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CONTRIBUTIONS OF COMMON SINGLE NUCLEOTIDE POLYMORPHISMSIN NOISE-INDUCED HEARING LOSS

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Abstract

Noise induced hearing loss (NIHL), is common sensory illness especially occur in industrial areas, about 10% population affected annually. NIHL is second occupational and sensori-neural hearing disability all over the world. Since the description between PON2, ATP2B2, CASP gene, Potassium recycling genes (KCNE1, KCNJ10, KCNQ1, KCNMA1, KCNQ4), SLC12A2, SLC26A4, connexins (GJB2, GJB3, GJB6), myosin 14 genes, CAT SNPs/haplotypes, cadherin 23 & protocadherin 15 (CDH23, PCDH15), HSP haplotypes (HSP70-hom, HSP70-1 and HSP70-2) there have been significant advances in the understanding and genetic manipulation of this disease. This review focused on the genes involved in Noise induced hearing loss (NIHL). But all these genes are studied separately in different populations. One large research plan has to be introduced to identify common genes involved in this disease. We should have to know the mechanism of involvement of these genes in this disease.

Keywords: *NIHL, PON2, ATP2b2, CASP gene, CAT, cadherin 23, connexins, HSP haplotypes*

INTRODUCTION

Hearing loss is a chronic sensory disability of ear which can be of both types, noise induced hearing lose, age related hearing loss or both (1-3). Both can exist at the same time which is difficult to trace and is due to the hair cells loss with spiral ganglion neurons degeneration (4). Center for disease control (CDC) announced hearing loss as third chronic disease in US and second pervasive type hearing loss (5, 6).

At the present time NIHL is worldwide sensori-neural risk disorder which influences socio-economic globally and occurs due to day by day exposure of noise with frequency notch at 4-6 kHz. It depends upon the exposure duration, type and strength of the noise. Two types of NIHL have been defined as temporary (TTS) and permanent (PTS) with the disturbance of mechanical as well as metabolic factors (7, 8). It is proportioned to the exposure of noise and left ear affects more than right one (9). Noise firstly affects the hair cells of which result Cochlear nerve fibers and spiral ganglion cells degenerate (10). WHO reported 1.3 billion people affected by hearing loss due to continuous sound exposure and about 10% world population suffering from NIHL (11). It is reported by the international standard (ISO-1999, 1990) when an individual exceeds the normal threshold hearing level then suffer from the hearing loss correlated also with the age and noise induction depend upon the noise frequency and exposure duration (12).

Genetically it is essential to properly diagnose the noise induce hearing loss which is exponentially increasing as a genetic trait and subject to selective evolution. Heavy instruments and tools are affecting our daily life while producing noise. Although less exposure of such noise leads to temporary loss of hearing ability which can lead to permanent with increasing noise exposure can lead to auditory loss permanently (13).
In industrial areas due to the sensory deficiency 10% population affected by Noise induced hearing loss (14). NIHL is second Sensi-neural occupational hearing loss (15, 16). It is alarming that about 500 million people are at risk of hearing defects throughout the world (17). Among different individuals, susceptibility to NIHL differs owing to a permutation of genetic as well as environmental factors (18).

Recently, the detection of Single Nucleotide Polymorphisms (SNPs) has been started as the as the risk of many different genetic diseases (19). These are point mutations found every 100-300 bp apart in the genome and their numbers vary in a specific genome. The use of SNPs is supposed to be an excellent tool to evaluate the genetic and clinical conditions of composite diseases in which many genes are thought to be involved, such as NIHL.

It is a multi-factorial disease in which large numbers of genes are involved and played functional as well as morphological role in inner ear. The involvement of potassium (K+) ion and heat shock protein (*HSP*) pathways involving genes was determined as a profound cause of the disease. Potassium (K+) recycling genes played role in hearing, as the defect in these genes cause multiple forms of hearing impairment (*KCNE1, GJB2, KCNQ1, KCNQ4, GJB3* and *GJB6*). Recent studies on HSP haplotypes (*HSP70-1, HSP70-2* and *HSP70-hom*) showed that the mutation in these haplotypes may be related to inclination of NIHL. Recently, the significance of protocadherin 15, myosin 14 genes and many other genes have been found to be associated (20).

HISTORY

In the 18th century, the disease of workers of Ramazzini's classic occupational medicine De Morbis Artificum first reported the noise induces hearing loss just because of high noise exposure. Ramazzini's discussions shows that hearing loss was related to both occupational and environmental which affects whole population not only individuals. In Egypt same study was done by coppersmiths of Venice (21).

NIHL clinical summary shows Sensi-neural insufficiency was around the 3,000 Hz – 6,000 Hz in the regions of audiograms while higher amount was around 6,000 Hz. In males, majority of the police force males (74.8%) were affected while their mean age was 35.55 ± 9.57 years. A study was performed on Royal Brunei Police Force in Darussalam showed that more cases of males (37.7%) than females (23.9%). This study also update us involvement of hypertension, age, diabetes, service duration and gender along with NIHL. (22).

In Tanzania NIHL prevalence was found of 47% (12% poor hearing loss, 35% mild hearing impairment). NIHL increases exponentially within a year of underground miners

(71%), open pit miners (28%), young age group (60%) between the 20 to 29 years of age (23).

A study in Nepal revealed the prevalence of NIHL in wood industry. From 88 carpenters and 36 sawyers, 16 of joiners (31%) and 27 of sawyers (44%) showed occupational NIHL whereas, levels of sound ranging from 71·2 to 93·9 dBA (24).

FACTORS ASSOCIATED WITH NOISE INDUCED HEARING LOSS (NIHL)

NIHL is a complex disorder mainly originated by a blend of a number of environmental as well as genetic factors (25). In all environmental factors that cause hearing loss, continuous noise exposure is the best known. Environmental factors associated with NIHL such as extreme heat, exposure to solvents especially organic ones, microbial infections, chemicals causing ototoxicity and smoking. In addition, factors like elevated blood pressure and other medical factors also make ear susceptible to noise (18). Propensity to noise injury differed among persons which described the role of genetic grounds in this field (26).

CAUSES

The main root of defect in occupational hearing was found to be cochlear hair cell injury (27). Free radicals discharge as a result of noise can destroy the cochlear epithelium, leading to NIHL(28).

Repeatedly noise exposure is the main reason behind hearing loss among wide range of secondary, non-auditory effects including sleep disorder, intellectual deficiency and cardiac disease (29). Noise-induced hearing loss (NIHL) with tinnitus affects 16% of the population globally (30).

CLINICAL FEATURES

The main feature of the disease is the sensory and neural hearing defect concerning primarily the high audiometric frequencies. An audiometric “notch,” is thought to be indicative of noise-induced damage (31).

PATHOPHYSIOLOGY

Noise contact mainly affects the lateral wall, organ of Corti and afferent neurons in the inner ear which considered as either provisional or endless hearing threshold shifts. Their functions and morphology are clearly different but at the molecular level scientists are unable to find clear difference. It is clear that hearing loss is because of the loss of cochlear hair cells in organ of corti, stria vascularis and afferent neurons. Some reports suggests reactive oxygen species (ROS) the reason behind hearing loss by which hair cells failure to grow. Reactive oxygen species damages mitochondrion which affects pro-apoptotic factors trigger the cellular apoptotic reaction. Loss of hair cells because of noise exposure results in Potassium dys-regulation between Hensen’s cells and hair cells present in organ of corti (30).

Whole genome and genome wide studies showed the association of genetic variations with NIHL. These studies reported polymorphisms in different pathways includes oxidative stress response pathways, involving *HSP70* and *SOD1* proteins; as well as potassium recycling pathways, concerning *KCNQ4* and*KCNE2* proteins (25).

COMMON GENES INVOLVED IN HEARING MECHANISM

Genes involved in NIHL are mainly involved in Structural Integrity of Stereocilia (mechano-sensing organelles of cochlear hair cells), Ion Homeostasis (Pumps, Channels and Connexins), Protective Pathways (Glucocorticoids and Stress Response) Oxidative Stress, and Other Processes (21).

PARAOXONASE2 GENE (PON2)

Paraoxonase2 genes categorized as *PON1*, *PON2* and *PON3* code for esterases, localized on "q" arm of chromosome 7 (q21.3–22.1). *PON2* gene present at the whole body and produce antioxidant effects while any change in its sequence which increase ROS and damage cochlear cell. *PON2* genetic analysis shows polymorphism of 'rs12026 and rs7785846' in sample of 94 male workers exposed to noise revealed a significant association with NIHL in Italy (28, 32).

ATP2B2

ATPase, calcium-transporting, plasma membrane 2 (*ATP2B2*) gene, encodes plasma membrane calcium transporting ATPase isoform2 (PMCA2) is located on "p" arm of the human chromosome 3 (3p25). The characteristic role of *ATP2B2* in hearing was specified by its increased level of communication in cochlear hair cells, where it played significant role in calcium homeostasis. *ATP2B2* is an influencing gene for NIHL and also its absence can direct towards the defects of auditory systems leading to hearing loss. Researchers have worked on rs1719571, rs3209637 and rs4327369 and they found involvement of these genes in NIHL (33).

CASP GENE

Hair cell death way is apoptosis, which is orderly organized by a specific gene. Caspases pathway activation is the essential connection in apoptosis. Caspases enzymes are encoded by *CASP* genes and are activated under the influence of an apoptotic signal by stepwise hydrolysis. When activated, cause structural and functional damage of the cell. According to recent studies, two SNPs in CASP3 gene (rs1049216. rs6948) have been associated with NIHL risk (34).

POTASSIUM RECYCLING GENES

Electrochemical gradient cross wises the cell cubicle and potassium flow in cochlea which are also vital for hearing and is maintained by the potassium recycling pathway genes. Subsequently, polymorphism in the potassium recycling genes leads to or may be associated with hearing loss. Genes involved are potassium voltage gated canal genes *KCNE1, KCNQ1* and *KCNQ4*. Potassium inwardly rectifying channel *KCNJ10* and

potassium calcium activated gated channel subunit *KCNMA1*. Sometimes mutations in these genes cause congenital deafness in humans (35).

STRESS RESPONSE GENES

Mild exposure to noise has been reported that it shields the ear from earsplitting music that is branded as "Sound Conditioning"(36). A number of methods are offered to explain it. Some other best developed natural mechanisms include antioxidant, heat shock and glucocorticoid signaling cascade. An important transcription factor is Heat shock transcription factor 1(Hsp70) that manages the inducible stress response protecting tissues and cells from numerous cellular as well as environmental stresses which is sometime called shock response (Morimoto et al. 1997). *Hsp70* gene expression in cochlea is up regulated by heat stress participating in protecting hair cells from consequent pressure of noise. It is reported that SNP rs2227956, rs1061581 and rs1043618 in Hsp70 has significant association with NIHL (6).

CAT

CAT SNPs/haplotypes are identified as the association connecting Noise exposure and these genes (37).

CADHERIN 23 (*CDH23*) & PROTOCADHERIN 15 (*PCDH15*)

CDH23 and *PCDH15* both play role in growth and maintenance of hair cells (38, 39).Proteins variation of *CDH23*, *PCDH15* damages the structure which is important from motorized stimuli to electrical signals. As a result of missense mutation one form converted to another (such as *CDH23* in *DFNB12*; *PCDH15* in *DFNB23*) causes deafness (40, 41). First reported cross sectional study in chinese industrial workers showed *CDH23* associated with NIHL (42).*CDH23* SNPs inspected in 93/101 workers showed hearing loss only two reported as associated with NIHL. SNPs of rs3802711 with T/T genotype were more prevalent than C/T genotype. When examined exon 7 from terminal position it was suggested that individuals with G/G genotype were more prone to noise than A/G genotype. When different parameters such as gender, age, noise history and smoking C/C genotype at the SNPs rs1227049 suggested as linked with G/G genotype. More than 35 SNPs in *CDH23* have been reported in controlled population which was associated with NIHL (43).

CONNEXINS

Connexins are intercellular channels known as gap junctions. The movement of small metabolites and molecules from cell to cell occurs by these gap junctions that form pores among neighboring cells (44, 45). Connexins 26 (*Cx26*) is encoded by GJB2 (*DFNB1*) which is a most common gene involved in deafness (46). 25delG mutation is most frequent mutation in Caucasians that eventually leads to the truncation of connexins 26 and hearing loss. Other mutations in *GJB1 (Cx32), GJA1 (Cx43), GJB3 (Cx31), GJB4 (Cx30.3)* and *GJB6 (Cx30)* have played an important role in non-syndromic hearing loss. In a study of

702 polish GJB 235delG carriers, no correlation was found between GJB2 and vulnerability to noise induced hearing loss (47). An important association was found for single nucleotide polymorphism (SNPs) in *KCNQ1, KCNJ10, GJB1, GJB2 and GJB4*, that is suggestive of these genes involvement in noise induced hearing loss. Future studies on these SNPs in other populations will be essential for confirmation of these genes role in NIHL (48).

Table I. Detail of genes involved in NIHL with reference to their different parameters

Pathways	Genes	Protein	Function	SNPs Involved	Location	References
Antioxidant Pathway	PON1, PON2 and PON3	Paraoxanase	Antioxidant	rs1202, rs 7785846,	7q (21.3-22.1)	(2, 28-32)
	ATP2B2	PMCA2	Calcium Homeostasis	Rs1719571, rs3209637, rs4327369	3p25	(2)
	SOD1 & SOD2	SOD	Superoxide metabolism	IVS3-23T/G and IVS3-60T/G	chromosomal region 21q22	(33, 34)
Apoptotic Pathway	CASP 3	Caspase 3	Apoptosis	Rs1049216, rs6948	4q35.1	(10)
Potassium Recycling Genes	KCNE1	-	strength of the cochlear amplifier	rs2070358, rs1805127, rs1805128	21q22.12	(32)
	KCNQ1	-	-	rs163171	11p15.5-15.4	(32)
	KCNQ4	-	-	rs34287852	1p34.2	(32)
	KCNJ10	-	-	rs1130183	1q23.2	(32)
	KCNMA1	-	-	-	10q22.3	(11)
Heat Shock	Hsp70	Hsp70	Sound conditioning	Rs2227956, rs1043618	Human chromosomes 6,14,21	(28, 32, 35)
	Cdh23 gene	Cadherin	congenital deafness(stereocilia at the top of sensory hair cells)	rs1227049, rs1227051, rs3802711	10q21–q22	(32, 36-39)
Gap junction protein	GJB2	Connexin 26	Deafness	235delG	13q12	(23, 40)
	MYH14	Myosin Heavy chain	-	Rs667907, rs588035	19q13.33	(28)

MYOSIN HEAVY CHAIN

People with *DFNA4* gene mutations can suffer from sensori-neural hearing loss. Non-muscle heavy chain that is encoded by gene *MYH14* is common mutation in *DFN4* (49). Inside a newborn mouse cochlea, *MYH14* expresses in organ of corti in cochlea, stria vascularis and other cells like Hansen cells, Claudius cells and epithelium layer of spiral prominence. Regardless of its roll in hearing loss and vital rolls in ear by other unconventional myosin, *MYH14* function is not known entirely. SNPs in the *MYH14* gene were among those 53 genes that were screened for NIHL in Poland and Sweden people.

rs667907 and rs588035 are the two SNPs that were found to have an association with NIHL susceptibility (48).

SOD1 & SOD2

The joint effect of SOD, catalase and other enzymes involved in glutaredoxin, anti-oxidative glutathione and thioredoxin systems is required for metabolism of the superoxide and their derived peroxides. Diminished activity in one the above components can lead to the decreased anti oxidative ability of component and enhanced ROS/RNS damage. From five single nucleotide polymorphisms, two intronic polymorphisms (SOD IVS3-23T/G and IVS3-60T/G) were found to be paralleled with noise induced hearing loss. However functional consequences that occur due to these polymorphisms are not clear due to the presence of polymorphism in intronic region (50).

CONCLUSION

By using prevention approaches and today's technology, occupational hearing loss can be prevented (63). Regular audiometric testing every year for the hearing loss detection along with preventive measures to bar any further loss is important (63, 64). Lost hearing of workers suffering from occupational hearing loss can't be reversed however can be optimized by clinical therapy including hearing aids fitting, lip-read learning and other compensative strategies. Precautionary measures, timely diagnosis of the disease, adopting intervention and clinical therapies, might help to greatly recover patients. Up till now, there is no test available at the genetic level to diagnose NIHL. Ongoing genetic studies on mice for underlying mutations will help in future for genetic susceptibility of noise induced hearing loss in humans. At present time it is not possible to sequence all those genes which play a dynamic role in resistance or susceptibility to noise for finding the variation in one individual. However, with advancements in the genome sequencing and expected decrease in cost, it may be possible one day in future to sequence a person's entire genome in a cost effective way aimed at understanding collective effects of the multiple genes that make a person subject to noise induced hearing loss.

References:

1. Sliwińska-Kowalska M, Pawelczyk M, Kowalski TJ. Genetic factors in susceptibility to age-and noise-related hearing loss. Polski Merkuriusz Lekarski: Organ Polskiego Towarzystwa Lekarskiego. 2006;21(124):384-8.
2. Yamasoba T, Lin FR, Someya S, Kashio A, Sakamoto T, Kondo K. Current concepts in age-related hearing loss: epidemiology and mechanistic pathways. Hearing research. 2013;303:30-8.
3. Fujimoto C, Yamasoba T. Oxidative stresses and mitochondrial dysfunction in age-related hearing loss. Oxidative medicine and cellular longevity. 2014;2014.
4. Kobel M, Le Prell CG, Liu J, Hawks JW, Bao J. Noise-induced cochlear synaptopathy: Past findings and future studies. Hearing research. 2017;349:148-54.
5. Yankaskas K, Hammill T, Packer M, Zuo J. Auditory injury-A military perspective. Hearing research. 2017;349:1.

6. Konings A, Van Laer L, Michel S, Pawelczyk M, Carlsson P-I, Bondeson M-L, et al. Variations in HSP70 genes associated with noise-induced hearing loss in two independent populations. European Journal of Human Genetics. 2009;17(3):329-35.
7. Heinrich U-R, Feltens R. Mechanisms underlying noise-induced hearing loss. Drug Discovery today: disease mechanisms. 2006;3(1):131-5.
8. Harding GW, Bohne BA, Vos JD. The effect of an age-related hearing loss gene (Ahl) on noise-induced hearing loss and cochlear damage from low-frequency noise. Hearing research. 2005;204(1-2):90-100.
9. Śliwińska-Kowalska M, Dudarewicz A, Kotyło P, Zamysłowska-Szmytke E, Pawlaczyk-Łuszczyńska M, Gajda-Szadkowska A. Individual susceptibility to noise-induced hearing loss: choosing an optimal method of retrospective classification of workers into noise-susceptible and noise-resistant groups. International journal of occupational medicine and environmental health. 2006;19(4):235-45.
10. Choi SH, Choi C-H. Noise-induced neural degeneration and therapeutic effect of antioxidant drugs. Journal of audiology & otology. 2015;19(3):111.
11. Yamashita D. Oxidative Stress in Noise-Induced Hearing Loss. Free Radicals in ENT Pathology: Springer; 2015. p. 147-61.
12. Dobie RA. The relative contributions of occupational noise and aging in individual cases of hearing loss. Ear and hearing. 1992;13(1):19-27.
13. Gong T-W, Lomax MI. Genes that influence susceptibility to noise-induced hearing loss. Noise-Induced Hearing Loss: Springer; 2012. p. 179-203.
14. Carlsson P-I, Van Laer L, Borg E, Bondeson M-L, Thys M, Fransen E, et al. The influence of genetic variation in oxidative stress genes on human noise susceptibility. Hearing Research. 2005;202(1-2):87-96.
15. Conway H, Simmons J, Talbert T. The purposes of occupational medical surveillance in US industry and related health findings. Journal of Occupational and Environmental Medicine. 1993;35(7):670-86.
16. Falasca V, Greco A, Ralli M. Noise induced hearing loss: the role of oxidative stress. Otolaryngol Open J. 2017;5:1-5.
17. Pawelczyk M, Van Laer L, Fransen E, Rajkowska E, Konings A, Carlsson PI, et al. Analysis of Gene Polymorphisms Associated with K+ Ion Circulation in the Inner Ear of Patients Susceptible and Resistant to Noise-induced Hearing Loss. Annals of human genetics. 2009;73(4):411-21.
18. Lavinsky J, Ge M, Crow AL, Pan C, Wang J, Salehi P, et al. The genetic architecture of noise-induced hearing loss: Evidence for a gene-by-environment interaction. G3: Genes, Genomes, Genetics. 2016;6(10):3219-28.
19. Schwender H, Ruczinski I, Ickstadt K. Testing SNPs and sets of SNPs for importance in association studies. Biostatistics. 2011;12(1):18-32.
20. Le TN, Straatman LV, Lea J, Westerberg B. Current insights in noise-induced hearing loss: a literature review of the underlying mechanism, pathophysiology, asymmetry, and management options. Journal of Otolaryngology-Head & Neck Surgery. 2017;46(1):41.
21. Rabinowitz PM. The public health significance of noise-induced hearing loss. Noise-induced hearing loss: Springer; 2012. p. 13-25.
22. Win KN, Balalla NB, Lwin MZ, Lai A. Noise-induced hearing loss in the police force. Safety and health at work. 2015;6(2):134-8.
23. Musiba Z. The prevalence of noise-induced hearing loss among Tanzanian miners. Occupational Medicine. 2015;65(5):386-90.
24. Robinson T, Whittaker J, Acharya A, Singh D, Smith M. Prevalence of noise-induced hearing loss among woodworkers in Nepal: a pilot study. International journal of occupational and environmental health. 2015;21(1):14-22.
25. Sliwinska-Kowalska M, Pawelczyk M. Contribution of genetic factors to noise-induced hearing loss: a human studies review. Mutation Research/Reviews in Mutation Research. 2013;752(1):61-5.
26. Smoorenburg GF. Speech reception in quiet and in noisy conditions by individuals with noise-induced hearing loss in relation to their tone audiogram. The journal of the acoustical society of America. 1992;91(1):421-37.
27. Liu Y-M, Li X-D, Guo X, Liu B, Lin A-H, Rao S-Q. Association between polymorphisms in SOD1 and noise-induced hearing loss in Chinese workers. Acta oto-laryngologica. 2010;130(4):477-86.

28. Li X, Cao J, Wang J, Song H, Ji G, Dong Q, et al. PON2 and ATP2B2 gene polymorphisms with noise-induced hearing loss. Journal of thoracic disease. 2016;8(3):430.
29. Basner M, Babisch W, Davis A, Brink M, Clark C, Janssen S, et al. Auditory and non-auditory effects of noise on health. The lancet. 2014;383(9925):1325-32.
30. Grondin Y, Bortoni ME, Sepulveda R, Ghelfi E, Bartos A, Cotanche D, et al. Genetic polymorphisms associated with hearing threshold shift in subjects during first encounter with occupational impulse noise. PLoS One. 2015;10(6):e0130827.
31. Committee HC. ACOEM evidence-based statement: noise-induced hearing loss. Journal of occupational and environmental medicine. 2003;45(6):579.
32. Baig A. Biological Properties, Clinical Implications and Role as Oxidative Biomarker of Human Paraoxonase: University of Karachi, Karachi.; 2018.
33. Zhang S, Ding E, Yin H, Zhang H, Zhu B. Research and Discussion on the Relationships between Noise-Induced Hearing Loss and ATP2B2 Gene Polymorphism. International Journal of Genomics. 2019;2019.
34. Wu Y, Ni J, Qi M, Cao C, Shao Y, Xu L, et al. Associations of genetic variation in CASP3 gene with noise-induced hearing loss in a Chinese population: a case–control study. Environmental Health. 2017;16(1):78.
35. Wangemann P. Supporting sensory transduction: cochlear fluid homeostasis and the endocochlear potential. The Journal of physiology. 2006;576(1):11-21.
36. Niu X, Canlon B. Protective mechanisms of sound conditioning. Advances in Otorhinolaryngology. 2002;59:96-105.
37. Konings A, Van Laer L, Pawelczyk M, Carlsson P-I, Bondeson M-L, Rajkowska E, et al. Association between variations in CAT and noise-induced hearing loss in two independent noise-exposed populations. Human molecular genetics. 2007;16(15):1872-83.
38. Müller U. Cadherins and mechanotransduction by hair cells. Current opinion in cell biology. 2008;20(5):557-66.
39. Sakaguchi H, Tokita J, Müller U, Kachar B. Tip links in hair cells: molecular composition and role in hearing loss. Current opinion in otolaryngology & head and neck surgery. 2009;17(5):388.
40. Bork JM, Peters LM, Riazuddin S, Bernstein SL, Ahmed ZM, Ness SL, et al. Usher syndrome 1D and nonsyndromic autosomal recessive deafness DFNB12 are caused by allelic mutations of the novel cadherin-like gene CDH23. The American Journal of Human Genetics. 2001;68(1):26-37.
41. Ahmed ZM, Riazuddin S, Ahmad J, Bernstein SL, Guo Y, Sabar MF, et al. PCDH15 is expressed in the neurosensory epithelium of the eye and ear and mutant alleles are responsible for both USH1F and DFNB23. Human molecular genetics. 2003;12(24):3215-23.
42. Yang M, Tan H, Zheng J, Wang F, Jiang C, He M, et al. Association of cadherin CDH23 gene polymorphisms with noise induced hearing loss in Chinese workers. Wei Sheng yan jiu= Journal of Hygiene Research. 2006;35(1):19-22.
43. Sliwinska-Kowalska M, Noben-Trauth K, Pawelczyk M, Kowalski TJ. Single nucleotide polymorphisms in the cadherin 23 (CDH23) gene in Polish workers exposed to industrial noise. American Journal of Human Biology. 2008;20(4):481-3.
44. Kikuchi T, Adams JC, Miyabe Y, So E, Kobayashi T. Potassium ion recycling pathway via gap junction systems in the mammalian cochlea and its interruption in hereditary nonsyndromic deafness. Medical electron microscopy. 2000;33(2):51-6.
45. Zhao H-B, Kikuchi T, Ngezahayo A, White T. Gap junctions and cochlear homeostasis. The Journal of membrane biology. 2006;209(2-3):177.
46. Gabriel H, Kupsch P, Sudendey J, Winterhager E, Jahnke K, Lautermann J. Mutations in the connexin26/GJB2 gene are the most common event in non-syndromic hearing loss among the German population. Human mutation. 2001;17(6):521-2.
47. Van Eyken E, Van Laer L, Fransen E, Topsakal V, Hendrickx J-J, Demeester K, et al. The contribution of GJB2 (Connexin 26) 35delG to age-related hearing impairment and noise-induced hearing loss. Otology & Neurotology. 2007;28(7):970-5.
48. Konings A, Van Laer L, Wiktorek-Smagur A, Rajkowska E, Pawelczyk M, Carlsson P, et al. Candidate Gene Association Study for Noise-induced Hearing Loss in Two Independent Noise-exposed Populations. Annals of human genetics. 2009;73(2):215-24.

49. Donaudy F, Snoeckx R, Pfister M, Zenner H-P, Blin N, Di Stazio M, et al. Nonmuscle myosin heavy-chain gene MYH14 is expressed in cochlea and mutated in patients affected by autosomal dominant hearing impairment (DFNA4). The American Journal of Human Genetics. 2004;74(4):770-6.
50. Mohammadi S, Mazhari MM, Mehrparvar AH, Attarchi MS. Cigarette smoking and occupational noise-induced hearing loss. European journal of public health. 2010;20(4):452-5.
51. Konings A, Van Laer L, Van Camp G. Genetic studies on noise-induced hearing loss: a review. Ear and hearing. 2009;30(2):151-9.
52. Fortunato G, Marciano E, Zarrilli F, Mazzaccara C, Intrieri M, Calcagno G, et al. Paraoxonase and superoxide dismutase gene polymorphisms and noise-induced hearing loss. Clinical chemistry. 2004;50(11):2012-8.
53. Li X-T, Li X, Hu F-F, Shen H-X, Cao J-L, Zhong L, et al. Association between paraoxonase 2 gene polymorphisms and noise-induced hearing loss in the chinese population. Journal of occupational health. 2013:12-0242-OA.
54. Wu S, Yu J, Jiao J, Chen G, Zhang C, Yu S. Association between PON2 gene polymorphisms and susceptibility to noise-induced hearing loss. Zhonghua lao Dong wei Sheng zhi ye Bing za zhi= Zhonghua Laodong Weisheng Zhiyebing Zazhi= Chinese Journal of Industrial Hygiene and Occupational Diseases. 2020;38(2):128-32.
55. Bhatt IS, Dias R, Washnik N, Wang J, Guthrie On, Skelton M, et al. Association Analysis of Candidate Gene Polymorphisms and Audiometric Measures of Noise-Induced Hearing Loss in Young Musicians. Otology & neurotology: official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology. 2020;41(5):e538.
56. Sherman L, Dafni N, Lieman-Hurwitz J, Groner Y. Nucleotide sequence and expression of human chromosome 21-encoded superoxide dismutase mRNA. Proceedings of the National Academy of Sciences. 1983;80(18):5465-9.
57. Jamesdaniel S, Rosati R, Westrick J, Ruden DM. Chronic lead exposure induces cochlear oxidative stress and potentiates noise-induced hearing loss. Toxicology letters. 2018;292:175-80.
58. Harrison GS, Drabkin HA, Kao F-T, Hartz J, Hart IM, Chu EH, et al. Chromosomal location of human genes encoding major heat-shock protein HSP70. Somatic cell and molecular genetics. 1987;13(2):119-30.
59. Grillet N, Schwander M, Hildebrand MS, Sczaniecka A, Kolatkar A, Velasco J, et al. Mutations in LOXHD1, an evolutionarily conserved stereociliary protein, disrupt hair cell function in mice and cause progressive hearing loss in humans. The American Journal of Human Genetics. 2009;85(3):328-37.
60. Morita Y, Hirokawa S, Kikkawa Y, Nomura T, Yonekawa H, Shiroishi T, et al. Fine mapping of Ahl3 affecting both age-related and noise-induced hearing loss. Biochemical and biophysical research communications. 2007;355(1):117-21.
61. Davis R, Kozel P, Erway L. Genetic influences in individual susceptibility to noise: a review. Noise and Health. 2003;5(20):19.
62. Di Palma F, Holme RH, Bryda EC, Belyantseva IA, Pellegrino R, Kachar B, et al. Mutations in Cdh23, encoding a new type of cadherin, cause stereocilia disorganization in waltzer, the mouse model for Usher syndrome type 1D. Nature genetics. 2001;27(1):103-7.
63. Themann C, Suter AH, Stephenson MR, editors. National research agenda for the prevention of occupational hearing loss—Part 1. Seminars in Hearing; 2013: Thieme Medical Publishers.
64. Chien W, Lin FR. Prevalence of hearing aid use among older adults in the United States. Archives of internal medicine. 2012;172(3):292-3.