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Review Article

Role of Genetic Factors in the Causation of Non-Syndromic Hearing Loss (NSHL) in Indian Population

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Abstract

Hearing loss affects about 70 million people worldwide, which can be inherited as either syndromic or non-syndromic forms. Approximately 50% of all childhood deafness is caused due to gene defects. The Non-syndromic hearing loss (NSHL) is extremely heterogenous trait inherited as autosomal recessive, autosomal dominant and X-linked and also due to mitochondrial mutations. In the present review genes causing non-syndromic hearing loss (NSHL) are classified based on their molecular function. GJB2 is most prominent deafness causing gene among the different populations including India, followed by other genes. The recent technological advances in target-enrichment methods and next generation sequencing has overcome the barriers possessed by the earlier methods and laid the path for comprehensive analysis of all the known genes causing non-syndromic hearing loss. The review mainly emphases on the genes causing non-syndromic hearing loss in Indian population and their molecular function. Identifying the genes responsible for hearing loss enables otolaryngologists, geneticist to apply molecular diagnosis by offering genetic testing which helps in prevention of the condition of non-syndromic hearing loss, proper diagnosis,

management, pre-natal diagnosis and to offer genetic counselling.

Keywords: Non-syndromic hearing loss; Genes; Gap junctions; Connexins; Myosins

1. Introduction

Hearing loss affects approximately 70 million people worldwide. The genetic aetiologies of hearing loss can be inherited as either syndromic or non-syndromic forms. Approximately 50% of all childhood deafness is due to gene defects. About 1 in 1000 children has prelingual hearing impairment [1], and 1 in 2000 is caused by a genetic mutation. 30% of the cases of prelingual deafness are classified as syndromic, while the remaining are non-syndromic. Non-syndromic hearing loss (NSHL) inherited as an autosomal recessive trait in 75-80% of the cases, 20% followed autosomal dominant mode, 2-5% inherited as X-linked pattern, and 1% due to mitochondrial mutations [2]. Autosomal recessive NSHL is prelingual, non-progressive and severe to-profound [3], whereas autosomal dominant NSHL is post-lingual and progressive [4]. X-linked affect males more severely than females.

So far, total 121 non-syndromic hearing loss genes have been identified. 49 genes accounts for Autosomal dominant non-syndromic hearing loss genes, while 76 genes are responsible for Autosomal recessive non-syndromic hearing loss and 5 genes for X-linked non-syndromic hearing loss [5]. Loci with dominant inheritance are represented by the abbreviation DFNA, followed by a HUGO Gene Nomenclature Committee accession. Loci with recessive inheritance are designated as DFNB, X-linked inheritance is represented by DFNX, modifier loci altering expression of other HL genes are represented by DFNM, while one Y-linked locus is called DFNY1 [5]. Studies in the families with NSHL from different regions of the world, with high rate of consanguineous marriages revealed significant number of recessive deafness genes [6]. Genes causing NSHL can be grouped based on their molecular function such as homeostasis, hair cell structure, transcription factors, cytokinesis, extracellular matrix, mitochondrial and other/unknown. In the present review a brief information is provided about the genes involved in the non-syndromic hearing loss (NSHL) along with their molecular function in the Indian Population.

2. Classification of NSHL Genes Based on Molecular Function

2.1 Cochlear Ionic Homeostasis

Homeostasis is a phenomenon whereby the flow of molecules into and out of a cell is regulated. Gap junctions, ion channels, and tight junctions are the important channels in maintaining the homeostasis in the inner ear. Also, genes coding for neuronal synapses and integral membrane proteins have been identified as key components of homeostasis.

2.1.1 Gap Junctions

Gap junctions are made up of the transmembrane protein called connexins. Connexon is a hemi channel formed by the combination of six connexins, a gap junction is created when two connexons are joined. Gap junctions allow the recycling of potassium ions back into the endolymph during mechanosensory transduction process in the inner ear. Various forms of deafness result due to mutations in connexins which alter the structure and function of the gap junctions. GJB2, GJB3, and GJB6

are the genes which code for connexins and mutations in these genes results in non-syndromic hearing loss [7]. While GJB4 and GJA were associated with hearing loss, with unknown mechanisms.

2.1.1.1 GJB2

Gap junction protein beta 2 (GJB2) gene is located on chromosome 13 q11-12 and codes for connexin 26. Mutations in GJB2 contributes up to 50% of recessive nonsyndromic hearing loss [8]. GJB2 is the most prominent deafness gene. GJB2 gene mutations were reported in 33 (10.9%) patients with congenital hearing impairment from Telangana, among them 6(18.2%) were carriers for the mutant allele. The most frequent mutation was p.W24X, which accounted for 87% of the mutant alleles. In addition to them the other six sequence variations identified in the GJB2 gene were c. IVS1+1G>A, c.167delT, c.235delC, p.W77X, p.R127H (polymorphism) and p.M163V [9]. Ramchander et al. (2005) found high prevalence of W24X mutation (6.5%), and low frequency of W77X (0.5%) and 235delC (0.5%) mutations in GJB2 in non-syndromic hearing impairment (NSHI) in the population of Andhra Pradesh, India [10].

A study carried out in eastern India to identify the genetic cause of deafness by screening GJB2 gene found homozygous mutation for 167 delT in twelve (15.58%) cases and heterozygous mutation in ten (12.99%) out of 77 NSHL cases [11]. Ram Shankar et al. (2003) identified biallelic mutations of GJB2 in 38 deaf cases along with three different mutations, ivs1(+1) G®A, W24X, and W77X. W24X was the most common mutation (18.1%) with a carrier frequency of 0.024 and showed founder effect for this mutation. In addition to these the other six polymorphisms observed were V27I, I111T, E114G, R127H, V153I, and R165W. Among these I111T was a novel polymorphism where isoleucine is replaced by a threonine [12]. Anu et al. (2009) from Kerala India reported that the mutations in connexin26 is responsible for 36% of non-syndromic sensorineural deafness [13]. Pawan et al. (2018) reported a range of GJB2 (Cx26) gene variants in children with non-syndromic hearing loss from Northern (Delhi, UP) and western (Gujarat) regions of India Among these p. Trp24Ter was the most common mutation [14]. Nayyar et al. (2011) from Pune India, reported GJB2 mutations, specifically for W24X in 26% (7/27) cases with non-syndromic congenital sensorineural hearing loss [15].

GJB2 mutations account for 28 to 63% of hearing loss in Europeans [16]. Mutations in GJB2 contribute very little to the underlying genetic cause of NSHL in the Saudi Arabian, African American, Caribbean Hispanic, Pakistani and Moroccan populations [17-20]. While, the Indonesian population lack GJB2 mutations in their deaf community [21]. These findings indicate that the same mutations may not be responsible for NSHL in different populations.

2.1.1.2 GJB3 and GJB6

Gap junction protein beta 3 (GJB3) gene is located on chromosome 1p34 and codes for connexin 31. Mutations in GJB3 result in an autosomal dominant inheritance pattern of nonsyndromic hearing loss [22]. Gap junction protein beta 6 (GJB6) gene is located on chromosome 13q12 and codes for connexin 30. Instrastrial fluid-blood barrier within the cochlear stria vascularis is disturbed due to

deficiency in connexin 30 [23]. GJB6 mutations are associated with both dominant and recessive type of non-syndromic deafness. Padma et al. from Hyderabad, India reported absence of GJB6 mutations in congenital hearing impairment [9]. In consistent to their results Seema et al. from Chandigarh, India also could not find any deleterious mutations in GJB6 in non-syndromic hearing loss [24]. The present studies demonstrated that the mutations in the GJB6 gene are not likely to be a main cause of non-syndromic deafness in Asian Indians.

2.1.2 Ion channels

2.1.2.1 KCNQ4

The potassium voltage-gated channel, KQT-like subfamily, member 4 gene (KCNQ4) is located on chromosome 1p34 and encodes for voltage-gated potassium Kv7.4 channel protein [25]. Mutations in KCNQ4 results in autosomal dominant hearing loss by impairing cell-surface potassium channel expression [26]. Bidisha et al. (2017) stated that the KCNQ4 mutation are absent in Bengali families with ADNSHL originated from West Bengal, India [27].

2.1.2.2 SLC26A4

Solute carrier family 26, member 4 gene (SLC26A4) is located on chromosome 7q31 and encodes a pendrin protein. Pendrin functions as a chloride-iodide transporter in the inner ear by controlling the pH of endolymph and allowing proper function of certain potassium and calcium channels [28]. In PDS and nonsyndromic deafness, about 150 SLC26A4 gene mutations have been identified and it may be the second most common cause of nonsyndromic hereditary hearing loss in the Caucasian population [29]. Defects in pendrin protein results in structural changes, that occur in the inner ear, which includes enlargement of vestibular aqueduct and endolymph sac [30]. Park et al. identified 11 novel mutant alleles of SLC26A4 in 17 (5.4%) of the 318 families with deafness. SLC26A4 linked haplotypes with recurrent mutations were consistent with founder effects. Mutations at SLC26A4 are common and account for about 5% of recessive deafness in south Asians and other populations [31].

2.1.3 Tight Junctions

2.1.3.1 CLDN14

Claudin 14 (CLDN14) gene is present on the chromosome 21q22.3, [32] which encodes a tight junction protein that maintains ionic composition of fluid at the basolateral surface of outer hair cells [33]. Mutations in CLDN14 results in the inhibition of the protein from forming tight junctions, which is very important for the hearing process. Claudin 14 absence from the tight junctions in the organ of corti, leads to altered ionic permeability of the paracellular barrier of the reticular lamina, and that prolonged exposure of the basolateral membranes of outer hair cells to high potassium concentrations might be the cause of hair cells death.

2.2 Auditory Neuron Synapse

2.2.1 OTOF

Otoferlin (OTOF) gene is located on chromosome 2p23.1 [34] and codes for otoferlin, a member of the mammalian ferlin family of membrane-anchored cytosolic proteins, and play a role in the composition of ribbon synaptic vesicles and affect the neurotransmitter release at the inner hair cell of cochlea. DFNB9 recessive deafness is caused due to mutations in OTOF gene [35]. 2-3% of non-syndromic hearing losses (NSHL) are resulted from

mutations in OTOF gene in some ethnic groups [36]. Recessive mutations were identified in the OTOF (p.R708X), SLC26A4 (p.Y556X) and CLDN14 (p.V85D) genes in hearing loss in Dhadkai village of Jammu and Kashmir, India. p.R708X mutation seemed to be the major cause of hearing impairment [37].

2.2.2 PJVK

PJVK gene encodes the PJVK protein which belongs to the gasdermin family. The encoded protein is found in vertebrates and required for the proper function of auditory pathway neurons. Flaws in this gene are a cause of DFNB59 and it was the first reported gene that leads to deafness via neuronal dysfunction along the auditory cascade. Numerous mutations have been found in the PJVK gene [38, 39]. The p.R183W mutation was identified in three Iranian families with non-syndromic deafness due to a neuronal defect [38].

2.3 Integral Membrane Proteins

2.3.1 TMC1

The transmembrane Channel-Like 1 (TMC1) gene is located on the chromosome 9q21.12 [40]. Allelic mutations in TMC1 may result in either autosomal dominant or autosomal recessive non-syndromic hearing loss. TMC1 is a transmembrane protein, although the exact function of it is not known, it may play a role in postnatal hair cell development and maintenance [40]. According to Pawan et al. (2014), TMC1 may be a common gene after GJB2 for nonsyndromic hereditary hearing loss in the Indian subcontinent. While c.100C>T is a common mutation in TMC1 [41]. In contrast Chandru et al. (2019) concluded that c.100C>T mutation is not a significant cause of deafness in the south Indian population [42].

2.3.2 TMIE

The transmembrane Inner Ear (TMIE) gene encodes a transmembrane protein without a known function, and mutations in TMIE result in DFNB6 deafness [43]. Autosomal recessive prelingual deafness that profoundly affects all frequencies is caused due to mutations in TMIE [44].

2.4 Hair Cell Structure

Hair cell structure is largely determinant of its ability to function properly, and is maintained by adhesion proteins, ciliary proteins, as well as myosins. Alterations in hair cell structure will result in various forms of hearing loss.

2.4.1 CDH23

Cadherin 23 (CDH23) encodes the cadherin protein which interacts with a macromolecular organizer harmonin b, to form a transmembrane complex that connects stereocilia into a bundle [45]. CDH23 interacts with protocadherin 15 (PCDH15) to form tip links that connect streocilia and control mechanoelectric transduction in the inner ear [46]. Autosomal recessive, nonsyndromic deafness DFNB12 is caused due to mutations in CDH23, and present with prelingual, moderate to profound sensorineural hearing loss (SNHL) without any vestibular impairment [47]. All the nonsyndromic cases are caused due to a missense substitution [48].

2.4.2 Ciliary Structure

2.4.2.1 STRC

Stereocilin (STRC) gene is located on chromosome 15q15 and encodes the stereocilin protein, which is associated with the hair bundles of stereocilia within the inner ear [49], and defines the autosomal recessive DFNB16 deafness locus. Mutations in

STRC result in two possible phenotypes. Villamar et al. demonstrated a family having non-progressive deafness that presented in early childhood with moderate impairment at low and middle frequencies and severe impairment at high frequencies [50]. While another study reported a separate family with DFNB16 deafness that had profound prelingual NSHL. Altogether, it is thought that the STRC gene is a major contributor to nonsyndromic bilateral sensorineural hearing loss (NBSNHI) among the GJB2 mutation negative probands, especially in those with mild to moderate hearing impairment [51]. According to Yoh et al. (2019), the occurence of STRC homozygous deletions was 1.7% in the hearing loss population and 4.3% among mild-to moderate hearing loss individuals. STRC deletions were the second most common cause of mild-to-moderate hearing loss after the GJB2 gene in Japan [52].

2.4.3 Myosins

Myosins are a family of motor proteins, which hydrolyze ATP to produce actin-based motility. Depending on their ATP-hydrolyzing domain myosins are differentiated into 30 families. Myosins plays an important role in the structure and movement of stereocilia within the inner ear. Mutations in myosin that alter the function of stereocilia result in sensorineural hearing loss. Nonsyndromic hearing loss is caused due to mutations in MYO3A, MYO6, MYO7A, MYO1C, and MYH9 genes.

2.4.3.1 MYO3A

Myosin IIIA (MYO3A) gene has been mapped to chromosome 10p11.1, and responsible for the DFNB30 locus, thought to function as a motor at the tip of stereocilia [53]. Progressive hearing loss, which first affects the high frequencies is caused due to mutations in MYO3A. In two unrelated Brazilian families with late onset non-syndromic hearing loss, whole exome sequencing identified a novel mutation (c.2090 T > G; NM_017433) in MYO3A gene [54].

2.4.3.2 MYO6

Myosin VI (MYO6) gene has been mapped to chromosome 6q13, and it move toward the minus end of actin filaments in the opposite direction that other characterized myosins move [55]. MYO6 transports intracellular vesicles and organelles, to enable the removal of molecular components that are released by treadmilling at the taper of the stereocilium [56, 57]. Autosomal dominant and autosomal recessive forms of nonsyndromic deafness that affect all frequencies are caused due to mutations in MYO6.

2.4.3.3 MYO7A

Myosin VII A (MYO7A) is located on chromosome 11q12-21, and designated as DFNA11. DFNB2 a second locus has been more within the MYO7A interval, at 11q13.5. MYO7A is associated with vestibular dysfunction, ranging from vertigo to complete absence of vestibular function in most of the cases [58]. MYO7A is essential to ensure stereocilia cohesion and a part of a functional unit, along with harmonin b and cadherin 23[59]. Nonsyndromic and syndromic forms of hearing loss may lie on the same phenotype range, whereby the presence of some residual protein function results in a less severe phenotype in nonsyndromic deafness [60]. Arun et al. from India identified a novel MYO7A insertion mutation in a four generation Usher syndrome (USH) family [61].

2.4.3.4 MYO15A

Myosin XVA (MYO15A) is located on chromosome 17p11.2 and responsible for the DFNB3 locus. MYO15A passages the whirlin protein and perhaps other molecular components to their normal location at the stereocilia tip for programmed elongation of the stereocilia in hair cells of cochlea [62]. Autosomal recessive prelingual deafness, moderate to severe or profound form is resulted due to improper functioning of MYO15A [63]. MYO15A gene role in the development of hearing loss was first identified in a village of Bengkala, Bali [64]. Elinaz et al. (2019) found a novel homozygote variant (c.9611_9612+8delTGGTGAGCAT) in the MYO15A gene which creates a shift in the reading frame starting at codon 3204 [65]. Out of 600 families screened, only 6 showed linkage to DFNB3, contributing only 1%. Thus, MYO15A is not a common cause of deafness in the Indian population [66].

2.5 Transcription Factors

Transcription factors are the proteins which binds to DNA domains and helps to initiate a program of increased or decreased gene transcription, and also plays an important role in cell's maintenance, development, response to neighbouring cells, and response to the environment of the cell.

2.5.1 EYA4

Eyes absent homolog 4 (EYA4) gene in humans is mapped to chromosome 6q23 [67] and is responsible for hearing loss at the DFNA10 locus [68]. EYA4 is a transcriptional activator that upsurges the rate of gene transcription in cells of the inner ear. Mutations in EYA4 leads to autosomal dominant pattern of progressive deafness that begins between the ages of 20-60 and affects all frequencies. Compared to other autosomal dominant deafness phenotypes the onset of DFNA10 deafness is late. Genetic screening for EYA4 mutations in a large cohort of Japanese hearing loss patients identified 11 novel EYA4 variants (3 frameshift, 3 missense, 2 nonsense, 1 splicing and 2 single-copy number losses) and two previously reported variants in 12 cases (0.90%) among the 1,336 autosomal dominant hearing loss families [69].

2.5.2 POU4F3

POU4F3 is a member of the family of POU domain transcription factors and located on chromosome 5q31, defines the DFNA15 locus. These protein group shares a POU-specific domain and a POU homeodomain, which are required for high-affinity binding to DNA target sites. Growth Factor Independent 1 (GFI1) gene is the target gene for POU4F3 [70]. Mutations in POU4F3 results in progressive hearing loss with autosomal dominant mode of inheritance, onset is between the ages of 15 and 30 and impairment becomes moderate to severe across all frequencies by age 50 [71]. However, few studies have shown a highly variable phenotypic profile with respect to onset, progression, and affected frequencies [72-74]. Full penetrance has been reported for this gene mutation. Yin et al. (2017) identified a novel missense variant of POU4F3 (c.982A>G, p. Lys328Glu) that co-segregated with the deafness phenotype in ADNSHL [75].

2.5.3 POU3F4

POU domain 3 factor 4 (POU3F4) gene is located on chromosome Xq21.1 [76], is a transcription factor responsible for an X-linked pattern of deafness, also

known as DFNX2 deafness [77]. Individuals affected with DFNX2 have a characteristic computerized tomography (CT) appearance of a dilated internal auditory canal along with temporal bone abnormalities that can range in severity. Regardless, of the sensorineural component advances over time and the deafness may present alongside vestibular dysfunction [78].

2.6 Cytokinesis

2.6.1 DIAPH1

DIAPH1 gene belongs to the formin family of proteins, and the gene locus has been mapped to 5q31 [79]. DIAPH1 may play a role in cytokinesis and establishment of cell polarity, and it is a profilin ligand and target of Rho that regulates polymerization of actin, the major component of the cytoskeleton of hair cells of the cochlea [80], thus thought to be essential for the structure and function of the stereocilia. Autosomal dominant, progressive, post lingual DFNA1 sensorineural hearing loss (SNHL) that begins with increased thresholds at low frequencies and progresses to involve all frequencies is caused due to DIAPH1 mutations [81]. Hearing loss starts at the age of 10 and progresses to profound deafness by the age of 30. DFNA1 individuals do not show any other symptoms or vestibular dysfunction.

2.6.2 ESPN

The ESPN (ESPN) gene is mapped to chromosome 1p36.31-36.11, and codes for the Espin protein, which is believed to function in the growth and maintenance of stereocilia and has a potent actin bundling activity in the inner ear [82]. ESPN defines the autosomal recessive DFNB36 deafness locus, and the affected individuals have a prelingual, profound hearing impairment associated with vestibular areflexia [83]. Mutations in the ESPN gene could cause recessive nonsyndromic deafness without vestibular areflexia [84]. ESPNb mutations, even reported in individuals with autosomal dominant nonsyndromic hearing loss without any vestibular involvement [82]. Boulouiz et al. (2008) by using genome-wide linkage analysis mapped the disease locus in a large consanguineous ARNSHL family from Morocco to the DFNB36 locus and a recessive ESPN mutation causing congenital hearing loss, but without vestibular dysfunction [84].

2.7 Extracellular Matrix Proteins

The extracellular matrix (ECM) of the auditory system enhances the dissemination and detection of sound within the Cochlea, and very important for the tectorial and basilar membrane that move physically as auditory stimuli are transmitted. Sensorineural hearing loss may result due to changes in the ECM membranes.

2.7.1 COL11A2

Collagen type11alpha2gene (COL11A2) gene is located on chromosome 6p21.3 [85], and codes for the collagen fibrils that form the structure of the tectorial membrane [86]. COL11A2 mutations results in autosomal dominant hearing loss at the DFNA13 locus [86], it is a post lingual mid-frequency hearing loss that begins at age of 20-40 years, and does not progress beyond presbycusis [51, 86]. Mutation in COL11A2 can also cause autosomal recessive non-syndromic hearing loss at the DFNB53 locus, characterized by a prelingual, profound, non-progressive hearing loss phenotype [87]. While, nonsyndromic hearing loss is simply the mildest phenotype associated with mutations in COL11A2. Chen et al. (2005) identified a novel locus on

chromosome 6p21.3 for ARNSHL and designated asvDFNB53. Homozygosity for the P621T mutation of COL11A2 was reported in all the deaf persons of a family, which was not seen this in 269 Iranian control [87].

2.7.2 COCH

Coagulant factor C homolog (COCH) gene is mapped to chromosome 14q12-13, and encodes the protein cochlin, which is expressed abundantly in the cochlea and vestibular labyrinth [88]. In the endoplasmic reticulum cochlin is synthesized and secreted into the extracellular space where it plays an integral part in mediating interactions among proteins. COCH mutations may disrupt the protein interactions, thereby altering the function of the extracellular matrix. COCH is linked with the DFNA9 locus [89], and inherited in an autosomal dominant fashion and presents as post lingual, progressive hearing loss, beginning at high frequencies and progressing towards 10-20 years to profound hearing loss at all frequencies [90]. DFNA9 may be caused by a gain-of-function or dominant- negative mutation [91].

2.7.3 TECTA

Alpha tectorin (TECTA) gene encodes a major non-collagenous component of the tectorial membrane called alpha tectorin, which bridges the stereocilia bundles of the hair cells [92], allowing them to move in unison. TECTA gene mutations cause hearing loss that is unique because it is a form of autosomal-dominant, congenital hearing loss. Characteristically autosomal dominant hearing impairment is not present at birth but TECTA is the exemption, which produce moderate to severe, nonprogressive hearing loss affecting predominantly middle frequencies [93]. The phenotype is linked to loci DFNA12 at chromosome 11q22-24 [94]. The autosomal recessive form of deafness has been related to TECTA at the DFNB21 locus [95], which presents as prelingual, severe hearing loss with a flat or U-shaped audiogram [96]. A Japanese study investigated the prevalence of hearing loss caused by TECTA mutations in families with autosomal dominant hearing loss and found mutations in 2.9% (4/139) of those families [97]. Thus, at last mutations in TECTA disrupt sound transmission to the stereocilia.

2.8 Mitochondrial Deafness

Mitochondria are the intracellular organelles that produce cellular energy in the form of ATP, and also contribute to cell-mediated death, or apoptosis, and are implicated in preventing cell damage by reactive oxygen species. Mitochondrial DNA is inherited maternally and encodes proteins necessary for their structure and function. Mitochondrial DNA (mtDNA) mutations cause a variety of systemic disorders including syndromic hearing loss as well as nonsyndromic sensorineural hearing loss. MTRNR1 and MTTS1 gene mutations have been commonly found to result in nonsyndromic deafness.

2.8.1 MTRNR1

MTRNR1 gene encodes for the 12s ribosomal RNA (rRNA). MTRNR1 gene mutations result in a maternally inherited nonsyndromic hearing loss, which worsens by exposure to aminoglycoside antibiotics [98]. MTRNR1mutations may cause tighter binding to aminoglycosides resulting in hypersensitivity to the antibiotic that become toxic to hair cells [99]. Due to MTRNR1 mutation, aminoglycoside reduce mitochondrial protein synthesis precluding normal cellular function [100]. A1555G is the most common mutation in MTRNR1,

which has been found in many families with maternally-inherited hearing loss as well as in individuals with aminoglycoside-induced hearing loss. The MTRNR1 gene penetrance is variable [101], and results in a range of phenotypes from normal hearing to profound deafness exist that implies the presence of a nuclear modifier [102, 103]. Low penetrance has been reported among the Chinese population [104].

2.8.2 MTTS1

Mitochondrial tRNA for serine (UCN) (tRNASer (UCN)) is encoded by MTTS1 gene and numerous progressive nonsyndromic hearing loss causing mutations have been identified in the MTTS1 gene. Penetrance due to MTSS1 mutation varies greatly together within and between families. MTTS1 mutations have also been shown to induce aminoglycoside hypersensitivity [105].

3. Genes with Unknown Function

3.1 TMPRSS3

The transmembrane protease, serine 3 (TMPRSS3) gene is located on chromosome 21q22 [106], and expressed in the spiral ganglion neurons and play a role in the process of aminoglycoside antibiotics induced deafness [107]. Lack of Tmprss3 results in decreased Kcnma1 potassium channels expression in inner hair cells [108]. TMPRSS3 mutations are related with DFNB8 and DFNB10 loci, which can be distinguished by phenotype. DFNB8 initiates at the age of 10 to 12, and advances over 5 year to profound deafness across all frequencies [106] While, DFNB10 is present at birth as severe SNHL, nevertheless individuals also present at late as 6 or 7 years of age [109]. Ganapathy et al. (2014) reported that the contribution of TMPRSS3, TMC1, USH1C, CDH23 and TMIE mutations for ARNSHL is low in India. TMPRSS3 contributes 1.2%, TMC1 1.6%, USH1C 1.8%, CDH23 1.8% and TMIE 1.6%. According to the study of Ganapathy et al. (2014), the spectra of alleles in the TMPRSS3, TMC1, USH1C and CDH23 genes in Indian populations appear to be relatively different from those observed in other population. Among the 33 mutations observed in the Indian population, 23 were not reported in other population [110].

3.2 WFS1

Wolfram syndrome 1 (WFS1) gene is located on chromosome 4p16 [111], and codes for extracellular matrix-integral glycoprotein of endoplasmic reticulum, signifying a role in membrane trafficking, protein processing and regulation of endoplasmic reticulum calcium homeostasis [112]. WFS1 is one of the only two genes, that results in a nonsyndromic, autosomal dominant low frequency sensorineural hearing loss. WFS1 mutations also cause syndromic form of hearing loss. WFS1 mutations have been associated to DFNA6, DFNA14 and DFNA38 locus. The DFNA6/14 loci can be singled out by S-shaped pure tone audiogram [113]. DFNA6/14/38 deafness has minimal progression, that is consistent with changes of presbycusis. The onset of DFNA14/ 6/38 is at the age of 5 to 15 years [114].

3.3 PCDH15

Protocadherin 15 (PCDH15) gene is located on chromosome 10q21.1, and interacts with cadherin 23 to form tip links of stereocilia [46]. DFNB23 a typical autosomal recessive hearing loss phenotype is caused due to missense mutations in PCDH15, which is a prelingual, severe to profound sensorineural deafness.

3.4 USH1C

Usher Syndrome 1C (USH1C) gene codes for harmonin protein, a PDZ domain protein that forms a complex with CDH23 to bundle stereocilia [45], is located on chromosome11p14.3, and codes for the USH1C gene mutations may result in either syndromic or nonsyndromic phenotype depending on the severity of the mutation. DFNB18, a non-syndromic phenotype, is a prelingual profound deafness. Both syndromic and non-syndromic phenotypes are inherited in an autosomal recessive pattern.

3.5 WHRN

Whirlin (WHRN) gene is located on chromosome 9q32-q34, and encodes whirlin, which interacts with MYO15A for stereocilia morphogenesis [115]. Mutations in WHRN causes DFNB31, a prelingual profound deafness [116].

4. Conclusion

Recent studies have been highlighted the prosperity of evidence of gene mutations in the aetiology of non-syndromic hearing loss (NSHL), which has intensely improved the knowledge and treatment options of non-syndromic hearing loss. Due to clinical and genetic heterogeneity of NSHL the complete understanding of the condition is still remains challenging. Despite of advances in the field of non-syndromic hearing loss in several populations, the exact distribution of these pathogenic genes in populations remains uncertain, indicating that the molecular epidemiology of NSHL differ among populations. The ultimate genetic cause of NSHL have been identified in families with consanguineous marriage. The present review presents an overview and description of the known genes involved in non-syndromic hearing loss (NSHL). Identifying the genes in non-syndromic hearing loss in Indian population will help in discovering its cause and deciphering the mechanisms underlying the condition. The extreme genetic heterogeneity of non-syndromic hearing loss makes diagnosis also difficult. The advent of Next Generation Sequencing (NGS) has revolutionized the genetic testing of congenital non-syndromic hearing loss, and more genes leading to hearing loss are discovered, whose functions will be better understood with the upcoming research in the area of deafness. There is a necessity to create awareness and precise genetic counselling to the families who are at high risk, and to establish genetic based diagnosis for NSHL for mutations which are prevalent in India. A comprehensive knowledge of genes and their function in the causation of non-syndromic hearing loss will provide better opportunities to identify the hearing loss causing mutations in patients and to provide prompt management, pre-natal diagnosis and improved genetic counselling.

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Conflict of Interest

None to declare.

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