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Mini Review

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Genetics of Hearing Impairment; An Indian Perspective

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Abstract

Deafness caused due to mutations in more than 400independent genes as a series of etiologically heterogeneous disorders. However, in diverse Indian population several studies have been conducted and causes for syndromic and non syndromic forms of deafness occurs because of the defects in just few genes. In India high prevalence of genetic disorders is associated with the consanguineous marriages. Each year in Indian population (approximately 1.2 billion) 30,000 infants are affected with this disorder; congenital hearing loss. For genetic counselling, early diagnosis for timely intervention and treatment options, knowledge of genetic causes of hearing loss is important. Now days in hospitals many sources and technologies are available for the testing of hearing loss. Translating genetic and genomic advances into population healthgains, one of the major strategy is population based screening. This review article of the deafness in Indian population deals with the major causes of deafness with special focus on Indian population.

Keywords: Hearing Impairment; Sensorineural Non Syndromic Hearing Loss; Gap Junction Beta 2; India; Genetic Variation

Abbreviations

HI: Hearing Impairment; HL: Hearing Loss; CMV: Cytomegalovirus; WHO: World Health Organization; dB: Decibel; NSS: National Sample Survey; SNHL: Sensorineural Non Syndromic Hearing Loss; GJB2: Gap Junction Beta 2; POU3F4: POU Class 3 Homeobox 4; EYA4: Eyes Absent Transcriptional Coactivator and Phosphatase 4; TFCP2L3: Transcription Factor CP2; TMC1: Transmembrane Channel-Like Protein 1; TMIE: Trans Membrane Inner Ear; KCNQ4: Potassium Voltage-Gated Channel Subfamily Q Member 4

Introduction

General introduction

One of the most common sensory disorders is Hearing Impairment (HI) which affects millions of people worldwide, this defect is due to multiple factors such as genetics and environmental. Childhood permanent congenital HL is 1.2 to 1.7 cases per1000 live births .Major causes for non-genetic SNHL include exposure to noise, bacterial and viral infection, ototoxic drugs etc. Hearing loss may occur when the noise levels exceed 75-80 dB [1]. It also depends on duration and number of exposures which also increase the risk. Bacterial and viral infections may also produce mild to severe hearing loss. With the development of rubella vaccine and Rhogam, CMV may have become the most common cause of congenital deafness and approximately 50%cases are affected by these environmental factors. The other 50% of cases are by due to inherited genetic factors [2]. The proteins which are involved in cytoskeletal and extracellular matrix components, receptors, ion homeostasis, transcription factors, cellular trafficking proteins, molecules of the cadherin superfamily may also be responsible for hearing impairment with or without syndromic characteristics in one or the other way [3]. These hereditary cases are again classified into syndromic and non-syndromic deafness. In that, around 30% are syndromic cases. Syndromic hearing loss is associated with about 400 named syndromes and associated auditory features being often variable as sensorineural or conductive, unilateral or bilateral, and progressive and stable. Physicians readily diagnose these syndromic associated hearing loss patients due to the recognisable features. The other 70% of inherited cases are nonsyndromic. Nonsyndromic hearing loss children are perfectly normal exception of hearing loss [1,2].

Screening of hearing impairment

Various countries throughout them have started screening of new born babies for hearing impairment as per World Health Organization (WHO) protocols. New born and infant hearing screening in some countries has become an early detection whereas in other countries, such screening is considered to be too costly and its value is questioned. Screening is performed on a national basis in China, the United States (non-compulsory), Germany and the Philippines (mandatory). Countries like Brazil, India, Seria, screening is performed at the district or other sub-national levels. Most commonly screening is done by nurses (China, Germany, Serbia, and the United States); by audiologists/technicians (Brazil, India); by midwives and physicians (Germany and Serbia) [4].

Grade of impairment Performance	Corresponding audiometric ISO value	Performance/speech discrimination score of better ear	Percentage of disability	Recommendations
0 – No Impairment	25dB or better (better ear)	No or very slight hearing problems. Able to hear whispers		
1 – Mild impairment	26 – 40dB (better ear)	Able to hear and repeat words spoken in normal voice at 1meter. (8100%)	< 40%	Counselling. Hearing aids may be needed
2 – Moderate Impairment	41 – 60dB (better ear)	Able to hear and repeat words spoken in raised voice at 1 meter. (50-80%)	40-50%	Hearing aids usually Recommended
3– Severe impairment	61 – 80dB (better ear)	Able to hear some words when shouted in better ear. (40-50%)	51-70%	Hearing aid needed. If no hearing aid available, lip-reading and signing. Should be taught.
4 – Profound impairment including deafness	81dB (greater or better ear)	Unable to hear and understand even a Shouted voice. (>40%).	71-100%	Hearing aid may help Understanding words. Additional rehabilitation needed. Lip-reading and sometimes signing essential

Table 1: WHO Hearing impairment grades [5].

Genetics of hearing impairment

Non-syndromic genetic deafness is inherited as the autosomal dominant (22%), autosomal recessive (75%) and X-linked (3%). Deafness associated genes are designated as the DFN-A (for autosomal dominate gene), DFN-B (for autosomal recessive gene) and DFN (for X-linked gene) [6,7]. Inheritance pattern of autosomal recessive deafness is typically found in normal hearing parent's child which will be born with bilateral, profound hearing impairment. Those are affected with autosomal dominant inheritance pattern, severity and progression varies and also has a hearing-impaired parent. X- Linked pattern of inheritance is very less common condition, which is associated with only sex chromosome. Most of the genetic hearing losses are interestingly caused by defects in the single gene. Till date more than 50 deafness causing genes have been studied, half of them are involved in the syndromic cases of deafness. More than 100 of genes are yet to be studied [7]. Connexin-26 gene is the most common nonsyndromic deafness causing gene worldwide. This is the gap junction protein, which is present in the inner ear and helps to regulate the K+ ion concentration which is importance in the hearing [5,8].

Auditory system is the one of the complex sound transduction process, and numerous genes are involved in this complex process of hearing. Previous studies on deafness targeted the genes and their products involved in the deafness. For non syndromic hearing loss around 80 genes chromosomal locations are reported and half the gene in these loci is mapped. From transcriptional factors (POU3F4, EYA4, TFCP2L3), motor molecules (myosin 2, 6,7 and 15), ion channel, transporter (pendrin, KCNQ4), integral membrane protein (TMC1, TMIE), adhesion molecules (cadherin and protocadherin), gap junction proteins (connexins 26, 30, 31 and 43), extracellular protein and many other novel molecules [9], these are the ranges of the genes protein products which are involved in the sound transduction mechanism. Understanding the function of these protein products will help to dig inside the complex mechanics of sound transduction in the inner ear [10].

Indian status

An individual is classified as hearing handicapped only when, hearing impairment is 70dB and above, in better ear or total loss of hearing in both ears.A person with hearing levels of 61 to 70dB is automatically excluded from the hearing handicap category, as per the Rehabilitation Council of India Act, 1992 by the Indian constitution [7,13].

Prevalence and incidence of disability

In India, 63 million people (6.3%) suffer from significant hearing loss [11]. Comparing the prevalence of disability, found in National Sample Surveys which conducted at different points oftime helps to get the idea about the magnitude of the disability. 58th

Round of NSS Survey estimated persons with disability to be 18.49 million (1.8 per cent of the total population) [7]. And also found that hearing disability was 2nd most common cause of among all disability and top most cause of sensory deficit. Loss was 9%in urban areas and it was 10% in rural areas.

According to previous study, hearing impairment was estimated that the number of person with hearing impairment per 100000 persons was 291; in Rural population it was higher; 310 per 100000 person and in urban regions it was 236 per 100000 person [11]. In the same study, about 32% of the people had profound (person could not hear at all or could hear only loud sounds) and 39% had severe hearing disability (person could hear only shouted words). As per the survey results about 7% of people were born with a hearing disability. About 56% and 62% reported the onset of hearing disability at ≥ 60 years of age in the rural and urban areas, respectively. The incidence of hearing disability during that year was reported to be 7 per 100000 populations [11,12].

Etiology for deafness

Dr. Mangal Singh., *et al.* sharing his 10 years' experience of deaf mute children and mentioned, 33% non-genetic causes of his total patients as the etiological agents.

Non-genetic cause: Non-genetic causes for Hearing disabilityis 33.3%.

Embryopathies

- a. Infection b. Toxaemia of pregnancy c. First trimester bleeding d. Ototoxicdrugs e. Jaundice f. Rh incompatibility

Perinatal causes (10.8%)

- a. Low Apgar score b. Low birth weight (<2.5 kg) or prematurity c. Breech presentation d. Post-term.

Post-natal causes (12.5%)

- a. Eruptive fever b. Meningitis c. Hyper bilirubinemiad. Traumatice. Cerebral palsy f. Delayed mi1estones.

Genetic cause: Genetic causes for Hearing disability is 15.8%.

Family history (10.8%)

- a. Paternal b. Maternal c. Siblings

Congenital syndrome (5.4%)

- Idiopathic (50.6%) [14].

Various Indian studies showed with regional variations 3 most common mutations are recorded namely, W24X, W77X, and 124 X and also 35delG and these were the major GJB2 mutations.

Found in the Indian families. The major mutation observed in the population is Bi-allelic W24X, Mutant alleles W77X, Q124X and MIV contributing by small numbers. In few families recorded with the 35delG mutation [10]. Biallelic W24X mutations, in north India showed the lower prevalence. And Indian studies showed W77X and Q124X mutations are occurred more common in the north. In the southern states of Tamilnadu, Karnataka, Kerala and Andhra Pradesh widespread mutation in the GJB2 gene was the biallelic W24X mutation [10]. Number of families and patients were included for the study so far in India was very less, hence it may not be true representative so more number of studies have to be done for the genetic knowledge.

Gene and Locus	Protein and Function	Nucleotide change	Amino acid change	Prevalence	Phenotype
DFNB1/GJB2 (13q12.11)	Connexin 26 gap junction protein is mainly involved in recycling of ions.	c.71G>A	W24X	3.886.7% [15,16]	Prelingual, usually severe to profound (can be variable)
		c.231G>A	W77X	0.5-5.9% [16,17]	
		35delG		10.9% [15]	
		235delC		0.5-3% [16,18]	
		Del of GAG at 360	Del E120	0.8-1.7% [15,19]	
		c.370C>T	Q124X	<1% [19]	
		c.487A>G	M163V	<1% [16]	
		c.95G>T	R32L	<1% [20]	
		IVS1+1G->A		0.3-4.68% [16,18]	
		167del T		<1% [16]	
		c.1A>G	M1V		
		c.408C>A	Y136X		
		c.98T>C	I33T		
		c.104T>G	I35S	<1% [19]	
		c.223C>T	R75W		
		c.427C>T	R143W		
		c.514T>A	W172R		
		c.511G>C	R184P		
		c.313_326del	K105fsX109		
		c.377_383dup	E129fsX211		

DFNB3/MYO1A (17p112)	Myosin15A; is a motor molecule required for actin organization sain the hair cells of the cochlea and is important for Maturation hair cell.	c.26668 A>T	N890Y	6 families [21,22]	Prelingual severe to profound sensorineura ldefeness. May be associated with a less severe hearing loss with some residual hearing at low frequencies.
		c.3758C4T	T1253I		
		c.4351C4A	D1451N		
		c.3898 A>T	K1300X		
DFNB9/OTOF (2p23.3)	Otoferlin involved in vesicle membrane fusion	IVS8-2A->G		1 family [23]	Prelingual to profound defeness. May be associated with auditory neuropathy.
DNFB8/10/TMPRSS3 (21q22.3)	Transmembrane serine protease 3 required for the development and mainainance of the inne rear or the contents of the perilymph and endolymph.	c.323_6G>A		1.2% [24]	Childhood onset (10-12 years) affecting all frequencies or preligual profound deafness.
		c.3466G>A	V116M		
		c.727G>A	G243R		
		c.1156T>C	C386R		
DFNB7/11/TMC1 (9q21.13)	Trans membrane channel like protein1; involved in mechano-electrical transduction of sound by cochlear hair cells.	c.100C>T	p.R34X		Prelingual profound hearing loss
		c. 237_6T>G			
		c. 453+2T>C			
		c.628_630del	p.I210del		
		c.800G>A	p.G267E	1.6% (24) (25)	
		c.1114G>A	p.V372M		
		c.1333C>T	p.R445C		
		c.1566+1G>A			
DFNB18/USH1C (11p15.1)	Pdz domain-containing protein is part of a transmembrane complex that connects stereocilia into a bundle necessary for normal hearing	c.i87C>T	p.R63H		Prelingual profound hearing loss
		c.267G>A	p.R89H		
		c.388-8T>A		51 Families (24) (26)	
		c.496+1G>A			
		c.598G>A	p.G200S		
		c.876+6T>C			
		c.i084C>T	p.Q362X		
		c. 1858C>T	p.R620C		
		c.2410G>A	p.A804T		
		c.2611G>A	p.A871T		
		IVS12+5G—C			
		IVS12+5G—C			
		IVS5+1G—A			
		238-239insC			
		769_ins36bp_insC			
DFNB12/CDH23 (10q22.1)	Cadherin23 expressed in the stereocilia. Allelic of hair cells, supports calcium-dependent cell-cell adhesion	c.189_190inC			Prelingual profound deafness
		c.415G>A	p.V1391		
		c.429 +4G>A			
		c.2752G>A	p.D918N	1.8% (24)	
		c.2968G>A	p.D990N		
		c.5101G>A	p.E1701K		
		c.5660C>T	p.T18871		
		c.7580C>T	p.S2527L		
DFNB6/TMIE (3p21.31)	Transmembrane inner ear-expressed gene involved in development of hair cellsrequired for correct development of stereocilia bundles. That is essential for the mechanoelectrical transduction of sound.	c.92A>G	p.E31G	1.6% (24)	Severe to profound prelingual deafness
		125-126insCGCC			
		250C>T	R84W 2	2 families (27)	

DFNB28/TRIOBP (22ql 3.1)	The Triobp-l is important for formation or stabilization of the	889C-+T	Q297X	4 families (28)	Prelingual severe to profound hearing loss
		3202_ 3203delCG	D1069fsXl O82		
		322<3226insC	R1078fsX 1083		
	cvtoskcletal structure of stereocilia and/or the cuticular plate, both actin-rich structures in sensory hair cells in the inner ear.	3349C> T	R11 17X		
DFNB39/HGF (7q21.11)	Hepatocyte growth factor.	c.482+ 1986 _1988delTGA		2 families (29)	Profound prelingual deafness involving all frequencies.
DFNB 15/GIPC3 (19p13.3)	GAIPc-terminus-interacting protein 3 required for postnatal maturation of the hair bundle and long-term survival of hair cells and spiral ganglion in the ear.	c.iS5T>G I	L262R	1 family (30)	Prelingual-onset hearing loss.

Table 2: Mutation of Nonsyndromic Hearing Loss in Indian population [31].

Conclusion

Persons with hearing impairment constitute significant portion of our population who can be contributing citizens. Efforts made to provide early diagnostic and therapeutic services and the efforts put forth to mainstream them will create an inclusive, barrier-free and rights-based society for persons with disabilities.

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