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Genetic Hearing Loss

Classification of Genetic Hearing Loss (Figure 1) (Table 1)

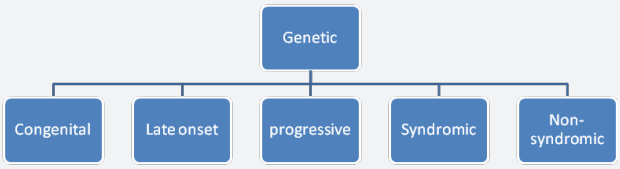

Figure 1: Classification of Genetic Hearing Loss.

Table 1: Genetic hearing loss based on type of hearing loss.

Type of HL	Inheritance	Audiological findings	Symptoms
Mid freq.SNHL	Autosomal dominant	Progressive SNHL from mid freq. to all freq.	Normal caloric responses. Temporal bone pathology, loss of organ of corti in basal turns with clumps of cells in the middle and apical turns. Stria vascularis atrophy, spiral ganglion deficient.
Progressive SNHL	Autosomal dominant	HFSNHL later LF also affected	Abrupt onset, Degeneration of organ of corti, spiral ganglion in lower cochlear turn patchy, cystic and degeneration of vestibule
Progressive mixed HL	Autosomal dominant	Progressive mixed HL	Mondini like formation on labyrinth. Dilated canaliscaulis cochlea
Unilateral SNHL	Autosomal dominant	Congenital mod- sev unilateral or bilateral SNHL	Normal vestibular function
Pro gressive Vesti bulo-cochlear dysfunction	Autosomal dominant	SNHL progressive	Vestibular disorder along with hearing loss
Familial ossicular malfor mation Normal external ear CHL	Autosomal dominant	CHL	Ossicular malformation of various kind
Congeni tal Severe to pro found SNHL	Autosomal recessive	Severe to profound SNHL	Normal vestibular function, absence of organ of corti, collapse of reissner's membrane, atrophy of stria vascularis, decrease in spiral ganglion cells
Conge nital Retroc ochlear HL	Autosomal recessive	Mild to moderate HL. RCP involvement	Steep slope at HF and discrepancy in both ears at HF
Congenital moderate SNHL	Autosomal recessive	Congenital non progressive moderate SNHL	Loss slightly higher in HF. Symmetrical type. Normal Vestibular function
Early onset progressive SNHL	Autosomal recessive	Severe SNHL(Early infancy)	Early onset. No hearing after 5-6 yrs. Normal vestibular function

Progressive HFSNHL	Autosomal recessive	HFSNHL	Normal vestibular system and progressive HL
SNHL due to mitochondrial inheritance	Mitochondrial inheritance	Progressive severe to profound SNHL at all freq.	
Congenital Severe SNHL	Autosomal dominant	Severe non progressive congenital SNHL	Variable vestibular responses, atrophy of stria vascularis in lower half of basal turn. Temporal bone changes, complete disappearance of organ of corti in basal turn with only a mound of undifferentiated cells evident
Congenital LF SNHL	Autosomal dominant	Moderate LF SNHL, non-progressive	Congenital onset , normal vestibular responses
Progressive LF SNHL with childhood onset	Autosomal dominant	Moderate LFSNHL, progressive up to moderately severe SNHL extending to all freq.	Onset during 1st or 2nd decade of life, Normal vestibular responses

Congenital Losses

a) Consanguinity

b) Paternal / maternal deafness

c) Ear anomalies (may occur with or without syndromes)

d) Single-Gene Disorders

Late onset

a) Neuro fibromatosis 2 (NF2)

Progressive: Some syndromes are of late onset

a) progressive in nature

b) Enlarged Vestibular Aqueduct

c) Osteogenesis Imperfecta

Hereditary Hearing losses

a) Syndromic or Non Syndromic

They can be of 3 types

a. Autosomal Dominant

b. Autosomal Recessive

c. X-linked

These cause:

i. Moderate to Profound SN or Mixed Hearing loss.
ii. Usually bilateral.

b) Non syndromic disorders

i. Dominant Hereditary Hearing loss

ii. Dominant Progressive Hearing loss

iii. Progressive adult onset hearing loss due to mitochondrial DNA mutations

iv. Recessive Hereditary SN HL

v. X-linked hearing disorder DFN2 ,DFN4 and DFN6

Congenital Hearing Loss

1) Hearing loss present by birth.

2) Genetically, it can be acquired due to various factors

Consanguinity

i. Common feature across many parts of the globe

ii. Marriage within relations

iii. Legal system in many cultures

iv. Known to be a significant cause of genetic hearing loss(Turan & Apaydin,2002)

v. Causes Congenital SNHL

Disruption in planar cell polarity pathway (PCP).

i. PCP- helps formation of polarized structure

ii. Regulates embryonic development

iii. Genetic disturbances causes disruption in PCP

Genetic mutation of GJB2

a) Siblings have higher incidence of autosomal recessive hearing impairment.

b) Increased risk of polygenic inheritance (Northern et al.)

c) Also, more common in near relations

i.1 st cousins- greater risk.

ii. Distant cousins- lesser risk

Paternal or maternal deafness

a) Either of the parent has hearing loss

b) SNHL common occurance

i. Deletion of genetic material on the long arm of chromosome 15

ii. Loss of multiple genes in that region

iii. SRTC on Chromosome 15 - cause of HL

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Single gene disorders

a)Single mutated gene- cause

b)Passes to generations in several ways

c)Genetic protein -non functional

d)Defect on autosome of X chromosome - affects one member of the gene pair or both carrying the same gene pair

e)Pattern of inheritance depends on the phenotype.

I. Ear anomalies

a) Congenital

b) Occurs in isolation

c) As a part of syndrome

d) Due to defective genes

II. Michel Aplasia

a) Complete agenesis of the petrous portion of the temporal bone

b) External and middle ear may be unaffected.

c) Autosomal dominant inheritance has been observed, but recessive inheritance is also likely.

i. Treatment: Vibrotactile devices have been of some help

III. Mondini Aplasia

a) Autosomal dominant

b)May not be bilateral.

c) Occurs with genetic syndromic disorders or can be with non genetic syndromic disorders

i. Treatment: Early habilitative intervention and conventional amplification

IV. Scheibe Aplasia

a) Cochlearsaccular dysplasia or pars inferior dysplasia

b) The bony labyrinth and the superior portion of the membranous labyrinth, including the utricle and semicircular canals are differentiated

c) Organ of Corti -poorly differentiated

d)Deformed tectorial membrane

e) Collapsed Reissner's membrane, which compromises the scala media

f) Autosomal recessive nonsyndromic trait.

i. Treatment: Conventional amplification with habilitative intervention

V. Alexander Aplasia

a) Cochlear duct differentiation at the level of the basal coil is limited with resultant effects on the organ of corti and ganglion cells

b) Causes high frequency hearing loss with adequate residual hearing in the low frequencies

i. Treatment: use of amplification.

VI. Enlarged Vestibular Aqueduct

a) An enlarged vestibular aqueduct apparently is the result of hydrodynamic changes and possibly labyrinthine membrane disruption.

b) Early onset sensorineural hearing loss,

c) Bilateral

d) Often progressive

e) May be accompanied by vertigo or incoordination.

f) Autosomal dominant inheritance.

g)Recessive inheritance is also possible

Semicircular Canal Malformations

1) Isolated lateral canal defects -most common inner ear malformations-identified on temporal bone imaging studies.

2) Superior semicircular canal deformities are always accompanied by lateral semicircular canal deformities

3) Lateral canal deformities often occur in isolation.

4) Recently, the genes responsible for development of microstructures in the cochlea have been identified.

5) For example, connexins are the channels that connect neighboring cells and allow passive transfer of small molecules.

6) It can be inherited by Autosomal recessive as in most cases and Autosomal dominant as in few cases.

7) These gap junction are important for the electric and metabolic coupling of neighboring cells.

8) These connexins development are coded in genes like Connexin 26, 30, 31

9) When these genes get mutated there will be non syndromic hearing loss.

Late onset genetic hearing loss

i. Occurs later in life

ii. 9 different types of genes localized

iii. DFNA10 on chromosome 6 - most common

iv. Connexin 6 also has impact

v.Mostly Age related hearing impairment

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vi. Can be triggered by environmental factors

vii. No exact gene identified till date.

Late onset Progressive genetic hearing loss

i. Autosomal dominant

ii. Occurs at any age

iii. It may be due to some defective genes that might cause deafness, but expressed later in life

iv. Osteogenesis Imperfecta

v. Osteogenesis imperfecta is characterized by :-

a) Bone Fragility

b) Blue sclera

c) Conductive, mixed, or sensorineural hearing loss

d) Hyper-elasticity of joints and ligaments.

e) Triangular face

f) Short stature

g) Hypermobile joints

h) Cardiovascular abnormalities

i) skin disorders.

I.Hearing loss is usually mixed and has a prevalence ranging from 26-78%.

II. Autosomal dominant with variable expressivity and incomplete penetrance.

III. Two genes for osteogenesis imperfecta have been identified,

a) COLIA1 on chromosome 17q

b) COLIA2 on chromosome 7q.

i. The hearing loss usually presents itself during the late 20s or early 30s.

ii. The conductive component of the hearing loss is attributed to the thickened and fixed stapes footplate, similar to what is seen in otosclerosis.

iii. The sensorineural component usually results from cochlear hair cell atrophy and atrophy of the stria vascularis.

iv. Also, anomalous bone formation in and around the cochlea may contribute to the sensorineural component of the hearing loss.

Syndromic hearing loss

i. A particular set of congenital signs repeatedly occurring in a generally consistent pattern is known as “syndrome”.

ii. Associated with malformation of the ear and other organs with medical problems involving other organs

iii. Around 400 genetic syndromes that cause hearing loss identified

iv. One of the contributing factors for pre lingual deafness

A syndrome may be caused by

a) a chromosomal problem,

b) a biochemical defect,

c)a mendelian genetic defect,

d) or an environmental agent.

Pattern of inheritance

i. Autosomal dominant inheritance

ii. Autosomal recessive inheritance

iii. X-linked inheritance

iv. Mitochondrial inheritance

Autosomal dominant inheritance

i. The pattern of inheritance is Autosomal dominant if individuals in each generation are affected;

ii. Both males and females are equally likely to be affected (Figure 2).

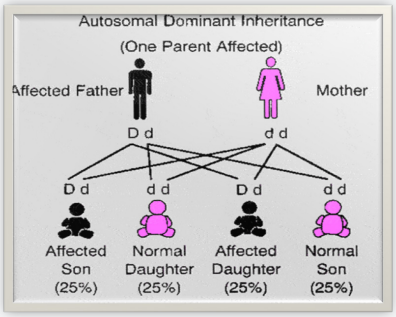

Figure 2: Autosomal Dominant Inheritance.

iii. Affected individuals are usually heterozygotes with one normal and one deleterious copy of the gene for the disorder, and each offspring of an affected individual has a 50% chance of inheriting the deleterious allele.

iv. There may be variable expression among affected individuals, and some who must have the deleterious allele may show no phenotypic signs.

Autosomal recessive inheritance

i. The mode of inheritance of a disorder is Autosomal recessive if the abnormal phenotype is expressed only in individuals who have two copies of the deleterious allele.

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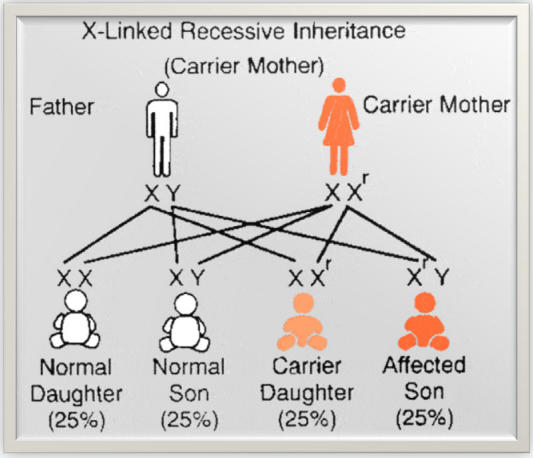

Figure 3: X-Linked Recessive Inheritance

Table 2: Hearing loss based on X linked inheritance.

Congenital SNHL	X-linked	Congenital severe SNHL	Mental deficiency, Normal vestibular function
Moderate SNHL	X-linked	Slow progressive moderate SNHL	Adolescent onset, slow progressive, Normal vestibular function
High freq. SNHL	X-linked	Non progressive HF SNHL	
Progressive mixed HL with perilymphatic gusher	X-linked	Moderate to severe mixed HL	Perilymphatic gusher after stapedectomy, vestibular hypofunction. Fixation of stapes footplate.

iii. Female have two X chromosomes and may be carriers, but are unlikely to be affected.

iv. Sons of carrier mother - 100% chance

v. Daughters - 50% and remaining will be 50% carriers.

vi. Note that, although females have two X chromosomes in a cell, in general one of the two is randomly activated early in embryonic development.

vii. Thus, females are mosaic, with each cell having one or other X chromosome active.

II. Mitochondrial conditions

i. Mitochondria are structures in the cell that produce the energy that cells need to survive.

ii. Neither the mitochondria nor the cell can exist without the other.

iii. Changes in the mitochondrial genes can also result in syndromes involving hearing loss (Table 3).

Table 3: Syndromes associated with Hearing loss.

Syndrome	Inheritance	Audiological findings	Symptoms
Nager acrofacial dyastosis syndrome(pre axial acrofacial dystosis)	Autosomal recessive inheritance	Congenital CHL, unilateral mixed HL, Hypoplasia of Helix , tragus and antitragus atresia, pre auricular tag	Abnormalities of radial ray, thumb aplasia, radial aplasia, down slanting palpebral fissures, malar zygomatic hypoplasia, cleft palate, retro-micrognathia, urogenital defects, ossicular defects, absence of incus and fused with ossicular mass, stapedial footplate fixed to oval window and absence of ossicles with rudimentary semicircular canal

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Goldenhar syndrome(Hemifacial microsomia)	Autosomal dominant inheritance	Anotia, dysmorphic ear, pre auricular tag (unilateral or bilateral) Atresia, CHL& sometimes SNHL	MR, anomalies of cervical spine, oral and mandibular anomalies, congenital heart defect, eye anomalies , renal anomalies, pulmonary anomalies, gastrointestinal anomalies
Townes Brocks Syndrome	Autosomal dominant inheritance	SNHL or mixed, dysmorphic pinnae, satyr form of loop ear	Triphalangeal thumb, imperforate anus, lop ear, ventriculo-septal defect, occasional cognitive impairment, absence of bones in feet and hands, renal anomalies
Lacrimo auricular dento digital syndrome	Autosomal dominant inheritance	Cup shaped ears, Mixed, CHL or SNHL, stiffness of the ME system, ossicular abnormalities	Naso lacrimal duct obstruction, hypoplasia of lacrimal puncta with occasional lack of tear formation, various pre-axial ray, radial anomalies, peg shaped or missing teeth with mild amelogensis imperfecta
Acro craniofacial dystososis	Autosomal recessive inheritance	Low set ears, pre auricular pits, thick and overturned helics with prominent crus of helix andt atresia CHLor SNHL Bilateral non progressive	Craniofacial anomalies, developmental delay, short stature, ventricular septal defect, bony obstruction of naso lacrimal
Di George syndrome sequence	Chromosomal &single gene disorder	CHL, absence of ossicles, anomalies of ME, Bilateral mondini anomaly	Hypoplasia of parathyroid gland & thymus interrupted aortic arch or truncus, arteriosis, CLP, eye anomalies, nasal abnormalities
Dysmorphic pinnae, MR and mixed HL	Autosomal recessive inheritance	CHL, mixed progressive, bilateral low set ears, hypoplasic crus	MR of varying degrees, congenital hearing loss may not be present
Dysmorphic pinnae, facial palsy & stapedial anomalies	Autosomal dominant inheritance with variable expresion		
Lop ear, micrognathia and CHL	Autosomal dominant inheritance		
Dysmorphic pinnae & CHL	Autosomal recessive inheritance		
Branchio oculofacial syndrome	Autosomal dominant inheritance		
Autosomal dominant aural atresia, microtia & CHL	Autosomal dominant inheritance with variable expresion		
Autosomal recessive aural atresia, microtia & CHL	Autosomal recessive inheritance		
Rasnussen syndrome(Aural atresia, vertical talus& CHL)	Autosomal dominant inheritance		
Aural atresia, microtia, aortic arch anomalies & CHL	Autosomal recessive inheritance		
Aural atresia, microtia, hypertelorism, facial clefting, CHL, (Bixler syndrome)	Autosomal recessive inheritance or X linked inheritance		
Aural atresia, microtia, unusual facies,pseudo-papilidium, Mixed HL	Autosomal dominant inheritance		

iv. Mutation in the mitochondrial genome can affect energy production through adenosine triphosphase synthesis and oxidative phosphorylation. Tissues that require high levels of energy are particularly affected.

v. Typically, mitochondrial diseases involve progressive neuromuscular degeneration with ataxia, ophthalmoplegia, and progressive hearing loss.

III. Mitochondrial mutation and syndromic hearing loss

i. Systemic neuromuscular syndromes such as Kearns Sayre Syndrome, mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes etc frequently have hearing loss as one of their clinical signs. It is due to heteroplasmic mutation.

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ii.[Homoplasmic mutation- most healthy individuals appear to have only a single mitochondrial DNA gene type which is homophasic but in many mitochondrial disease, the mitochondrial DNA population is mixed which is the heteroplasmic condition].

iii. SNHL caused by Diabetes Mellitus is inherited by A3243G in the gene for tRNA.

iv. Late onset HL develops after onset of diabetes

v.In addition to diabetes mellitus, diabetic insipidis, otic atrophy and hearing loss have been well described as the Wolfram syndrome usually an autosomal recessive condition.

a) A3243G

i. Gene defect on mitochondrial DNA (mt DNA).

ii. Associated with deletion in the mitochondrial genome.

iii. A & G stand for - Adenine & Guanine.

iv. 3243 stands for - position of transposition.

v. The convention adopted for describing transposition defects is to show the correct neucleotide (A), then show position of transposition (3243) and then incorrect nucleotide (G).

1) Mitochondrial Mutation and Ototoxicity

i. Aminoglycoside ototoxicity is a common cause of acquired hearing loss. (Prezant et al 1993)

ii. They analysed 3 chinese families where individuals developed HL after the use of aminoglycosides.

iii. Found that mitochondrial ribosomes and mitochondrially encoded 12S rRNA gene are the locus of such predisposition to toxicity.

b)1555DELG

i. The hearing loss is sensorineural and may be progressive.

ii. Those who have this condition may have sudden hearing loss when exposed to aminoglycoside antibiotics (e.g., neomycin, gentamycin, streptomycin, kanamycin, tobramycin, or amikacin).

Non syndromic hearing loss

iii. Hearing impairment (HI) is the most common sensory impairment, affecting 1/650 newborns (Mehl & Thomson,2002).

iv. 30% of the cases, a specific syndrome can be identified.

v. The remaining 70% of cases are non syndromic (Marazita et al, 1993; Morton, 1991).

vi. NS SNHL is almost genetically heterogeneous, with the number of involved genes estimated to be over one hundred.

vii. At present, pedigree analysis and audiometric morphology are still the most popular means of attempting a sub-categorization of the isolated types of genetic hearing loss.

viii.Genes of non-syndromic disorder are designated as DFN,

a) DFNA: Nonsyndromic deafness, autosomal dominant

b) DFNB: Nonsyndromic deafness, autosomal recessive

c) DFNX: Nonsyndromic deafness, X-linked

ix. Several recessive and dominant loci have been mapped to the same chromosome regions.

IV. Genes related to nonsyndromic deafness

ACTG1, CDH23, CLDN14, COCH, COL11A2, DFNA5, ESPN, EYA4, GJB2, GJB6, KCNQ4, MYO15A, MYO6, MYO7A, OTOF, PCDH15, POU3F4, SLC26A4, STRC, TECTA, TMC1,TMIE, TMPRSS3, USH1C, and WFS1 genes cause nonsyndromic deafness, with weaker evidence currently implicating genes GJB3, and MYO1A.

i. Most of the autosomal recessive loci cause pre-lingual severe to profound hg loss.

ii. An exception is DFNB8, in which the hearing impairment is post lingual and rapidly progressive.

iii. Most of the autosomal dominant loci cause post lingual hearing impairment.

iv. Some exceptions are DFNA3, DFNA8 etc.

v. X linked non syndromic hearing loss can be either pre or post lingual.

vi. Disorder due to DFN3 has mixed hearing loss

vii. DFNA1 (medical condition): Dominantly inherited hearing loss that occurs without any other symptoms - i.e. is not associated with any other condition.

viii Type 1 involves a defect of the Drosophila diaphanous gene on chromosome 5q31.

ix. Regulation of acting polymerization in haircells of the inner ear.

x. The non syndromic hearing loss can again inherited by Autosomal dominant or recessive or X - linked or even mitochondrial inheritance.

xi. There are many genes responsible for the complete development of cochlea and other auditory structures.

xii. Any mutation in these genes can cause malformation of inner ear.

xiii. Arrest in normal development or aberrant development of inner ear structures may result in hearing impairment.

xiv. Computerized temporal bone imaging techniques reveal that about 20% of children with congenital sensorineural hearing loss have subtle or severe abnormalities of the inner ear.

xv. About 65% of such abnormalities are bilateral; 35% are unilateral.

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V. Autosomal dominant non- syndromic HL

i. Dominant progressive hearing loss is a type of non-syndromic

ii. Non-congenital sensorineural hearing loss

iii. Variable in age of onset and rate of progression.

iv. It is inherited in an autosomal dominant pattern.

v. Age of onset can vary from early childhood in some families to early adulthood in others.

vi. Presymptomatic gene carriers may demonstrate elevated thresholds for stapedial reflexes and positive signs for recruitment.

vii. Eventually the disease progresses to the level of severe to profound hearing loss.

viii. More than 12 genes causing dominant progressive hearing loss have been localized.

ix. Konigsmark and Gorlin defined four types of dominant progressive hearing loss:

a)early onset

b)high frequency

c)midfrequency

d)low frequency

Heterogeneity has been documented for each subtype as exemplified by four types of high frequency dominant progressive hearing loss identified by audiogram configuration within family groups.

VI. Autosomal recessive non syndromic HL

Konigsmark and Gorlin divided nonsyndromic recessive sensorineural hearing loss into three subtypes.

These are

i. congenital severe-to-profound,

ii. congenital moderate,

iii. and early onset

VII. Autosomal Dominant Auditory Neuropathy

i. AN - clinically heterogeneous set of hearing disorders, neural functions are impaired but the OHCs of the cochlea appear to function normally.

ii. Some families show autosomal dominant patterns of inheritance and affected members usually have peripheral neuropathy.

iii. Kovach et al - mutation of PMP22 gene associated with Charcot- Marie - Tooth syndrome as a possible link to some of the characteristics of neuropathy, chromosome affected is 8q24.

c)PMP22 Gene

i.' Peripheral Myeline Protein 22 gene' provides instructions for making protein called PMP22.

ii. This protein is major component of myelin. This is produced primarily by schwan cells.

iii. PMP22 may also play a role in regulating cell division and maturation, cell shape etc.

iv. Charcot-Marie-Tooth Disease and hereditary neuropathy are associated with PMP22 mutation

v. The early onset subtype usually progresses rapidly from onset at age 1 ½ years to profound loss by age 6.

vi. Genetic linkage studies have identified at least 15 gene loci for recessive nonsyndromic hearing loss.

vii. The gene DFNB2 on chromosome 13q may be the most common and has been identified as connexin 23.

viii. Another gene, DFNB1, also found on chromosome 13 codes for a connexin 26 gene gap junction protein.

VIII. X - linked non - syndromic hearing loss

i.At least 6 loci on the X-chromosome for nonsyndromic hearing loss are known.

ii. Two types of nonsyndromic

They are

a) early onset rapidly progressive type

b) and a moderate slowly progressive type

IX.Mitochondrial Inheritance of non syndromic hearing loss

i. Majority of mutations are a cause of maternally inherited multisystem disorder.

ii. Mitochondrial inheritance is by MTRNR1 and MTTS1.

iii. May lead to severe to profound SNHL

iv. MTRNR1 causes mitochondrial inheritance which further induces HL by aminoglycoside

X. Mitochondrial Determined Hearing Impairment

i. The mitochondrial DNA molecule encodes 13mRNA and 2 rRNA and 22 tRNA, that are required for assembling a functional mitochondrial protein synthesizing system.

ii. The 13mRNAs are translated on mitochondrian specific genetic code into 13 proteins which are required to form the five enzyme complexes required for oxidative phosphorylation.

iii. These complexes are involved in electron transport and ATP synthesis.

iv.With rare exception, mitochondrial DNA is transmitted only through mother.

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v. This leads to expectation that a defect in mitochondrial gene should lead to disease equally in both sexes, but can only be transmitted through maternal line.

XI.Presbycusis

i. Another condition associated with acquired heteroplasmic mutations and hearing loss is presbycusis.

ii. Since mitochondrial DNA mutations and the resulting loss of oxidative phosphorylation activity seem to play an important role in the aging process, it is not unlikely that mitochondrial mutations in the auditory system can also lead to presbycusis).

iii. These mutations are thought to be associated with insidious decline in physiological and biochemical performance of an organ and to contribute significantly to the ageing process and ultimately death.

iv. Accordingly, suggests that presbyacusis is due to deletions and in particular a 4977 nucleotide deletion which is also called "common deletion".

XII. Noise Induced Hearing Loss NIHL

A. Guy Van Camp

i. KCNE1 show the version of the gene associated with increased risk to noise causes the encoded ion channel to open more rapidly than the normal version.»

ii. This defective gene could be responsible for making people sensitive to noise.

CONNEXIN 26 (Figure 4)

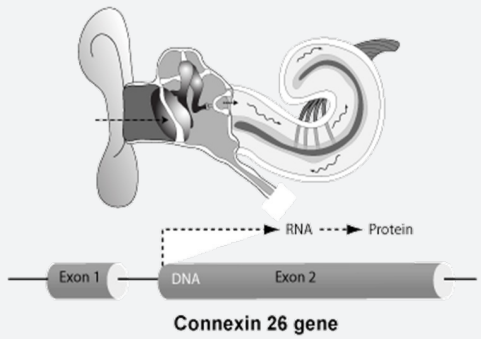

Figure 4: Connexin 26 gene.

a) Connexins are transmembrane proteins that form channels allowing rapid transport of ions or small molecules between cells.

b) Gap junctions are clusters of intercellular channels that allow direct communication between cells.

c) Cx26 is one member of a family of related gap junction channel forming proteins each of which is commonly named from its molecular weight (Cx26, Cx30 etc.).

d) The genes for 20 different connexin proteins are present in the human genome.

e) There are two types of connexins, alpha and beta, named GJA or GJB followed by a number

f) The connexins of one cell align symmetrically with those of its neighbor to create continuous aqueous pores that functionally couple the adjacent cells.

g) Connexins aggregate in the plane of the plasma membrane to form a gap junction plaque.

h) Connexin genes involved in deafness are GJBJ (Cx32), which is also responsible for X- linked Charcot Marie Tooth disease , GJB3 (Cx31) involved in both deafness and a skin disease.

i) Several connexin genes (GJB1, GJB2, GJB3, GJB6 and GJA1) have been found mutated in patients with non-syndromic and/or syndromic deafness indicating an important role of these proteins.

j) As development proceeds, expression of these two genes was found in various subtypes of fibrocytes, either within the spiral limbus or along the spiral ligament, as well as in the basilar membrane cells, in the Reissner's membrane cells, and in subsets of the cellular elements of the cochlear ganglion.

k) The genes for 20 different connexin proteins are present in the human genome.

l) There are two types of connexins, alpha and beta, named GJA or GJB followed by a number

mGjb3 and Gjb1 expression was spatiotemporally modulated within the sensory hair cells and the various supporting cells that compose the developing organ of Corti.

n)A transitory expression of Gjb1 was found in the basal and intermediate cells of the stria vascularis of auditory system.

o) Everyone has two copies of this gene, but if each parent has a flawed, recessive copy of the GJB2/ Connexin 26 gene, the baby may be born with hearing loss.

p) This is because the mutation is suspected of disrupting potassium flow in the inner ear.

q) Approximately 50% of childhood non syndromic recessive hearing loss is caused by mutations in the connexin 26 (Cx26 gene (GJB2/DFNB)

r) The most common mutation that is found in the connexin 26 gene is 35delG, which means that a G is deleted at position 35.

s) This is because the mutation is suspected of disrupting potassium flow in the inner ear.

t) Approximately 50% of childhood non syndromic recessive hearing loss is caused by mutations in the connexin 26 (Cx26 gene (GJB2/DFNB)

u) The most common mutation that is found in the connexin 26

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gene is 35delG, which means that a G is deleted at position 35.

v) More than 90 different mutations have been found in the coding sequences of connexin 26.

w) Most are rare, but a few are relatively common in particular populations (e.g. 267delT and 235 delC in Ashkenazi Jewish and Asian populations, respectively).

1) Multifactorial Genetic Disorders

i.Some disorders appear to result from a combination of genetic factors interacting with environmental influences.

ii.Examples of this type of inheritance associated with hearing loss include clefting syndromes, involving conductive hearing loss, and the microtia/hemifacial microsomia/Goldenhar spectrum.

iii.Goldenhar's syndrome has been described as autosomal dominant in some families, although this may simply represent clustering.

iv. Findings in this syndrome include preauricular tags/pits, vertebral anomalies such as hypoplastic or hemivertebrae in the cervical region, epibulbar dermoids, and coloboma of the upper lid. Other conditions believed to represent multifactorial inheritance are increased susceptibility to hearing loss and hyperlipidemia.

2)Autosomal Chromosomal Syndromes

i. Middle ear and mastoid disease are often observe in Down syndrome children, but sensorineural hearing loss may also be present.

ii. Trisomy 13, which is often lethal in the newborn period, can have significant sensorineural hearing loss in the survivors. Turner's syndrome, monosomic for all or part of one X chromosome, presents generally in female as gonadal dysgenesis, short stature, and often webbed neck or shield chest.

iii.They will also have sensorineural, conductive, or mixed hearing loss, which can be progressive and may be the first evidence of the syndrome in prepubertal females.

3) Otosclerosis

i. Otosclerosis is caused by proliferation of spongy type tissue on the otic capsule eventually leading to fixation of the ossicles and producing conductive hearing loss.

ii. Hearing loss may begin in childhood but most often becomes evident in early adulthood and eventually may include a sensorineural component.

iii. Otosclerosis appears to be transmitted in an autosomal dominant pattern with decreased penetrance, so only 25% to 40% of gene carriers show the phenotype. The greater proportion of affected females points to a possible hormonal influence.

iv. Recent statistical studies suggest a role for the gene COLIA1 in otosclerosis, and measles viral particles have been identified within the bony overgrowth in otosclerotic foci, raising the possibility of an interaction with the viral genome.

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