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Manuscript (Review Article)

A comprehensive review on inherited Sensorineural Hearing Loss and their syndromes

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Abstract

Hearing impairment is an immensely diagnosed genetic cause, 5% of the total world population effects with different kind of congenital hearing loss (HL). In third-world countries or countries where consanguineous marriages are more common the frequency rate of genetic disorders are at its zenith. Approximately, the incidence of hearing afflictions is ostensibly 7-8:1000 individuals whereas it is estimated that about 466 million peoples suffer with significant HL, and of theses deaf cases 34 million are children's up to March, 2020. Several genes and colossal numbers of pathogenic variants cause hearing impairment, which aided in next-generation with recessive, dominant or X-linked inheritance traits. This review highlights on syndromic and non-syndromic HL (SHL and NSHL), and categorized as conductive, sensorineural and mixed HL, which having autosomal dominant and recessive, and X-linked or mitochondrial mode of inheritance. Many hundred genes involved in HL are reported, and their mutation spectrum becomes very wide.

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Mapping of pathogenic genes in consanguinity family is facilitated to understand the disease history. Review presents the bases of HL and also focused on various genetic factors that cause deafness like the basics of genetic inheritance, and classic and well-characterized inherited factors of it. It also overviews the application of linkage analysis, SNPs genotyping and whole exome sequencing methods, in mapping and identification of new locus, causative genes and their variants in families inherited with HL. Conclusively, this review supports researchers in understanding the location of chromosome, the causative genes and specific locus which causing deafness in humans.

Keywords: Hereditary HL, genetics of syndromic and non-syndromic HL, methods for diseased locus/gene identification

Introduction

Deafness or hearing failures are seen as an extenuate form [1], in human it is one of the high prevailing neurosensory deficits that harshly negotiate the life value of individuals and can cause their social separation [2]. Both genetics and environmental factors cause hearing failure [3], and the genetic factors contributes about 50% of all hearing loss (HL) patients [4]. The worldwide estimated results report as of March, 2020 defines rounded 466 million peoples suffer with significant HL, and of theses deaf cases 34 million are children's (under 6 years old) (WHO MARCH 2020). Furthermore, before maturity 3/1000 children become deaf [5]. According to WHO prediction, hearing disability will affect ~900 million (or 1:10 peoples) by 2050 [6]. Basically, HL was categorized in two main groups non-syndromic sensorineural HL (NSHL) and syndromic sensorineural HL (SSHL). Genetic subsidizing factors to NSHL are remarkably diverse coverings, over autosomal (recessive and dominant), to X-linked (recessive and dominant), to mitochondrial patterns of inheritance [7]. The SSHL, hearing disability appeared with multiple physiological anomalies (diseases), and it is limited only to the inner ear [8].

Many hundreds or even thousands of genes are involved in hearing process and helps in proper functioning of inner ear, which is the most sensitive part of the ear in human body (figure 2B). Several genes and their expressed protein families like (Myosin family, Gap-junction family and solute carrier proteins etc.) in inner ear function as, in control of adhesion of hair cell, in neurotransmitter release, intercellular transport, maintenance of ionic homeostasis and protection of cytoskeletons of hair cells, which supports to hear a sound [9, 10].

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During the period of last 10-12 years, the identification rate of causative genes associated with hearing loss becomes very high. Several hundred genes associated with hearing loss are reported, and their mutation spectrum becomes very wide, so that identification of disease-causing mutation is still more difficult. Linkage studies and auto zygosity methods used for mapping and identification of pathogenic genes in consanguineous families and with the advancement in technologies, Next-generation Sequencing, target-enrichment method and sanger sequencing makes it easy to identifying the novel gene and their variant in inherited heterogeneous disorders [11-14]. Whole Exome Sequencing (WES), used as stream-line approach now a days, for identifying the disease causing (causative) gene variants (mutation), which results specific phenotypic disorder [10, 15]. This review presents an overview and description of the currently known genes related to hereditary HL. It reviews the basics of genetic inheritance, and also focusing on the classic and well-characterized, inherited factors that cause deafness. Brief overview of this review study shown in figure 1.

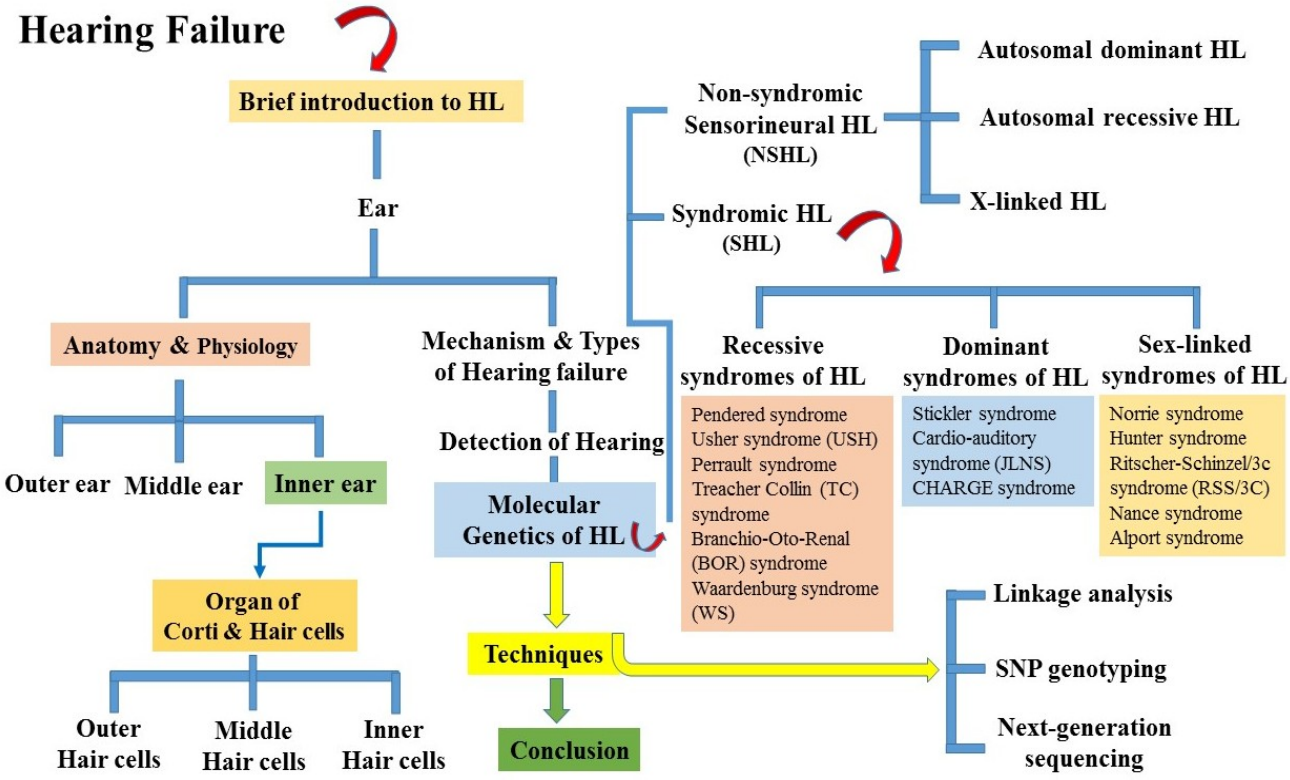

Figure 1: Overview and schematic illustration of complete review of literature.

Ear anatomy and physiology

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Auditory system of mammals is highly sensitive, integrated and the most complicated structure, which is planned to achieve both functions of interpreting the sound waves in an organized manner to nerve impulse and also to sustain the balance of the body. The vestibular systems of the human ear specific to sustain the balance of the body are composed of two parts: the membranous labyrinth and the bony labyrinth [16]. The function of the human ear is to collect sound waves from the sounding and interpret of these sound waves of different sound frequencies of range 20 to 20,000 Hz [17, 18]. Ear can be defined as a microcomputer or an analytic microphone, that conducts sound waves towards the brain in type of nerve impulse, and it is divided into three structural partitions, which works like a unit; the outer ear; pinna, the auditory canal, and the tympanic membrane, middle ear; tympanic cavity, Ossicles bones (incus, malleus, and stapes), middle ear muscles and Eustachian tube, and the inner ear that perform two functions, transduction of sound waves into neurochemical signals which completed in cochlea, a main functioning organ of the ear and to maintains the optic fixation and support to sustain sanding body posture that takes place in the vestibular system during the process of movement (figure 2A) [19-21].

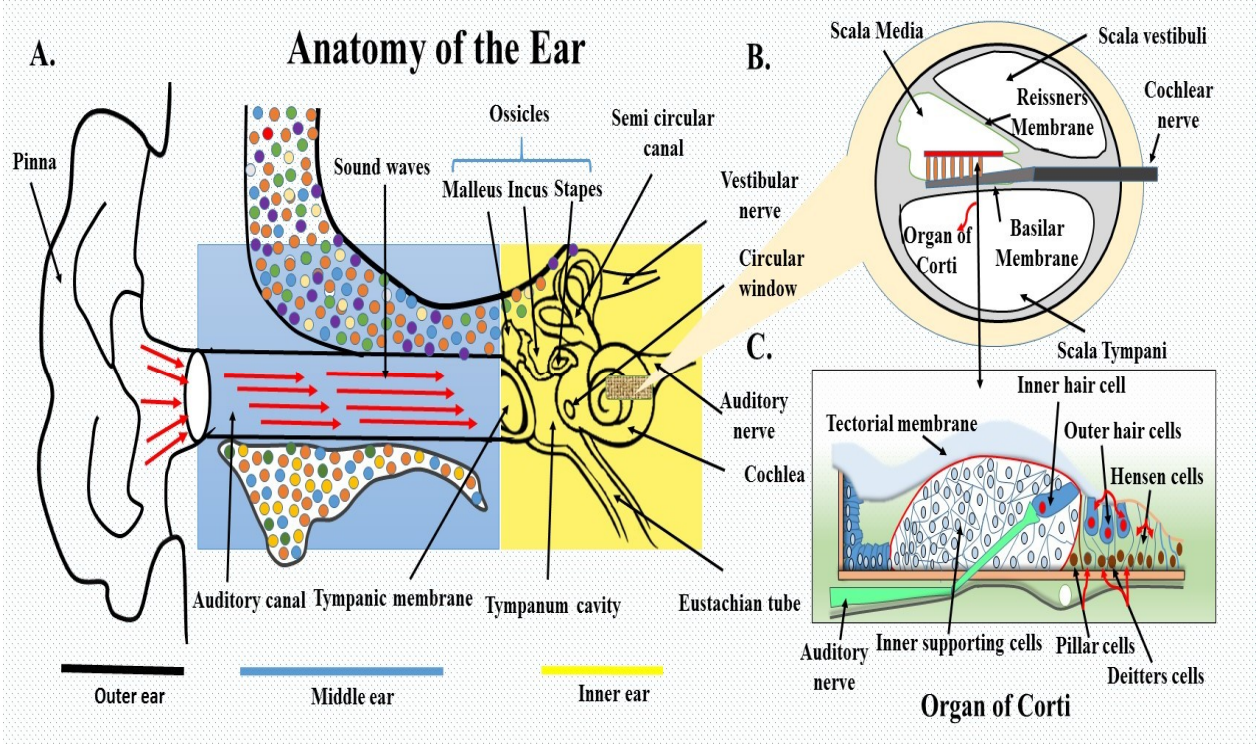

Figure 2: A. Outer ear the pinna and auditory canal separated from the middle ear by tympanic membrane. Ossicles (Malleus, Incus and Stapes) are positioned in middle ear and they connected

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to the Eustachian tube at the back of nose. The inner ear holds Cochlea and vestibular structures specific to generate nerve impulse and sustain balance of the body**. B.** Cochlea; the boney tube, filled with perilymph, in which membranous labyrinth floats filled with endolymphatic fluid. Perilymph separates the Scala media to Scala tympani. **C.** A cross-section of single piece Cochlea display comprehensive picture of the membranous labyrinth, and the Basilar membrane keeps the epithelial cells of hearing –the organ of Corti. The organ of Corti holds; inner hair cells (IHC's), three outer hair cells (OHC's), Hensen cells (HC's), Deitters cells (DC's), Pillar cells (PC's) and the Inner Supporting cells (ISC's) respectively. The auditory nerve linked to inner hair cell at their tip-link.

Organ of corti and hair cells

The power of identifying and separating the variable frequencies sounds of human cochlea mainly based on the portion of sensory epithelia named as organ of Corte; at the sensorineural end, the organ necessary for listening a sound (figure 2C) [22]. It contains placodal origin (membranous labyrinth) polarized epithelial cells (supporting and hair cells), the basil membrane (specialized basement membrane having layer of matrix), tectorial membrane and nerve endings [19, 23, 24]. In mammals, two types of hair cells are present, the inner hair cells (IHCs) and outer hair cells (OHCs). The "IHCs" actually the type of true sensory cell, transmits impulses through the auditory nerve, and OHCs are obliging in to increase the working capacity of the cochlea, quantitatively (increased sensitivity) and qualitatively (increased selectivity) [25, 26]. The name "hair" cell was derived from the tuft of stereocilia that protrude from the apical domain of every cell [21, 27, 28].

Mechanism and types of hearing failure

Hearing failure may be partial or complete and it developed either in response of a damage, injury, physiological causes or congenital diseases which specify as conductive HL [29].Whereas when any injury or damage occurs in the inner ear, brain or vestibular nerve caused sensorineural hearing loss (SNHL), and mixed hearing damage caused both conductive and SNHL. The SNHL mostly occurred due to genetic variations in genes that regulate the intracellular transport, the adhesion of hair cells, ionic homeostasis, neurotransmitter release and structure of hair cells results to damage of the cochlea and the inner ear [30]. In the current century, with new inventions of genetic variants in congenital hearing loss, new treatment opportunity and genetic counseling have appeared and improved in accessibility [31].

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Detection of hearing

Hearing level of suspects was evaluated through behavioral testing and pure tone audiometry. Behavioral testing includes visual reinforcement audiometry (VRA) and behavioral observation audiometry (BOA) [32]. VRA is used for testing hearing level of child between age from six months to 2 ½ years and can provide reasonable complete information for audiogram while the BOA is used for evaluating the hearing level of infants from birth to six month age and this kind of testing is highly dependents on the skills of the testing persons, and is subject to error [33, 34]. Pure tone audiometry means to identify the minimum frequency on which a person "hear" a pure tone, whereas the "bone conduction audiometry, depends on the sound waves reach the ear through a vibrator consists on the forehead mastoid bone, now the thresholds depend on the condition of the inner ear, by bypassing the outer and middle ear and the calculated/obtained values are plotted on a graph paper [35-38], for sample of audiogram (figure 3).

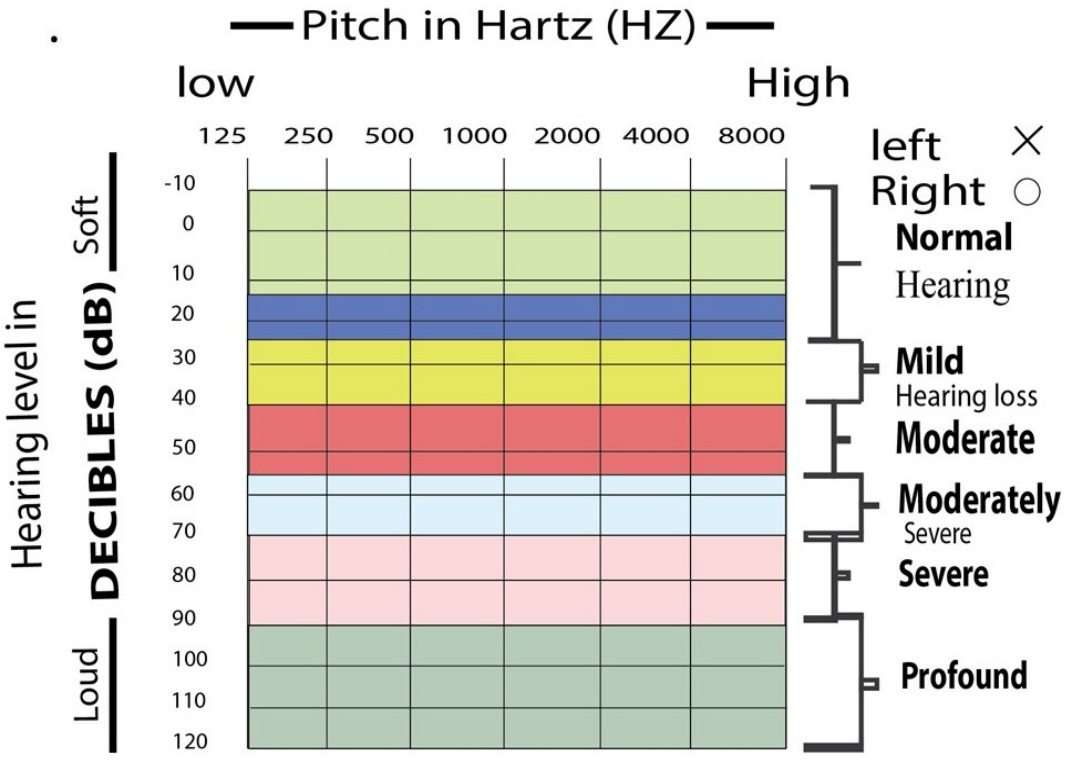

Figure 3: The audiogram sample, defining various types of hearing loss constructed on the basis of types of ear defect. Horizontal axis represents frequencies in "Hz" while the vertical axis on the graph represents sound intensity in "dB", and this graph is defined as an audiogram. In

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audiogram, the right ear is denoted with the symbol "O" and the left ear is denoted with symbol "X".

Molecular genetics of HL

Hearing failure is the most common sensory impairment. It shows highly heterogeneous behavior. The early 1990s, the identification and localization of genes causing deafness/HL is started, but till 1994 only a few gene loci have been mapped/identified on human genome; causing hearing loss/deafness either NSHL/SHL [27, 39]. Inherited HL consists 50–60% of all HL cases. The inherited form of HL is further classified to different categories [40-42]. Recent advances in genetics and genomics have led us to identification of over 300 SHLs and more than 100 chromosomal loci and more than 40 genes responsible for NSHL [30, 43, 44]. Better understanding of impaired genes and their structure and function will open a new window for screening as well as the genetic approach to treatment of HL. In contrast, the identification of the single causative gene of linking in NSHL becomes very difficult in a single family, because it needs positional cloning; the linkage analysis and WES make it feasible.

Non-syndromic sensorineural Hearing Loss (NSHL)

Hereditary HL (HHL) is an immensely studied neurosensory disorder in worldwide. It is highly heterogeneous genetic disorder, and most often autosomal recessive and non-syndromic is approximately 80% of congenital HL [11, 45-48]. Most of the studies on NSHL predominantly focused on three main aspects; the kind of hearing defect, its degree of severity, and the configuration or inheritance pattern. Almost 60% cases of the congenital HL are on the account of genetic factors [49]. In humans hearing failure is a sensory disability that ambits from mild, moderate, severe and profound. Approximately, the profound HL is comprised of 20-25%, while a higher ratio of individuals is damaged with moderate to severe HL [50].

Moreover, the NSHL are sorted in consonance with their inheritance patterns; as autosomal (dominant or recessive) or X-linked. Autosomal inheritance patterns of NSHL found ubiquitous, while the X-linked inheritance pattern found tremendously rare [51]. In pre-lingual HL; inherited X-linked trait (1%-3%), autosomal recessive trait (70%-80%), while autosomal dominant trait (12%-24%), and mitochondrial (2%-3%) are observed [52]. In the NSHL, either an autosomal dominant or recessive inheritance pattern characterizes thrilling genetic heterogeneity, as more than hundreds specific deafness-causing genes and loci have been mapped and reported to date (table 1), among these

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causative-genes, most of them were reported from Pakistan according to hereditary hearing loss homepage [53].

Table 1: Pathogenic genes, locus and their positions on chromosomes, causing non-syndromic hearing loss in Humans

MUTATED GENES OF HEREDITARY NON-SYNDROMIC HEARING LOSS							
Autosomal Recessive Inheritance				Autosomal Dominant Inheritance			
Gene	**Locus**	**Location**	**Ref.**	**Gene**	**Locus**	**Location**	**Ref.**
GJB2	*DFNB1*	*13q12*	[54]	*DIAPH1*	*DFNA1*	*5q31*	[55]
MYO7A	*DFNB2*	*11q13.5*	[56, 57]	*KCNQ4*	*DFNA2A*	*1p34*	[58]
MYO15A	*DFNB3*	*17p11.2*	[59, 60]	*GJB3*	*DFNA2B*	*1p35.1*	[61]
SLC26A4	*DFNB4*	*7q31*	[62, 63]	*IFNLR1*	*DFNA2C*	*1p34.1 – 1p36.12*	[64]
unknown	*DFNB5*	*14q12*	[65]	*GJB2*	*DFNA3A*	*13q11-q12*	[54]
TMIE	*DFNB6*	*3p14-p21*	[65, 66]	*GJB6*	*DFNA3B*	*13q12*	[67]
TMC1	*DFNB7/11*	*9p13-q21*	[68, 69]	*MYH14*	*DFNA4*	*19q13*	[70]
TMPRSS3	*DFNB8/10*	*21q22*	[71-73]	*CEACAM16*	*DFNA4B*	*19q13.32*	[74]
OTOF	*DFNB9*	*2p22-p23*	[72]	*GSDME*	*DFNA5*	*7p15*	[75]
CDH23	*DFNB12*	*10q21-q22*	[76]	*WFS1*	*DFNA6*	*4p16.3*	[77]

unknown	*DFNB13*	*7q34-36*	[78]	*LMX1A*	*DFNA7*	*1q21-q23*	[79, 80]
unknown	*DFNB14*	*7q31*	[78]	*TECTA*	*DFNA8*	*11q22-24*	[81]
GIPC3	*DFNB15*	*3q21-q25*	[82, 83]	*COCH*	*DFNA9*	*14q12-q13*	[84]
STRC	*DFNB16*	*15q21-q22*	[85]	*EYA4*	*DFNA10*	*6q22-q23*	[86]
unknown	*DFNB17*	*7q31*	[87, 88]	*MYO7A*	*DFNA11*	*11q12.3-q21*	[89]
USH1C	*DFNB18*	*11p14-15.1*	[90]	*TECTA*	*DFNA12*	*11q22-24*	[81]
unknown	*DFNB19*	*18p11*	[91]	*COL11A2*	*DFNA13*	*6p21*	[92]
unknown	*DFNB20*	*11q25-qter*	[93]	*WFS1*	*DFNA14*	*4p16.3*	[94]
TECTA	*DFNB21*	*11q*	[95]	*POU4F3*	*DFNA15*	*5q31*	[96]
OTOA	*DFNB22*	*16p12.2*	[97]	*unknown*	*DFNA16*	*2q24*	[98]
PCDH15	*DFNB23*	*10p11.2-q21*	[99]	*MYH9*	*DFNA17*	*22q*	[100]
RDX	*DFNB24*	*11q23*	[101]	*unknown*	*DFNA18*	*3q22*	[102]
GRXCR1	*DFNB25*	*4p13*	[103]	*ACTG1*	*DFNA20*	*17q25*	[104, 105]
unknown	*DFNB26*	*4p31*	[106]	*unknown*	*DFNA21*	*6p21*	[107]
unknown	*DFNB27*	*2q23-q31*	[108, 109]	*unknown*	*DFNA22*	*6q13*	[110]
TRIOBP	*DFNB28*	*22q13*	[111]	*unknown*	*DFNA23*	*14q21-q22*	[112]

CLDN14	*DFNB29*	*21q22*	[113]	*unknown*	*DFNA24*	*4q*	[114]
MYO3A	*DFNB30*	*10p11.1*	[115]	*unknown*	*DFNA25*	*12q21-24*	[116]
WHRN	*DFNB31*	*9q32-q34*	[117]	*ACTG1*	*DFNA26*	*17q25*	[118]
CDC14A	*DFNB32/105*	*1p13.3-22.1*	[119]	*unknown*	*DFNA27*	*4q12*	[120]
unknown	*DFNB33*	*9q34.3*	[121]	*GRHL2*	*DFNA28*	*8q22*	[122]
ESRRB	*DFNB35*	*14q24.1-24.3*	[123]	*unknown*	*DFNA30*	*15q25-26*	[124]
ESPN	*DFNB36*	*1p36.3*	[125]	*unknown*	*DFNA31*	*6p21.3*	[126]
MYO6	*DFNB37*	*6q13*	[127]	*unknown*	*DFNA33*	*13q34-qter*	[128]
unknown	*DFNB38*	*6q26-q27*	[129]	*NLRP3*	*DFNA34*	*1q44*	[130]
HGF	*DFNB39*	*7q21.1*	[131]	*DFNA36*	*DFNA36*	*9q13-q21*	[69]
unknown	*DFNB40*	*22q*	[132]	*WFS1*	*DFNA6*	*4p16.3*	[77, 94]
ILDR1	*DFNB42*	*3q13.31-q22.3*	[133]	*DSPP*	*DFNA39*	*4q21.3*	[134]
ADCY1	*DFNB44*	*7p14.1-q11.22*	[135]	*P2RX2*	*DFNA41*	*12q24-qter*	[136]
unknown	*DFNB45*	*1q43-q44*	[137]	*unknown*	*DFNA42*	*5q31.1-q32*	[138]
unknown	*DFNB46*	*18p11.32-p11.31*	[139]	*unknown*	*DFNA43*	*2p12*	[140]
unknown	*DFNB47*	*2p25.1-p24.3*	[141]	*CCDC50*	*DFNA44*	*3q28-29*	[142]
CIB2	*DFNB48*	*15q23-q25.1*	[143, 144]	*unknown*	*DFNA47*	*9p21-22*	[145]

MARVELD2 / BDP1	*DENB49*	*5q12.3-q14.1*	[146]	*MYO1A*	*DFNA48*	*12q13-q14*	[145]
unknown	*DENB51*	*11p13-p12*	[147]	*MIRN96*	*DFNA50*	*7q32.2*	[148]
COL11A2	*DENB53*	*6p21.3*	[149]	*TJP2*	*DFNA51*	*9q21*	[150]
unknown	*DENB55*	*4q12-q13.2*	[151]	*unknown*	*DFNA52*	*4q28*	[138]
PJVK	*DENB59*	*2q31.1-q31.3*	[152]	*unknown*	*DFNA53*	*14q11.2-q12*	[153]
SLC22A4	*DENB60*	*5q23.2-q31.1*	[154]	*unknown*	*DFNA54*	*5q31*	[155]
SLC26A5	*DENB61*	*7q22.1*	[156]	*TNC*	*DFNA56*	*9q31.3-q34.3*	[157]
unknown	*DENB62*	*12p13.2-p11.23*	[158, 159]	*unknown*	*DFNA57*	*19p13.2*	[160]
LRTOMT/ COMT2	*DENB63*	*11q13.2-q13.4*	[161]	*unknown*	*DFNA58*	*2p12-p21*	[162]
unknown	*DENB65*	*20q13.2-q13.32*	[163]	*unknown*	*DFNA59*	*11p14.2-q12.3*	[164]
DCDC2	*DENB66*	*6p21.2—22.3*	[165, 166]	*SMAC/DIABLO*	*DFNA64*	*12q24.31-q24.32*	[167]
LHFPL5	*DENB66/67*	*6p21.31*	[168]	*TBC1D24*	*DFNA65*	*16p13.3*	[169]
S1PR2	*DENB68*	*19p13.2*	[170]	*CD164*	*DFNA66*	*6q15-21*	[171]
BSND	*DENB73*	*1p32.3*	[172]	*OSBPL2*	*DFNA67*	*20q13.33*	[173]
MSRB3	*DENB74*	*12q14.2-q15*	[174, 175]	*HOMER2*	*DFNA68*	*15q25.2*	[176]

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SYNE4	*DENB76*	*19q13.12*	[177]	*MCM2*	*DFNA70*	*3q21.3*	[178]
LOXHD1	*DENB77*	*18q12-q21*	[179]	KITLG	*Unknown*	12q21.32-q23.1	[180]
TPRN	*DENB79*	*9q34.3*	[181]	*PTPRQ*	*DFNA73*	*12q21.31*	
Unknown	*DENB80*	*2p16.1-p21*	[182]	*DMXL2*	*Unknown*	*15q21.2*	[183]
Unknown	*DENB81*	*19p*	[83]	*MYO3A*	*Unknown*	*10p12.1*	[184]
Unknown	*DFNB83*	*2p25.1-p24.3*	[185]	*REST*	*DFNA27*	*4q12*	[120]
PTPRQ/ OTOGL	*DENB84*	*12q21.2*	[186]	*COL11A1*	*DFNA37*	*1p21*	[187]
Unknown	*DENB85*	*17p12-q11.2*	[188]	*PDE1C*	*Unknown*	*7p14.3*	[189]
TBC1D24	*DENB86*	*16p13.3*	[190]	*TRRAP*	*Unknown*	*7q22.1*	[191]
ELMOD3	*DENB88*	*2p12-p11.2*	[192]	*PLS1*	*Unknown*	*3q23*	[193]
KARS	*DENB89*	*16q21-q23.2*	[194]	*SCDS*	*Unknown*	*4q21.22*	[195]
Unknown	*DENB90*	*7p22.1-p15.3*	[196]	*SLC12A*	*Unknown*	*5q23.3*	[197]
SERPINB6	*DENB91*	*6p25*	[198]				
CABP2	*DENB93*	*11q12.3-11q13.2*	[199]	**SEX-LINKED INHERETANCE**			
FAM65B	*DENB104*	*6p22.3*	[200]	**Gene**	**Locus**	**Location**	**Reference**

CDC14A	*DFNB32/105*	*1p13.3-22.1*	[201]	*PRPS1*	*DFNX1*	*Xq22*	[202]
GIPC3	*DENB95*	*19p13*	[203]	*POU3F4*	*DFNX2*	*Xq21.1*	[204]
Unknown	*DENB96*	*1p36.31-p36.13*	[205]	*Unknown*	*DFNX3*	*Xp21.2*	[206, 207]
MET	*DENB97*	*7q31.2-q31.31*	[208]	*SMPX*	*DFNX4*	*Xp22*	[209]
TSPEAR	*DENB98*	*21q22.3-qter*	[203, 210]	*AIFM1*	*DFNX5*	*Xq26.1*	[211]
TMEM132E	*DENB99*	*17q12*	[205, 212]	*COL4A6*	*DFNX6*	*Xp22.3*	[51]
PPIP5K2	*DENB100*	*5q13.2-q23.2*	[213]	*Unknown*	*DFNY1*	*Y*	[214]
GRXCR2	*DENB101*	*5q32*	[210, 215]				
EPS8	*DENB102*	*12p12.3*	[212]				
WBP2	*Unknown*	*17q25.1*	[216]				
ESRP1	*Unknown*	*1p13.3*	[217]				
MPZL2	*Unknown*	*11q23.3*	[218]				
CEACAM16	*Unknown*	*19q13.31-q13.32*	[187]				
GRAP	*Unknown*	*17p11.2*	[219]				
SPNS2	*Unknown*	*17p13.2*	[220]				
CLDN9	*Unknown*	*16p13.3*	[221]				

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Syndromic Hearing Loss (SHL)

Childhood congenital SHL is a major cause of birth defects in developed countries. There are many reasons are existed to study and identify the etiology of the HL [222]. Approximately 30% of all reported HL cases have several clinical anomalies with HL and termed as SHL [49]. These are differentiated from other types of HL on the basis of associated symptoms in several vital organs [223]. It is estimated that above 400 different syndromes of HL were reported and the majority of the cases had been identified with the pathogenic genes [49]. This literature review focuses on the most common syndromes that highly diagnosed in various populations and their linked pathogenic genes (table 2). Major syndromes with HI are Alport, Stickler, Jervell & Lange-Nielsen, Waardenburg and Usher syndromes etc. Stickler and Waardenburg syndromes have dominant inheritance patterns, while the syndromes having autosomal recessive inheritance patterns are Usher and Jervell & Lange-Nielsen syndrome and the Alport syndrome is usually inherited with X-linked inheritance pattern [69, 224].

Table 2: Syndromes, Mutated Genes, and their chromosomal location

Syndrome	**Location**	**Gene**	**Locus**	**PHENOTYPE**
Alport Syndrome	*Xq22*	*COL4A5*	…	X-linked and autosomal recessive, progressive highly prevalent SNHL; specific form of glomerulonephritis. The recessive genes are COL4A6 and COL4A4 respectively.
	2q36-q37	*COL4A3*	…	
	2q36.3	*COL4A4*		
Branchio-oto-renal syndrome	*14q21.3-q24.3*	*SIX1*	*BOS3*	Autosomal dominant, pre-auricular ear pits, brachial pits and Sinuses, pinna abnormalities and renal hypoplasia.
	19q13.3	*SIX5*	*BOR2*	
	1q31	*unknown*	...	
	8q13.3	*EYA1*	*BOR1*	
Charge syndrome	*7q21.11*	*SEMA3A*	...	Inherited as autosomal dominant, it represents Acronym Coloboma, Atresia, ear anomalies, Heart defects,
	8q12.2	*CHD7*	...	

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				and retarded development and growth.
Jervell & lange-nelsen syndrome	*11p15.5*	*KCNQ1*	*JLNS1*	Inherited as autosomal recessive, congenital profound SNHL with missing vestibular function and is also commonly known as QT syndrome.
	21q22.1-q22.2	*KCNE1*	*JLNS2*	
Norrie syndrome	*Xp11.3*	*NDP*	*NDP*	Inherited as X-linked progressive SNHL mostly appeared in second life decade, intellectual disability and congenital retinal detachment.
Penderd syndrome	*7q21-34*	*SLC26A4*	*PDS*	Progressive high-frequency SNHL and inherited as autosomal recessive, with thyroid failure, incomplete partitioning of the cochlea and enlarged vestibular aqueducts.
	5q35.1	*FOX11*	*PDS*	
	1q23.2	*KCNJ10*	*PDS*	
Stickler syndrome	*12q13.11-q13.2*	*COL2A1*	*STL1*	Inherited as autosomal dominant inheritance pattern, Affects Cleft palate, flat center-face, highly frequent SNHL, retinal detachment and high myopia; arthropathy.
	1p21	*COL11A1*	*STL2*	
	6p21.3	*COL11A2*	*STL3*	
	6q13	*COL9A1*	...	
	1p34.2	*COL9A2*	...	
TREACHER COLLIN SYNDROME	*5q32-q33.1*	*TCOF1*	*TCOF1*	Inherited as autosomal dominant inheritance pattern, results in symmetrical and bilateral pinna abnormalities with mental issues, coloboma of lower eyelids, spars in eyelashes, cleft palate, hypoplasia of mandible and zygomatic complex.
	13q12.2	*POLR1D*	*POLR1D*	
	6p21.1	*POLR1C*	*POLR1C*	

USHER SYNDROME	*14q32*	*nonexistent*	*USH1A*	RP (Retinitis pigmentosa) with SNHL. Type 1 of usher syndrome, profound congenital SNHL, absent vestibular response and RP (Retinitis pigmentosa) develops in the first life decade. In type 2 of the usher syndrome, sloping congenital SNHL, with normal vestibular response and Retinitis pigmentosa (Verpy et al.) develops in the early and late onset of life; while in case of Usher syndrome type 3, progressive SNHL with erratic vestibular response and erratic period of the RP (Retinitis pigmentosa) develops.
	11q13.5	*MYO7A*	*USH1B*	
	11p15.1	*USH1C*	*USH1C*	
	10q22.1	*CDH23*	*USH1D*	
	21q21	*Unknown*	*USH1E*	
	10q21-22	*PCDH15*	*USH1F*	
	17q24-25	*SANS*	*USH1G*	
	15q22-23	*Unknown*	*USH1H*	
	15q23-q25.1	*CIB2*	*USH1J*	
	10p11.21-q21.1	*Unknown*	*USH1K*	
	1q41	*USH2A*	*USH2A*	
	3p23-24.2	*Unknown*	*USH2B*	
	5q14.3-q21.3	*VLGR1*	*USH2C*	
	9q32	*WHRN*	*USH2D*	
	3q21-q25	*CLRN1*	*USH3*	
	5q31.3	*HARS*	*USH3B*	
	10q24.31	*PDZD7*	*ModiferGene*	
WAARDENBURG SYNDROME	*2q35*	*PAX3*	*WS1*	SNHL with pigmentary anomalies of skin, eye, and hair. In type 1; autosomal dominant with hypoplasia of alaenasi, synophrys and dystopia
	3p14.1-p12.3	*MITF*	*WS2A*	

	1p21-p13.3	*unknown*	*WS2B*	canthorum appears. In type 2; autosomal dominant and facial features and dystopia canthorum are absent. In type 3; autosomal dominant and is also known as Klein-Waardenburg syndrome: upper limb abnormalities plus type 1 syndrome. while in type 4; autosomal recessive and also known as Waardenburg-Shah Syndrome: Hirschsprung disease plus type 2 syndrome.
	8p23	*unknown*	*WS2C*	
	8q11	*SNAI2*	*WS2D*	
	2q35	*PAX3*	*WS3*	
	13q22	*EDNRB*	*WS4*	
	20q13.2-q13.3	*EDN3*	*WS4*	
	22q13	*SOX10*	*WS4*	
PERRAULT SYNDROME	*5q23.1*	*HSD17B4*	...	Inherited as autosomal recessive inheritance pattern results in congenital SNHL, intellectual disability, and other neurological disorders, gonadal dysgenesis in women.
	5q31.3	*HARS2*	...	
	19p13.3	*CLPP**	*DFNB81*	
	3p21.31	*LARS2*	...	
	17q11.2	*ERAL1*	...	
HUNTER SYNDROME	*Xq28.11*	*iduronate-2-sulfatase (I2S)*	...	Hunter syndrome faced deficiencies in iduronate-2-sulfatase activity and stored a variety of glycos-amino-glycans in a broad diversity of tissues
RITSCHER-SCHINZEL/3C SYNDROME	*8q24.13*	*K1AA0196*	...	characterized by congenital heart defects, craniofacial abnormalities, cerebellar brain malformation, and intellectual disability
	Xp11.23	*CCDC22*	...	
NANCE SYNDROME	*Xp22.2-p22.1*	*NHS*	...	congenital cataract, short fingers, dysmorphic traits, broad nose, and dental abnormalities

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Recessive syndromes of HL

Pendered syndrome

Pandered first time was reported in 1986, and later after series by Faser in 1964 [225]. It is diagnosed as goiter and thyroid dysfunction owing to the iodide organification defects with deafness. *SLC26A4* encoded "Pendrin" an anion transporter protein, and in 1997 a pathogenic variant of this gene was first time identified and later in various studies different variants were also identified that coded [226-229]. In the majority of the affected individuals, goiter was developed during the second decade of life; caused due to the improper supply of iodide in the thyroid, even though affected persons are euthyroid [32]. Defects in iodide transporter caused thyroid abnormalities and defects in chloride transporter caused HL and abnormal development of the cochlea. In the cochlea, abnormal fluid flux developed due to impaired chloride transporter, leading to HL and large vestibular aqueduct [32].

Usher syndrome (USH)

Usher syndrome develops by functional loss of dual sensory systems; the visual and audio-vestibular systems. Clinically it was classified into three subtypes (USHI, USH2 and USH3) and this classification is based on the existence or non-existence of vestibular dysfunction, the severity of HL and the time when night blindness developed [230]. It has been predicated, USH is 3-6 % of the total congenital deaf population, 50 % of the deaf-blind population and 8-33 % of affected individuals with "Retinitis pigmentosa (RP)". In various populations, the frequency of USH is between 3.5-6.2:100000, and the carrier frequency ranges 1:100 individuals [230]. USH become more prevalent in those states having small, isolated and beard population, including Pakistan, Israel, France, (Poitou-Charentes region), Finland and Accadian population of Louisiana, North Sweden and the United States [231].

Studies of clinical and molecular genetics USH have exposed extensive clinical and genetic heterogeneity. Genes of USH encode proteins of various classes/families, including motor proteins, scaffold proteins, proteins trans-membrane receptors and cell adhesion molecules [230, 232]. It is hypothesized that USH causing proteins are from those protein groups that are functional inside the inner ear to regulate the hair bundle's morphogenesis [34, 230]. Behavioral and Mental harms (psychotic symptoms and schizophrenia-like disorder) are also linked with USH. In Usher patients, neuro-imaging examination reports scatter involvement of central nervous system (CNS),

signifying a probable function of CNS injury in the pathogenesis of psychiatric manifestations [233].

Perrault syndrome

The relationship of abnormal development of gonads and deafness was studied in 1951 for the first time and later termed as Perrault syndrome [234]. It is a rare disorder consisting of abnormal gonadal development such as ovarian abnormalities with SNHL in affected females [235, 236], and only deafness in men [237]. So far, about 40 females globally were reported in different studies with this autosomal recessive disorder [235, 238]. Intellectual abnormalities, cerebellar ataxia, motor and sensory peripheral neuropathies were reported in some females with this syndrome. Beyond 10 pathogenic genes are to be identified that causes premature ovarian failure heterogeneously [239, 240].

Treacher Collins (TC**) syndrome**

In 1846, first time Thomson and later on in 1847 Toynbee reported this syndrome [241, 242]. Berry discussed an abnormality in colobomata of the lower eye-lid [243]. It is a rare syndrome. There are two types with respects to severity: minimal severity includes oblique pulperal fissures and major severity includes craniofacial development such as hypertelorism, micrognathia, maxillary-hypoplasia, high arched plate, conductive HL, external malformation and narrow nostrils [244-246]. The occurrence rate of this syndrome is between 1:25000 and 1:50000 [244, 245]. *TCOF1, POLR1D* and *POLR1C* have been identified to cause this syndrome. Transmission of these genes takes place through the autosomal dominant or autosomal recessive pattern of inheritance [245, 247-249]. Ontological, ophthalmological and dental abnormalities have also been seen in the diagnosed patients with TC syndrome [249].

Branchio-Oto-Renal (BOR) syndrome

Branchio-Oto-Renal syndrome, a developmental disorder inherited with an autosomal recessive pattern, and is distinguished by the occurrence of renal and gill vault defects combined with HL. In the early two-phase of life, the malformations of the urinary tract are the major cause of chronic renal failure [250, 251]. Commonly, the dispersion ratio of the BOR syndrome in the general population is 1:40,000 individuals, whereas in deaf children's its ratio is about 2% of the total deaf population. The early onset of the HL varies from childhood to adulthood [250, 252]. The clinical

expression of BOR has a wide range of inter- and intra-family variability, and become assumed the occurrence rate of BOR syndrome is reduced [253]. The syndrome BOR and their main features that diagnosed in 93% of the affected subjects, is HL either it is neurosensory, conductive or mixed. In addition to ear defects, branchial arch and kidney problems have been described in various kinds of BOR syndrome in other organic systems. Among these dysfunctions, the association of the lacrimal duct system is more common [251, 254-259].

Waardenburg syndrome (WS)

Waardenburg is pigmentary disorders with sensorineural HL, a rare genetic disorder with the prevalence rate of 1:40,000 individuals, and is inherited with a recessive mode of inheritance. This congenital disorder is developed due to the abnormalities in the embryonic neural crest. The majority of the deaf population is congenital HL and is also develops in late-onset due to encephalitis, meningitis and complications faced during prematurity [260]. Depending on the addition of medical anomalies with HL, It is further divided into four different types, as WS1, WS2, WS3 and WS4 [261]. The WS1 is associated with dystopia canthorum, while the WS2 developed without dystopia, and these are the main subtypes of WS. The WS1 is developed by the failures of neural crest, but the WS2 is developed due to the failure of specific melanocyte [261].

Dominant syndromes of HL

Stickler syndrome

Gunnar Stickler in 1965 first time reported Stickler syndrome with predicted frequency of 1:10,000 births. It develops in addition of connective tissue anomalies with HL, including retinal detachment, cataract, ocular anomalies of myopia, early arthritis, spondyloepiphyseal dysplasia, underdeveloped cleft-plate and HL of either conductive or sensorineural [262, 263]. The cause of retinal detachment with HL was highly diagnosed sign of Stickler syndrome [262]. it occurs primarily in the 2nd period of life, with cataracts developing primarily in the fourth decade [264].This syndrome is further classified into type-1 and type-2 Stickler syndrome, and on the basis of vitreo-retinal phenotype, type-1 diagnosed with congenital vitreous irregularity and developed as mutations in *COL2A1*, whereas type-2 is diagnosed with congenital vitreo-retinal irregularity [265, 266]**.** It is inherited either autosomal recessive or dominant inheritance pattern. Mutations in *COL11A1, COL2A1* and *COL11A2* are responsible for dominant inheritance pattern,

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while the mutations in *COL9A1* and *COL9A2* are responsible for recessive inheritance pattern [262, 267-270].

Cardio-auditory (Jervell and Lange-Neilsen) syndrome (JLNS)

In 1957, cardio-auditory syndrome designated as Jervell and Neilsen syndrome was studied in the Norwegian family [271]. It is genetically related to sensorineural HL, associated with syncopal episode and initiated with ventricular arrhythmias and unusual repolarization, illustrated by extended "QT" pause on electrocardiogram [272]. Long QT syndrome categorized into different classes on the basis of two clinical phenotype and inheritance patterns, like syndrome Romano-Ward, inherited as autosomal dominant, while syndrome JLNS inherited as autosomal recessive inheritance pattern [273]. The incidence of RWS is approximately 1:2000 in all societies [274], whereas the JLNS develops in patients when bi-allelic heterozygous mutation in *KCNQ1* or *KCNE1* are originates [273-275]. JLNS is a very severe cardiac arrhythmia. It is genetic syndrome and its gene contains*α* and *βsubunits* [276-278]. A high inflow of sodium ions causes cardiac action potential through the depolarization phase. Increased calcium ions in-flow and repolarization lead to the development of the plateau-phase. This repolarization is due to the component that quickly activating and a slowly activating factor *IK*. Mutation in *KCNQ1* lead to loss of IK function which belongs to ventricular repolarization prolongation and result in ventricular arrhythmias (*LQT* syndrome) and also congenital bilateral deafness in its result (JLNS) [271, 279, 280]. There is another life hazardous ventricular arrhythmia termed as type-2 Short *QT* syndrome (SQTS) considered due to ventricular repolarization shortening [280, 281].

Charge syndrome (CS)

CS diagnosed ear abnormalities including deafness and vestibular disorder with anomalies of heart defects, growth retardation, atresia of the choanae, coloboma of the eye, genital or urinary abnormalities, and is inherited with the autosomal dominant pattern with occurrence rate of 1:8500 - 15000 live births [282-285]. Genetically variation in *7(CHD7) genes* considered the major cause of CS, which encodes a chromo-domain helicase DNA binding protein. According to clinical diagnostic research following the above criteria, among the people registered in different studies 70%-90% individuals are reported as the victim of CS [286-292].With respect to molecular biology, the abnormalities yet not completely understood. Recent research has proved that *CHD7* plays a vital role in the development of multi-potent migratory cells inside the neural crest. From

neural tubes, these migratory cells migrate towards the several parts of the embryo and differentiated into much different type of tissues like craniofacial and heart structure. A few *CHD7* genes have been studied that was responsible for the development of neural crest [291, 293]. Lalani *et al* reported that a gene *SEMA3E* having the same molecular process is responsible for charge syndrome [287].

X-Linked syndromes of HL

Norrie syndrome (NS)

Norrie Disease (ND), is a rare X-linked disorder inherited with recessive inheritance pattern, and it developed mainly in the form of early onset of child vision loss with HL [294]. Persons with ND may grow blindness at birth, cataract, nystagmus and increased intraocular pressure [295]. Affected males could transfer the mutated gene to their daughters. Carrier females inherit the pathogenic variant to her offspring in any pregnancy. Females who transmit the pathogenic variant will be a carrier or will be unaffected. On the other hand, carrier male will be affected [296]. In 1992, a mutation in the NDP gene (Pseudoglioma) was identified that is responsible for ND and later in 2020 a missense variant of this gene was identified [297-299]. Norrie gene expression encoded a protein; and this secretory protein containing a knot-motif of cysteine with 133 amino acids. In the growth vascular system of the retina, Norrie protein plays a vital role [300]. Norrie is related to mucin-like proteins. Mucin has characteristic features owing to the existence of a knot-motif of cysteine, and it's a structural and functional motif found in many growth factors. Other than the biochemical factors, molecular aspects also involved in the NS, like in eye signal transduction pathway "*Wnt-receptor-β-catenin*" is involved in the failure of hyaloid vessels, and in addition it also functional in the growth of retina, and in this pathway it works as a ligand [296, 301, 302].

Hunter syndrome (HS)

HS is a metabolic storage disorder that effect the breakdown of sugar in the body with a frequency rate of 1:34000 and 1:162000 individuals [303-305]. It develops by genetic variations in *iduronate-2-sulfatase*gene, inherited as X-linked pattern and also known as Muco-poly-sacchari-dosis II [306-308]. It is predominantly present in males, and reported a prevalence rate of typically 1:100,000 individuals [309]. The patient show symptoms like, thick skin, develop macrocephaly,

coarse facies, abnormalities in cardiac valves, hepatosplenomegaly, joint construction, deafness, airway compromise, cranial nerve and degeneration of central nervous system [310].

Ritscher-Schinzel/3c syndrome (RSS/3C)

RSS/3C (crania-cerebro-cardiac) is commonly recognized a heterogeneous developmental abnormality, clinically it is much rarely diagnosed and is characterized by congenital heart defects, craniofacial abnormalities, cerebellar brain malformation and intellectual disability [311]. 80% of the RSS/3C patients have cardiac problems, which can comprise septal defects, tetralogy of Fallot, hypo-plastic left heart, double outlet right ventricle, pulmonic stenosis, aortic stenosis, and additional valvar anomalies. A lot of affected individuals confirm symptoms of Dandy-Walker malformation, posterior fossa cysts, ventricular dilatation and cerebellar vermis hypoplasia [312]. In RSS/3C syndrome, facial dimorphism is defined as a prominent forehead, occiput, micrognathia, lowest ears, depressed nasal bridge and down-slanting palpebral fissures. In this syndrome, the phenotypic manifestation is varied as well as the cerebellar and cardiac manifestations do also not constantly exist. Therefore, through diagnosis, dysmorphic features of craniofacial pattern become crucial [312, 313]. A study on the Canadian population reports homozygous sequence variants, in *K1AA0196*, that encodes strumpellin which is the subunit of WASH complex, as the type of *RSS/3C* syndrome [311, 312]. Another study on Austrian family, founded a missense variant in *CCDC22*, that maps on sex chromosome *Xp11.23*, show X-linked inheritance pattern and features related to syndrome *RSS/3C* [311] .

Nance syndrome

Walter Nance and Horan was reported as a rare X-linked hereditary disorder and famous as Nance-Horan syndrome (NHS) [314, 315]. In 1990 a pathogenic variant was the first time mapped at cytogenetic location *Xp21.1-Xp22.3* that was responsible for NHS [316-318]. Therefore, with a minute disparity of phenotype, several varied mutations were identified causing NHS [319-321]. This syndrome is distinguished from other syndromes due to the presence of congenital cataracts, dental abnormalities, anteverted pinnae, broad nose and short fingers with HL [44, 322, 323]. Furthermore, in literature mental retardation and illustrations of autism in NHS are also reported, but these results are more conflicting [324]. A bulk of available literature was concentrating on genetic factors of NHS and congenital cataracts with partial illustrations of oral findings [222, 325-327]. In patients of NHS, the description in the morphology of molar, use of the term "bud

molar" is recommended. The relative mixture of congenital cataracts, bud-shaped molars, and screwdriver-shaped incisors are the key medical symptoms of NHS [44, 328].

Alport syndrome (AS)

AS is a rare X-linked renal failure (glomerulo-nephritis) syndrome initially reported in 1927 [329], and is characterized by HL with renal failure, lamellated glomerular basement membrane, and hematuria. In the case of nephritis, AS with ultra-structural faults in *BGM* (glomerular basement membranes) of affected individuals, altered and affected the protein structure [330]. Renal transplantation, in affected individuals with AS, shows graft and tolerant survival rates as compared to affect individuals of other renal diseases. Patients suffered in *"ESKD"* (end-stage kidney disease), owing to AS have analogous patients and grafts survival to those affected individuals with other reported causes of *"ESKD"*. Early management and diagnosis indicate positive results in individuals of the affected group [330]. It also diagnosed with anomalies of several ocular phenotypes, including Corneal and retinal manifestations [331, 332].

Methods used in mapping/identification of causative-genes

Mapping/identification of the pathogenic gene, in large size consanguineous families, is facilitated by linkage analysis and auto-zygosity. Variable inheritance patterns, inherited with deafness/HL genes, have been identified in countries like Pakistan, Iran, Tusinia, India, Palestine and Turkey. Several hundred genes have been reported which have a strong association with HL, and the mutation spectrum of these reported genes becomes very wide so that the identification of pathogenic mutations is still difficult. The development of advanced techniques like; Next-generation Sequencing and target-enrichment method, makes it easy to identify the novel gene and mutations, especially in disorders having a heterogeneous mode of inheritance. During the period of the last 10-12 years, the identification rate of causative genes associated with HL becomes very high. WES used as a first-line approach nowadays, for identifying the pathogenic gene variants that discharge a specific phenotypic disorder [333]. Without any conflict, this method is so expansive, but it provides high yield results.

Linkage analysis

Linkage analysis method is successfully used for verifying the genetic location of the pathogenic gene in the lack of any other abnormality (e.g., co-inherited disorders, no cytogenetic abnormality,

known protein product or good candidate gene). Precise duplicates of the genomic region encouraging the pathogenic genes are co-inherited with the disease within a family; these consequences confirmed the lack of recombination among the pathogenic variants and the adjacent genetic markers, owing to their close proximity. In a family, subjects who share a disease will typically share alleles at the marker close to the pathogenic gene. Fastidious alleles segregated with the disease often variate among the families, reflecting allelic heterogeneity or ancestral genetic recombination or event. Linkage analysis results are described as LOD score, results are reported, that representing the comparative likelihood that a disease locus and a genetic marker are linked genetically; instead of them are genetically unlinked. LOD minimum +3 score characteristically predicted verification of linkage and LOD score of -2 or less it indicates that region is not linked to the disease [334, 335].

Linkage analysis is a method supportive in developing connections between the loci; i.e. two loci present on the identical chromosomes are expected to be linked if the observable fact of crossing-over does not separate them. During the process of recombination (crossing over) in meiosis the homologous chromosomes share their segments. Parental combinations are the original arrangement of alleles on the two chromosomes whereas the new combinations are originated after crossing over and denoted as recombinant. If two loci are actually slammed to each other on the same chromosome, then very few chances will happen they are separated through a recombination event. Haplotypes are the set of alleles for different markers or genes on the same chromosomes. The phrase linkage refers to the loci, not to definite alleles at these loci. Linkage analysis is a technique, which is most likely to be used to find the location, in genetic material, for the pathogenic gene [334, 335].

SNP Genotyping

In genetic studies, the single nucleotide polymorphism (SNP; a type of genetic variant) markers found sportive. Approximately, in humans about 10 Million SNPs exist, and it made the study of genome-wide scan association become easier; with the completion of HapMap Project and microarray techniques. The addition of microarray and HapMap technique limits the number of SNPs required for genotyping, approximately 0.25-1 million as compared to 10 million, that considers sufficient for gene mapping. For automated SNPs genotyping, Affymetrix and Illumine

are two commercially available platforms are available. The basic principles of these two apparatus are the same, but it differs from each other in a few aspects [336].

Next-generation sequencing

The exome holds, exons of all the genome, and is represented as the coding regions of the genes. In a complete human genome, the exons are the only 1%. However, more than 70-80% of the pathogenic mutations are identified in this coding region of the genome. For this reason, whole-exome sequencing is an extra-ordinary accurate method to study the different inheritance patterns such as autosomal dominant, recessive and sex-linked traits in HHL. Designed for whole exome sequencing, three basic platforms are available, namely Applied Biosystems SOLiD [337], Roche 454 [338], and Illumina Genome Analyzer [337, 338]. The design and chemistry of every platform are specific but the working principle of each platform is the same.

Conclusion

Gene depiction and variant screening will untie the functional characteristics and permit to develop phenotype-genotype association. Mutations in genes or the interaction of several disordered genes caused HL and other genetic disabilities. Hearing impairment in adults is a major high prevailing disability, connected with severe psychosocial and communication issues, and face severe health care cost with financial problems at individual and societal level. Hearing impairment is divided into two broad categories; one is without clinical abnormality defines NSHL, while other with clinical abnormalities defines SHLs. This complete review exposes the latest developments in this field, and also focusing on different genetic players involved in it and various methods used in different studies to find these pathogenic genes and their variants. Various equipment's and molecular approaches now available and under study to improve hearing in patients but these technologies have limited access due to serious implications like health policies, rules-regulations and high cost. Whereas, there is no proper treatment are still available for syndromic hearing impairment. In simple hearing loss doctors solved some level of hearing issues with cochlear implant and hearing aids, but in case of syndromic hearing impairment the patient still faces problems e.g. in Usher syndrome retinal complication still remains unresolved. Furthermore, delineation of pathogenic variants linked to hearing damage enables recommendations to hearing specialist for handling the patients that make sure the batter quality of life. Initial detection of HL ensures to early mediation and healthier patient results. Linkage analysis, SNP genotyping and

Next generation sequencing method are most likely be used, and WES method is one of them highly used in most of the genetic studies to-date for quick and accurate findings of mutated genes. This study suggested that functional characterization of these variants will help to better understand the pathophysiology of disease and will improve the procedures of genetic testing and genetic counselling.

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