Autosomal Dominant Non-Syndromic Hearing Loss

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Autosomal dominant non-syndromic hearing loss (HL) typically occurs when only one dominant allele within the disease gene is sufficient to express the phenotype. Therefore, most patients diagnosed with autosomal dominant non-syndromic HL have a hearing-impaired parent, although de novo mutations should be considered in all cases of negative family history. To date, more than 50 genes and 80 loci have been identified for autosomal dominant non-syndromic HL. DFNA22 (*MYO6* gene), DFNA8/12 (*TECTA* gene), DFNA20/26 (*ACTG1* gene), DFNA6/14/38 (*WFS1* gene), DFNA15 (*POU4F3* gene), DFNA2A (*KCNQ4* gene), and DFNA10 (*EYA4* gene) are some of the most common forms of autosomal dominant non-syndromic HL. The characteristics of autosomal dominant non-syndromic HL are heterogenous.

genetic hearing loss | autosomal dominant inheritance | non-syndromic hearing loss

1. Inheritance

Autosomal dominant inheritance occurs when only one dominant allele within the disease gene (located on one of the autosomal chromosomes) is sufficient to express the phenotype [1]. Therefore, a heterozygous parent with autosomal dominant non-syndromic HL (DFNA) has a 50% chance of passing it on to their children [1][2]. However, if one parent is homozygous, all offspring may inherit the disease. If both parents are heterozygous and affected by autosomal dominant non-syndromic HL, 75% of the offspring have the chance of inheriting the disease [1]. Males and females are equally likely to inherit the mutation [1][2]. Most patients diagnosed with autosomal dominant non-syndromic HL have a hearing-impaired parent [2]. However, although the family history is rarely negative, it may appear to be negative due to late-onset HL in a parent, reduced penetrance of the pathogenic variant in an asymptomatic parent, or a de novo variant [2]. In particular, de novo mutations are possible causes of genetic HL and should be considered in all cases of sporadic HL [3]. It is often difficult to distinguish between syndromic and non-syndromic HL, as symptoms can sometimes appear later. Furthermore, some genes (e.g., *WFS1* and *ACTG1*) cause both syndromic and non-syndromic HL [4].

Unlike autosomal recessive non-syndromic HL (in which the majority of cases are caused by mutations in the *GJB2* gene), autosomal dominant non-syndromic HL does not have a single identifiable gene responsible for the majority of cases worldwide [2].

In Europe, the most common forms of autosomal dominant non-syndromic HL are DFNA22 (*MYO6* gene) and DFNA8/12 (*TECTA* gene), accounting for 21% and 18% of all cases, respectively [5]. Other frequent forms of autosomal dominant non-syndromic HL in Europe are DFNA20/26 (*ACTG1* gene), DFNA6/14/38 (*WFS1* gene), and DFNA15 (*POU4F3* gene), accounting for 9%, 9%, and 6.5% of all cases, respectively [5]. *KCNQ4* (DFNA2A) and *EYA4* (DFNA10) genes contribute 2.5% each, while the remaining genes are residually represented [5]. De novo mutations have been described in several genes, such as *GJB2* (DFNA3A) [6][7], *ACTG1* (DFNA20/26) [8][9], *TECTA* (DFNA8/12) [10], *MYH14* (DFNA4A) [10], *CEACAM16* (DFNA4B) [11], *ATP2B2* (DFNA82) [12], and *WFS1* (DFNA6/14/38) [13].

2. MYO6 Gene

Mutations in the *MYO6* gene can cause either autosomal dominant non-syndromic HL (DFNA22) or autosomal recessive non-syndromic HL (DFNB37) [4]. DFNA22 is caused by a heterozygous mutation in the myosin VI gene (*MYO6*) on chromosome 6q14 [4]. Myosin VI is an actin-based motor protein which plays a key role in the endocytic and exocytic membrane trafficking pathways. In the inner and outer hair cells of the organ of Corti, myosin VI serves as an anchor and maintains the structure of the stereocilia [14]. Autosomal dominant HL associated with *MYO6* mutations was reported in large Italian [15], Danish [16], Belgian [17][18], Dutch [19], German [20], and Austrian [21] families. However, several cases of DFNA22 were described in China [22][23][24], Japan [25][26], the Republic of Korea [27], and Brazil [28]. HL is typically post-lingual (often occurs during childhood), is slowly progressive, ranges from a mild to profound degree, and may be associated with mild cardiac hypertrophy [4][29]. Volk et al. suggested a favorable outcome of cochlear implantation in patients with DFNA22 [20].

3. TECTA Gene

Autosomal dominant non-syndromic sensorineural deafness 8/12 (DFNA8/12) is caused by heterozygous mutations in the *TECTA* gene on chromosome 11q23 [4]. Missense mutations of *TECTA* cause DFNA8/12, while nonsense mutations cause autosomal recessive non-syndromic HL (DFNB21) [4]. The *TECTA* gene encodes alpha-tectorin, one of the major non-collagenous components of the tectorial membrane of the inner ear that bridges the stereocilia bundles of the sensory hair cells [30]. HL associated with *TECTA* missense mutations was reported in families from different European countries, including Belgium [31][32], Austria [33][34], France [35], Sweden [36], Spain [37], and The Netherlands [38][39][40][41]. However, autosomal dominant non-syndromic HL caused by TECTA mutations was also reported in Japanese [42][43][44][45], Turkish [46], American [30][47], Korean [48][49], Brazilian [50], Chinese [22][51][52], Mongolian [53], and Algerian [54] families. HL can be present before the child learns to speak (prelingual) or begin in childhood (first or second decade of life). The characteristics of HL depend on the domain in which the mutations occur: missense mutations in the *zona pellucida* domain lead to mid-frequency sensorineural HL (“U-shaped” or “cookie bite” audiometric configuration), while missense mutations in the *zonadhesin region* cause high-frequency sensorineural HL (“sloping” audiometric configuration). HL is progressive if cysteine residues are affected [4][30].

4. ACTG1 Gene

Autosomal dominant non-syndromic sensorineural deafness 20/26 (DFNA20/26) is caused by heterozygous mutations in the *ACTG1* gene on chromosome 17q25 [4]. Mutations in the *ACTG1* gene can be associated with autosomal dominant non-syndromic HL (DFNA20/26) and Baraitser–Winter syndrome (a rare condition characterized by ptosis, colobomata, neuronal migration disorder, distinct facial anomalies, and intellectual disability) [4][55]. The *ACTG1* gene encodes gamma actin, which is a major actin protein in the cytoskeleton of auditory hair cells and is essential for the maintenance of stereocilia [55]. In Europe, DFNA20/26 was reported in Dutch [56][57][58], Norwegian [59], Spanish [60], and Italian [55] families. Mutations in the *ACTG1* gene were also frequently described in American [61][62][63][64], Chinese [8][65][66][67][68], Korean [69][70][71], and Japanese [72][73][74] populations. HL is typically diagnosed in the first or second decade of life and affects high frequencies ("sloping" audiometric configuration). It is progressive and tends to become profound by the sixth decade of life [4].

5. WFS1 Gene

Autosomal dominant non-syndromic sensorineural deafness 6/14/38 (DFNA6/14/38) is caused by heterozygous mutations in the *WFS1* gene on chromosome 4p16 [4]. The DFNA6, DFNA14, and DFNA38 loci were initially described separately but were later found to be associated with pathogenic variants in the same gene (*WFS1*) [75]. Mutations in the *WSF1* gene can be responsible for both autosomal dominant non-syndromic HL (DFNA6/14/38) and Wolfram syndrome (an autosomal recessive disorder characterized by diabetes mellitus, diabetes insipidus, optic atrophy, and high-frequency sensorineural HL) [4][75]. The *WFS1* gene encodes "Wolframin", a transmembrane protein located in the endoplasmic reticulum and ubiquitously expressed [75]. DFNA6/14/38 was largely described in the United States of America [76][77][78][79][80][81], Japan [82][83][84][85][86][87], and China [13][66][88][89][90][91][92][93][94]. In Europe, DFNA6/14/38 was reported in Dutch [75][95][96][97], Swiss [98], Danish [99], Hungarian [100], Finnish [101], and German [102] families. Other cases of DFNA6/14/38 were observed in Taiwan [103], the Republic of Korea [104][105], Iran [106], and India [107]. HL is generally congenital, limited to low frequencies (2000 Hz and below), and slowly progressive (without reaching a severe-to-profound range). It may be associated with tinnitus, but speech perception is typically good [4]. Interestingly, although Wolframin is equally expressed in the basal and apical turns of the cochlea, HL involves the low frequencies in DFNA6/14/38 and the high frequencies in Wolfram syndrome [75].

6. POU4F3 Gene

Autosomal dominant non-syndromic sensorineural deafness 15 (DFNA15) is caused by heterozygous mutations in the *POU4F3* gene on chromosome 5q32 [4]. The *POU4F3* gene encodes a transcription factor which plays a key role in the maintenance of inner ear hair cells [108]. DFNA15 was largely described in Israeli [109][110][111][112] and Chinese families [22][66][113][114][115][116][117][118]. In Europe, DFNA15 was widely reported in The Netherlands [119][120][121][122]. Other cases of DFNA15 were observed in the Republic of Korea [69][123][124], Brazil [125][126], Japan [72][127], and Taiwan [128]. HL is post-lingual (onset varies between the second and sixth decades of life), bilateral, and

progressive [4]. It is characterized by high intrafamilial variability and tends to progress to the severe-to-profound range. Audiometric configuration can be sloping or flat [4]. HL may also be associated with vestibular dysfunctions, including areflexia [129].

7. KCNQ4 Gene

Autosomal dominant non-syndromic sensorineural deafness 2A (DFNA2A) is caused by a heterozygous mutation in the *KCNQ4* gene on chromosome 1p34.2 [4].

The protein encoded by the *KCNQ4* gene forms a potassium channel that plays a key role in the regulation of neuronal excitability, particularly in the sensory cells of the cochlea [130]. Autosomal dominant HL due to *KCNQ4* mutations was reported in Indonesian [131], American [132][133][134][135][136], Japanese [137][138][139][140], Taiwanese [141][142][143], Canadian [144], Brazilian [145], Pakistani [146], Iranian [147], Chinese [148][149][150][151], and Korean [152][153][154][155] families. In Europe, DFNA2A was observed in French [133][156], Dutch [133][138][157][158][159][160][161], Belgian [133][158], and Spanish [162] families. HL is generally diagnosed between 5 and 15 years old and is initially limited to high frequencies, with later involvement of the middle and high frequencies. It tends to be severe by age 50 [4]. Most patients had associated tinnitus but no vestibular symptoms except in a few cases [140].

8. EYA4 Gene

Autosomal dominant non-syndromic sensorineural deafness 10 (DFNA10) is caused by heterozygous mutations in the *EYA4* gene on chromosome 6q23 [4]. The *EYA4* gene encodes a member of the eyes absent (EYA) family of proteins, which is a transcriptional activator required for proper eye development as well as for the maturation and maintenance of the organ of Corti. Mutations in *EYA4* can also cause a syndromic variant characterized by HL and dilated cardiomyopathy [163]. DFNA10 was observed in large American [164][165][166][167][168], Australian [169], Indian [107], Korean [170][171][172], Chinese [163][173][174][175][176][177][178], Brazilian [126], and Japanese [179][180] families. In Europe, HL due to mutations in the *EYA4* gene were reported in Belgian [165][167][181][182], Norwegian [181], Hungarian [183], Swedish [184], Dutch [185], Italian [186], Slovakian [187], and Spanish [188] families. HL is typically progressive and often involves all frequencies, although initially, it may be limited to middle frequencies. The onset of HL is highly variable [4]. The audiometric configuration of truncating variants tends to be flat, while that of non-truncating variants tends to be sloping [179]. DFNA10 patients are considered the least responsive to cochlear implantation [169].

9. Characteristics of Hearing Loss

The characteristics of autosomal dominant non-syndromic HL are heterogenous. Most autosomal dominant loci cause post-lingual HL, with onset ranging from childhood to late adulthood. However, HL tends to occur in childhood, adolescence, or early adulthood. Moreover, a non-negligible number of loci are associated with congenital HL, including DFNA3A (*GJB2* gene), DFNA3B (*GJB6* gene), DFNA6/14/38 (*WFS1* gene), DFNA7

(*LMX1A* gene), DFNA8/12 (*TECTA* gene), DFNA13 (*COL11A2* gene), DFNA19 (unknown gene), DFNA23 (*SIX1* gene), DFNA24 (unknown gene), DFNA27 (*REST* gene), DFNA30 (unknown gene), DFNA37 (*COL11A1* gene), DFNA40 (*CRYM* gene), DFNA59 (unknown gene), DFNA66 (*CD164* gene), DFNA69 (*KITLG* gene), DFNA71 (*DMXL2* gene), DFNA78 (*SLC12A2* gene), DFNA80 (*GREB1L* gene), DFNA84 (*ATP11A* gene), DFNA87 (*PI4KB* gene), and DNA89 (*ATOH1* gene). The degree of HL at onset ranges from mild to profound. Most cases of HL are progressive and worsen over the years, with the exceptions of DFNA8/12 (*TECTA* gene), DFNA13 (*COL11A2* gene), DFNA19 (unknown gene), DFNA23 (*SIX1* gene), DFNA24 (unknown gene), DFNA40 (*CRYM* gene), DFNA59 (unknown gene), DFNA66 (*CD164* gene), DFNA69 (*KITLG* gene), DFNA76 (*PLS1* gene), DFNA78 (*SLC12A2* gene), and DFNA80 (*GREB1L* gene), which tend to be stable. Interestingly, DFNA16 (unknown gene) is characterized by fluctuating HL that often benefits from treatment with oral steroids [189]. Audiometric configuration is highly variable, although it often tends to be sloping, with the high frequencies more involved, especially at the onset of HL. A flat audiometric configuration is also frequent. However, some loci are associated with rising audiometric configuration, and HL is limited to the low frequencies: DFNA1 (*DIAPH1* gene), DFNA6/14/38 (*WFS1* gene), DFNA44 (*CCDC50* gene), DFNA49 (unknown gene), DFNA54 (unknown gene), DFNA56 (*TNC* gene), DFNA57 (unknown gene), and sometimes DFNA11 (*MYO7A* gene), and DFNA69 (*KITLG* gene).

DFNA1 and DFNA6/14/38 are the most common forms of autosomal dominant non-syndromic HL affecting the low frequencies. DFNA1 is due to mutations in the *DIAPH1* gene on chromosome 5q31 and causes progressive low-frequency HL, resulting in a profound degree by the fourth decade of life [190][191]; conversely, DFNA6/14/38 is due to mutations in the *WFS1* gene on chromosome 4p16 and does not progress to profound HL [192]. The “U-shaped”, “saucer”, or “cookie bite” audiometric configuration indicates mid-range frequency HL and can be associated with some autosomal dominant loci, including DFNA8/12 (*TECTA* gene), DFNA13 (*COL11A2* gene), DFNA31 (unknown gene), DFNA37 (*COL11A1* gene), DFNA66 (*CD164* gene), and DFNA72 (*SLC44A4* gene). Although non-syndromic HL is typically not associated with other clinical manifestations, some autosomal dominant loci can cause other signs or symptoms than HL, such as thrombocytopenia (DFNA1), vertigo or vestibular dysfunction (DFNA7, DFNA9, DFNA11, DFNA15, DFNA16, DFNA36, DFNA54, DFNA69, DFNA78, and DFNA82), cochleosaccular dysplasia (DFNA17), hypertrophic cardiomyopathy (DFNA22), preauricular pits, hypodysplastic kidney, and vesicoureteral reflux (DFNA23), autoinflammatory disorders (DFNA34), dentinogenesis imperfecta (DFNA39), absent or malformed cochleae and eighth cranial nerves (DFNA80), and incomplete cochlea partition and enlarged vestibular aqueduct (DFNA87).

10. How Knowledge of Genetic Mutations May Influence Treatment

All children diagnosed with sensorineural HL should be screened early for genetic mutations to ensure timely appropriate treatments (e.g., hearing aid or cochlear implant), personalized rehabilitation programs (e.g., in the presence of additional symptoms), prognosis (e.g., stable, progressive, or fluctuant HL), and family planning [2]. The team evaluating and treating these children should consist of an otolaryngologist with expertise in the management of pediatric otologic disorders, an audiologist experienced in the assessment of childhood HL, a

clinical geneticist, a speech-language pathologist specializing in working with children affected by HL, and a pediatrician [2]. For children with severe-to-profound HL, hearing aids may be insufficient for HL rehabilitation, and cochlear implantation should be considered.

Cochlear implantation has a high probability of being effective if the mutated lesion is located in the hair cells or afferent synapses between hair cells and the auditory nerve, such as in patients with pathogenic variants in *GJB2*, *COCH*, *MYO7A*, *ACTG1*, or *MYO6* genes. Conversely, cochlear implants are generally less effective if genetic mutations affect auditory nerve function [20][193][194][195][196]. Moreover, genetic testing is useful not only for predicting performance after cochlear implantation but also for assessing residual hearing, estimating progression, and successful hearing preservation, leading to the most appropriate selection of candidates and electrodes [195].

As a matter of fact, better knowledge regarding genotype–phenotype correlation and cochlear implant outcome may provide effective auditory rehabilitation and would reduce unnecessary procedures, thereby limiting both surgical risks and healthcare costs [196].

11. Current Limitations and Future Trends

The genetics of non-syndromic HL are constantly evolving, and there are currently many limitations of knowledge in this field. The etiology of some patients with evident familial HL still remains unknown. Indeed, intra-familial variability in sensorineural HL is common not only from parent to child in dominant cases but also between siblings [197]. Many pathogenic variants affecting known deafness genes may go undetected using current diagnostic algorithms because they reside in non-coding (intronic and regulatory) sequences or unannotated exons [198]. Therefore, consideration should be given to implementing whole exome or whole genome sequencing with a virtual panel as the gold standard for genetic testing in HL instead of targeted gene sequencing panels [199].

Currently, many children with mild or progressive forms of HL remain undiagnosed during their critical period of speech development and neuroplasticity. Therefore, it appears to be a priority to develop a new cost-effective method of universal genetic screening that ensures early diagnosis of genetic HL in order to identify potential comorbid conditions and guide treatments [200].

In recent years, there have been major advances in the development of gene therapy vectors to treat sensorineural HL in animal models, representing a promising approach to prevent or slow down genetic HL. Interestingly, gene therapy is not limited to the addition of a healthy copy of the defective gene but may also involve gene silencing or editing through nucleic acid-based strategies, including antisense oligonucleotides, siRNA, microRNA, or nuclease-based gene editing [201]. However, many issues are still unresolved, such as the temporal window for therapeutic intervention, the need for viral vector optimization, the safety of surgery, and the type of immune response [202].

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