem(≥35 dB) for adults above 15 years. However, the highest rate of hearing impairment (≥35 dB) in adults has been reported in the South Asian region (21.4%) following by Eastern Europe and Central Asia (13.9%, 2.9%-51.0%).[15]

Since people in the developing countries do not have the same health services as in the western countries do, it seems very important to study causes of HL in these countries. As an example in the Middle East, there are several comprehensive studies performed in Iran. According to the statistics results, there are nearly 450000 HL patients but only 121000 of them have been identified by the State Welfare Organization.[13]

This data reflects the necessity of family orientation programs to control the consanguineous marriages which is as high as 38.6% in this area.[13,16]

As sanitary indexes are improved, the role of genetics in HL is becoming more important.[17,18] So far, over 400 syndromes with HL have been mentioned in OMIM. Among them, the most common syndromes are Usher syndrome and Pendred syndrome followed by Alport syndrome, Waardenburg syndrome, Branchio-oto-renal syndrome and Stickler Syndrome(10)and it is estimated that approximately 1% of human genes (200 to 250 genes) are responsible for inherited HL.[13]

Nomenclature schemes for HL loci use the symbol DFN, followed by the pattern of inheritance such as X-linked (DFNX), autosomal dominant (DFNA), autosomal recessive (DFNB) and Y-linked (DFNY). Moreover, hierarchical numbering system describes the individual members e.g. DFNB1 which is the first identified locus causing autosomal recessive HL.[8]

The majority of genetic HL is without any abnormality in other organs categorized as non-syndromic HL (NSHL) and has various mode of inheritance.[6] More than 100 loci and 55 genes may be involved in non syndromic HL.[13]

Autosomal recessive non-syndromic hearing loss forms (ARNSHL) described for the first time in 1846, and they are the severest forms of congenital HL with defect in cochlea.[19] ARNSHL are commonly pre-lingual, more severe and exclusively sensorineural forms of HL.[20]

The most studied genes involve in ARNSHL are MYO15A (in DFNB3 locus), SLC26A4 (DFNB4), CDH23 (DFNB12), TMC1 (DFNB7/11), OTOF (DFNB9), TMPRSS3 (DFNB8/10) and TMHS (DFNB67). However, due to the prevalence and importance, the majority of researches have focused on the DFNB1 loci.[21]

Guilford and co-workersin 1994 introduced DFNB1 as the first locus of ARNSHL on chromosome 13q12-q13z.[8] Most of consanguine families of different kinfolk were related to the DFNB1 locus.[22]

Recent studies have shown that the inheritance of 75% nonsyndromic HL are autosomal recessive, 10-20% autosomal dominant and 1-5% are X-linked recessive.[13,23]

Common phenotypes of autosomal dominant form of deafness consist of late onset, mild and progressive forms of HL. Almost 25 genes and > 60 loci have been reported for autosomal dominant non syndromic hearing loss (ADNSHL). Although there is not enough evidence on the role of mutations in ADNSHL, mutations in some genes including WFS1, KCNQ4, COCH and GJB2 have been recommended to be involved.[10,24,25]

The X-linked forms of deafness have been presented either prelingual or progressive in different families. The frequency of X-linked forms of HL (DFNX) is less than ARNSHL and ADNSHL and 5 loci and 3 genes (POU3F4, SMPX and PRPS1) have been suggested for DFNX.[26] The only one locus on chromosome Y, is PCDH11Y (encoding Protocadherin) and has been reported to be involved in DFNY1 in a large Chinese family (7 generations) with the age of onset ranging from 7 to 27 years.[26]

Molecular Pathology of HL is a scientific discipline dealing with the development of molecular approaches to study, diagnosis and classification of various human diseases including cancer, infectious diseases and genetic disorders such as HL.[27,28]

In healthy individuals, cells contain thousands of molecules of mitochondrial DNA with identical sequence and genotype, a phenomenon known as homoplasmy. However, in many mitochondrial diseases, mutations often co-exist with their wild type in different proportions which are known as heteroplasmy. Heteroplasmy varies from one tissue to another and even within the cells of a tissue. There are only a few genes associated with mitochondrial HL; 2 examples are MT-RNR1 that encodes mitochondrial 12S ribosomal RNA and MT-TS1 which encodes mitochondrial transfer RNA serine 1. Both of these genes are known to cause nonsyndromic mitochondrial HL.[29]

At least 120 genes have been reported to be associated with HL. Gap junction is a major communication system for the rapid exchange of different component between neighbor cells. Therefore, it also has an important role in auditory transduction, thorough recycling endolymphatic potassium ions. Connexin 26 (GJB2) expressed in a variety of tissues such as cochlea which is a member of family encoding the gap junction proteins.[24,30,31]

Although several genes involve in causing deafness, mutations in connexin 26 (GJB2) have been shown to play a very important role in developing ARSNSHL in many populations depending on geographical location and ethnicity.[8,24,32-35] In Caucasians and Spainish/Italian populations, 50% and 79% of HL shave respectively been reported to be occurred due to mutations in GJB2 gene.[21,36]

In the Middle East, however, the prevalence seems different. For instance a comprehensive study on HL in Iran showed that an average of 14-20% of the HL in several region of Iran is due to mutation in GJB2 gene.[21,36,37] This finding indicates that the involvement of this gene in Western populations is higher than Iranian population.[37-39] Furthermore, different geographical areas in Iran showed different abundance. The rate of mutations in GJB2 gene is respectively 38%,22% and 9% in the North (e.g. Golestan, Gilan, Mazandaran), North West (e.g. Azerbaijan) and North East (Gorgan) of Iran, respectively.[37-39] Alternatively similar studies showed the

prevalence of GJB2 mutations around 25% and 6.1% in Turkey and Pakistani populations, respectively.[40,41]

CONCLUSION

One of the most common sensory defects influencing human is HL. After the mental retardation, HL is the most common adverse sensory neural defect in humans.[37,39] A severe early HL restricts childhood from acquisition speech ability and literacy. The later onset of HL can also affect the quality of life negatively.[42]

HL is classified base on multiple criteria. Genetic factors can be involved in 50% of the cases. Nonsyndromic HL can be transmitted through any Mendelian inheritance patterns, but the majority of them are ARNSHL. Almost 50 genes are involved in HL. Also approximately 200 to 250 genes have been predicted to cause HL.[37,39]

One of the problems during genetic counseling is low public education and understanding of the genetic causes of HL in the Middle East(4). The researches have determined at least10 genes and several loci in nearly 2000 HL family in Iran. However, in Iran, most studies on ARNSHL have been centralized on DFNB1 (GJB2) mutation, as about 18% of HL are result of GJB2 gene mutations. The rate of GJB2 gene mutations in Iran is less than Caucasian populations and more studies would reveal the role of other loci in ARNSHL pathogenesis in Iranian population. Understanding the genetic origin of HL and the molecular mechanism of hearing process are important in modulating genetic counseling and new treatments.[37,39] It will also help to design therapeutic strategies to cure HL using recent advances such as stem cell therapy.[43]

Hopefully, new technologies like next generation sequencing can help detecting new genes for HL in future. Recognizing these factors can definitely help families in reducing the rate of disease. The present study was performed to explain briefly the genetics, molecular biology and epidemiology of HL in Middle East especially in Iran aiming to help better genetic screening, diagnosing disease and genetic counseling.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

ACKNOWLEDGMENT

This work was supported by Shahrekord University of Medical Sciences by grant numbers of 1873 (MSJ) and 1724 (MHC).

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How to cite the article: Karami-Eshkaftaki R, Ahmadinejad F, Aghaei S, Hashemzadeh-Chaleshtori M, Jami MS. Hearing Loss: A review on molecular genetics and epidemiologic aspects. Int J Epidemiol Res. 2017; 4(2): 166-172.