Global Journal of Otolaryngology
ISSN 2474-7556

Juniper Publishers
key to the Researchers

Review Article
Special Issue – March 2017
DOI: 10.19080/GJO.2017.05.555665

Glob J Otolaryngol

Genetic Hearing Loss- Syndromes

(Figure 1) Autosomal dominant

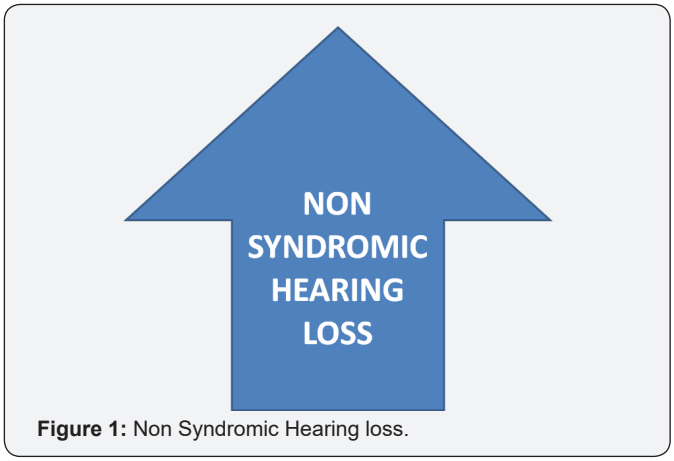

Figure 1: Non Syndromic Hearing loss.

Locus name- DFNA

a) Some cause pre-lingual deafness, progressive and affects all frequencies and sometimes downward sloping type hearing loss

b) Mostly post-lingual deafness affecting all frequencies and begins in any decade of life.

Autosomal recessive

Locus name- DFNB

a) Some cause post-lingual deafness, can be stable or progressive and causes moderate to profound hearing loss.

b) Most of them cause pre lingual, can be stable or progressive and causes moderate to profound hearing loss (Tables 1 & 2) (Figure 2).

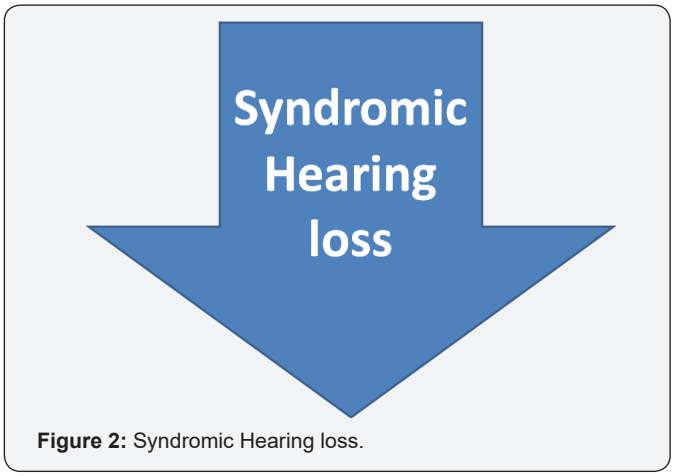

Figure 2: Syndromic Hearing loss.

Table 1: X- Linked NSHI.

Locus Name	Gene Symbol	Onset	Type and Degree	Frequencies
DFNX1 (DFN2)	PRPS1	Post-lingual	Progressive sensorineural; severe to profound	All
DFNX2 (DFN3)	POU3F4	Pre-lingual	Progressive, mixed; variable, but progresses to profound	All
DFNX4 (DFN6)	SMPX	Postlingual	Progressive sensorineural; mild to profound	All

Table 2: Mitochondrial NSHI.

Gene Symbol	Mutation	Severity	Penetrance
MT-RNR1	961 different mutations	Variable	Highly variable, aminoglycoside induced
	1494C>T		
	1555A>G		
MT-TS1	7445A>G		Highly variable
	7472insC		
	7510T>C		
	7511T		
MT-CO1	7444G>A	Severe to profound	Complete, aminoglycoside associated; associated with MT-RNR1 1555A>G

Apert Syndrome

i. AKA= Acrocephalosyndactyly

Single gene autosomal dominant caused by the mutation of FGFR2 gene, located on the long arm of chromosome 10 at 10q26

Audiological findings

a) CHL-mild to moderate

b) chronic middle ear disease

c) ossicular anomalies

Symptoms

i. CNS growth affected

ii. craniofacial & limb abnormalities

iii. mitten hand

iv. low set ears posteriorly rotated

v. synostosis of one or more ossicles

vi. Fixation of footplate of stapes

vii. Reduced ME space

viii. ET dysfunction

ix. Syndactyly of fingers and toes

x. Brachymelia

xi. MR

xii. Hydrocephaly

xiii. Cognitive imparment

Waardenburg Syndrome

a) It is the most common form of inheritable congenital deafness.

b) Genetic Analysis Distal end of band 2q35gene responsible is: PAX3

c) There is a significant amount of variability of expression in this syndrome.

There may be unilateral or bilateral sensorineural hearing loss in patients and the phenotypic expressions may include pigmentary anomalies and craniofacial features.

Symptoms

a) Marked facial asymmetry

b) Lagophthalmos

c) A drooping right corner of the mouth.

d) Absence of naso-frontal angle

e) Eyebrow hypertrichosis

f) Upturned nasal tip

g) Shortened upper lip

h) Pronounced cupid's bow.

I. Type I: Waardenburg syndrome is characterized by evidence of dystopia canthorum and the full symptomatology of the disease.

a) Narrow nose

b) Marked hypoplasia of the nasal bone,

c) Short philtrum

d) Short and retro positioned maxilla.

e) Convergent strabismus (blepharophimosis)

f) Reduced visibility of the medial sclera

g) The head circumference, clivus length, and facial depth are smaller in affected individuals with this syndrome.

II. Type II: Waardenburg syndrome is a heterogeneous group with normally located canthi (without dystopia canthorum).

a) Sensorineural hearing loss (77%)

b) Heterochromia iridium (47%) is the 2 most important diagnostic indicators for this type.

III. Type III- Waardenburg syndrome (Klein-Waardenburg syndrome) is similar to type I but is also characterized by musculoskeletal abnormalities

a) Aplasia of the first 2 ribs

b) Lack of differentiation of the small carpal bones

c) cystic formation of the sacrum

d) Abnormalities of the arms

e) Amyoplasia and stiffness of the joints

f) Bilateral cutaneous syndactyly

g) mental retardation

h) Microcephaly

i) severe skeletal anomalies.

IV. Type IV: Waardenburg syndrome (Shah-Waardenburg syndrome) is the association of Waardenburg syndrome with congenital aganglionic megacolon (Hirschsprung disease).

A. Dystopia canthorum is found in 41.2-99% of persons with Waardenburg syndrome.

a) The distance between the inner angles of the eyelids is accompanied by increased distance between the inferior lacrimal points.

b) Hageman and Delleman divided Waardenburg syndrome into 2 variants: with dystopia canthorum and without.

I. Congenital deafmutism occurs in 9-62.5% of persons with Waardenburg syndrome.

II. Different combinations of hearing loss occur: unilateral or bilateral, severe or moderate, total or moderate.

 How to cite this article: Genetic Hearing Loss- Syndromes. Glob J Oto 2017; 5(3): 555665.. DOI: 10.19080/GJO.2017.05.555665.

Fisch separated Waardenburg syndrome into the following distinct types according to audiogram results.

a) Patients with total deafness and little residual hearing at the lower frequency

b) Patients with a moderate degree of deafness with uniform hearing loss in the lower and middle frequency with improvement in the higher frequency

i. Pigmentary disturbances of hairs in Waardenburg syndrome include 2 types of alterations: white forelock and premature graying of scalp hair, eyebrows, cilia, or body hair.

ii. The white forelock is observed in 17-58.4% of persons with Waardenburg syndrome and involves the forehead (and both medial eyebrows), the vertex, or another part of scalp.

iii. The white forelock may be evident at birth or soon afterward, or it may develop later.

iv. Poliosis may persist throughout life or may disappear in the first years of life and reappear later.

v. Patients with Waardenburg syndrome become prematurely gray in 7% of cases.

Stickler Syndrome

a) Cleft palate and severe myopia are its characteristics features.

b) Significant sensorineural hearing loss or mixed hearing loss is present in about 15% of cases, whereas hearing loss of lesser severity may be present in up to 80% of cases.

c) Autosomal dominant- COLI1A1, COLI1A2,COL2A1, COL2A2 and several others

Norrie Syndrome

Norrie syndrome is a sex-linked disorder that includes congenital or rapidly progressive blindness

Alport Syndrome

a. Alport syndrome involves hearing loss associated with renal impairment of varying severity.

b. When a genetic mutation occurs, connecting structures in both the inner ear and kidney become increasingly fragile, resulting in progressive hearing impairment and kidney disease

c. Eustation tube dysfunction occurs secondarily to the cleft palate and results in conductive hearing loss.

d. Ossicular abnormalities may also be present.

Branchio-oto-renal Syndrome

a. Branchio-oto-renal syndrome is estimated to occur in 2% of children with congenital hearing impairment.

b. Seventy-five percent of patients with branchio-oto-renal syndrome have significant hearing loss.

Treacher Collins Syndrome

a. Conductive hearing loss is present 30% of the time, but sensorineural hearing loss and vestibular dysfunction can also be present.

b. Ossicular malformations are common in these patients.

c. The syndrome is transmitted autosomal dominant with high penetrance gene located on 5q-32-q33.1, TREACLE

Neurofibromatosis

1) Mental retardation, blindness, and sensorineural hearing loss can result from central nervous system tumors.

2) Neurofibromatosis is classified as types 1 and 2.

3) Autosomal dominant 22q12.2.

4) NF2 is a tumor supressor gene

5) Acoustic neuromas are usually unilateral and occur in only 5% of affected patients.

6) Neurofibromatosis type 2, which is a genetically distinct disorder, is characterized by bilateral acoustic neuromas.

7) Bilateral acoustic neuromas are present in 95% of affected patients and are usually asymptomatic until early adulthood.

Ushers Syndrome

a. Usher's syndrome has a prevalence of 3.5 per 100,000 populations.

b. Sensorineural hearing loss and retinitis pigmentosa characterize the syndrome.

I. Usher type 1 patients have congenital bilateral profound hearing loss and absent vestibular function

II. Type 2 patients have moderate losses and normal vestibular function.

III. Type 3 demonstrate progressive hearing loss and variable vestibular dysfunction and are found primarily in the Norwegian population.

Pendred Syndrome

a. Pendred's syndrome includes thyroid goiter and profound sensorineural hearing loss.

b. Hearing loss is progressive in about 15% of patients.

The majority of patient present with bilateral moderate to severe sensorineural hearing impairment, with some residual hearing in the low frequencies.

How to cite this article: Genetic Hearing Loss- Syndromes. Glob J Oto 2017; 5(3): 555665. DOI: 10.19080/GJO.2017.05.5556665.

Otopalatodigital Syndrome

a) Otopalatodigital syndrome includes hypertelorism, craniofacial deformity involving supraorbital area, flat midface, small nose, and cleft palate.

b) Patients are short statured with broad fingers and toes that vary in length, with an excessively wide space between the first and second toe.

c) Conductive hearing loss is seen due to ossicular malformations. Affected males manifest the full spectrum of the disorder and females may show mild involvement.

d) The gene has been found to be located on chromosome Xq28.

Wildervaank Syndrome

a. Wildervaank's syndrome is comprised of the Klippel-Feil sign involving fused cervical vertebrae, sensorineural hearing or mixed hearing impairment, and cranial nerve 6 paralysis causing retraction of the eye on lateral gaze.

b. This syndrome is seen most commonly in female because of the high mortality associated with the X-linked dominant form in males. Isolated Klippel-Feil sequence includes hearing impairment in about one third of cases.

c. The hearing impairment is related to bony malformations of the inner ear.

Jervell and Lange-Neilsen Syndrome

a. Jervell and Lange-Neilsen syndrome is a rare syndrome that consists of profound sensorineural hearing loss and syncopal episodes resulting from a cardiac conduction defect.

b. Genetic studies attribute one form of Jervell and Lange-Neilsen syndrome to homozygosity for mutations affecting a potassium channel gene (KVLQT 1) on chromosome 11p15.5, which are thought to result in delayed myocellular repolarization in the heart. The gene KCNE1 has also been shown to be responsible for the disorder.

Hereditary Meniere's syndrome

a. Recurrent severe unilateral headaches

b. variable results of vestibular function tests

c. Vertigo and vomiting

Audiological findings: fluctuating SNHL

Unilateral or bilateral

Assymetrical and progressively deteriorates

Mild to severe HL

Autosomal recessive transmission

Charge

a. Coloboma, Heart anomalies, Atresia, Choanae, Retarded growth and development, Genital hypoplasia and ear anomalies

b. Autosomal dominant inheritance

c. CHL, SNHL or mixed, trough shaped configuration and vestibular anomalies

Symptoms

a. CNS impairment

b. Brain malformation

c. Facial paresis

d. Facial assymetry

e. Microcephaly

f. Low set posteriorly rotated ears

g. Micrognathia

h. Nasal root

i. Semicircular canal

j. Hypoplasia

k. Heart anomalies

l. Tracheoesophageal fistula

m. Genital anomalies

n. Scoliosis

o. Short neck

Crouzon syndrome (Craniofacial dyostosis)

I. Mutation of single gene FGFR2 located on the long arm of chromosome 10 at 10 q 26

II. Autosomal dominant inheritance with variable expression

III. CHL common. Mild to moderate stenosis of EAC, chronic middle ear disorder and ossicular anomalies

Symptoms

a. Maxillary hypoplasia

b. Malocclusion

c. Soft tissue hypertrophy of hard palate

d. Cognitive impairment

e. Increased intracranial pressure

f. Bulging eyes

g. Dental crowding

 How to cite this article: Genetic Hearing Loss- Syndromes. Glob J Oto 2017; 5(3): 555665.. DOI: 10.19080/GJO.2017.05.555665.

h. Abnormality of cranial and facial bones

i. Cleft palate

j. synostosis

Down Syndrome

a. Trisomy of the 21st chromosome.

b. Gene located on 21q22.3

c. CHL, SNHL or mixed, chronic middle ear infection, serous otitis media and middle ear effusion, ET dysfunction, structural abnormalities of cochlea and decreased length

Symptoms

a. CNS impairment

b. Mental retardation

c. Alzheimer's disease

d. Hypotonia

e. Cerebral and cerebellar hypoplasia

f. Brachycephaly

g. Microcephaly

h. Macroglossia

i. Small ears, stature

j. Obesity

k. Small fingers

l. Branchydactyly

Hunter syndrome

a. X- linked recessive inheritance. Gene mapped to Xq 28 and is labelled as IDS

b. CHL, Chronic middle ear disorder, glue ear, progressive HL

Symptoms

i. Short stature,

ii. cognitive defects,

iii. Thick lips,

iv. alveolar ridge hypertrophy,

v. thickening of palate,

vi. abnormal retinal pigmentation,

vii. retinal degenration,

viii. corneal opacities,

ix. heart, liver and spleen problems

Apert syndrome

i. AKA= Acrocephalosyndactyly

Single gene autosomal dominant caused by the mutation of FGFR2 gene, located on the long arm of chromosome 10 at 10q26

Audiological findings

a. CHL-mild to moderate

b. chronic middle ear disease

c. ossicular anomalies

Symptoms

i. CNS growth affected

ii. craniofacial & limb abnormalities

iii. mitten hand

iv. low set ears posteriorly rotated

v. synostosis of one or more ossicles

vi. Fixation of footplate of stapes

vii. Reduced ME space

viii. ET dysfunction

ix. Syndactyly of fingers and toes

x. Brachymelia

xi. MR

xii. Hydrocephaly

xiii. Cognitive imparment

Waardenburg syndrome

a. It is the most common form of inheritable congenital deafness.

b. Genetic Analysis Distal end of band 2q35gene responsible is: PAX3

c. There is a significant amount of variability of expression in this syndrome.

There may be unilateral or bilateral sensorineural hearing loss in patients and the phenotypic expressions may include pigmentary anomalies and craniofacial features.

Symptoms

a. Marked facial asymmetry

b. Lagophthalmos

c. A drooping right corner of the mouth.

d. Absence of naso-frontal angle

How to cite this article: Genetic Hearing Loss- Syndromes. Glob J Oto 2017; 5(3): 555665. DOI: 10.19080/GJO.2017.05.5556665.

e. Eyebrow hypertrichosis

f. Upturned nasal tip

g. Shortened upper lip

h. Pronounced cupid's bow.

A. Type I: Waardenburg syndrome is characterized by evidence of dystopia canthorum and the full symptomatology of the disease.

a) Narrow nose

b) Marked hypoplasia of the nasal bone,

c) Short philtrum

d) Short and retro positioned maxilla.

e) Convergent strabismus (blepharophimosis)

f) Reduced visibility of the medial sclera

g) The head circumference, clivus length, and facial depth are smaller in affected individuals with this syndrome.

B. Type II: Waardenburg syndrome are a heterogeneous group with normally located canthi (without dystopia canthorum).

a) Sensorineural hearing loss (77%)

b) Heterochromia iridium (47%) are the 2 most important diagnostic indicators for this type.

C. Type III: Waardenburg syndrome (Klein-Waardenburg syndrome) is similar to type I but is also characterized by musculoskeletal abnormalities

a) Aplasia of the first 2 ribs

b) Lack of differentiation of the small carpal bones

c) cystic formation of the sacrum

d) Abnormalities of the arms

e) Amyoplasia and stiffness of the joints

f) Bilateral cutaneous syndactyly

g) mental retardation

h) Microcephaly

i) severe skeletal anomalies.

D. Type IV: Waardenburg syndrome (Shah-Waardenburg syndrome) is the association of Waardenburg syndrome with congenital aganglionic megacolon (Hirschsprung disease).

a) Dystopia canthorum is found in 41.2-99% of persons with Waardenburg syndrome.

i. The distance between the inner angles of the eyelids is accompanied by increased distance between the inferior lacrimal points.

ii. Hageman and Delleman divided Waardenburg syndrome into 2 variants: with dystopia canthorum and without.

b) Congenital deafmutism occurs in 9-62.5% of persons with Waardenburg syndrome.

c) Different combinations of hearing loss occur: unilateral or bilateral, severe or moderate, total or moderate.

Fisch separated Waardenburg syndrome into the following distinct types according to audiogram results.

a) Patients with total deafness and little residual hearing at the lower frequency

b) Patients with a moderate degree of deafness with uniform hearing loss in the lower and middle frequency with improvement in the higher frequency

c) Pigmentary disturbances of hairs in Waardenburg syndrome include 2 types of alterations: white forelock and premature graying of scalp hair, eyebrows, cilia, or body hair.

d) The white forelock is observed in 17-58.4% of persons with Waardenburg syndrome and involves the forehead (and both medial eyebrows), the vertex, or another part of scalp.

e) The white forelock may be evident at birth or soon afterward, or it may develop later.

f) Poliosis may persist throughout life or may disappear in the first years of life and reappear later.

g) Patients with Waardenburg syndrome become prematurely gray in 7% of cases.

Stickler Syndrome

i. Cleft palate and severe myopia are its characteristics features.

ii. Significant sensorineural hearing loss or mixed hearing loss is present in about 15% of cases, whereas hearing loss of lesser severity may be present in up to 80% of cases.

iii. Autosomal dominant- COLI1A1, COLI1A2,COL2A1, COL2A2 and several others

Norrie Syndrome

Norrie syndrome is a sex-linked disorder that includes congenital or rapidly progressive blindness

Alport Syndrome

i. Alport syndrome involves hearing loss associated with renal impairment of varying severity.

ii. When a genetic mutation occurs, connecting structures in both the inner ear and kidney become increasingly fragile, resulting in progressive hearing impairment and kidney disease

iii. Eustation tube dysfunction occurs secondarily to the

 How to cite this article: Genetic Hearing Loss- Syndromes. Glob J Oto 2017; 5(3): 555665.. DOI: 10.19080/GJO.2017.05.555665.

cleft palate and results in conductive hearing loss.

iv. Ossicular abnormalities may also be present.

Branchio-oto-renal Syndrome

a) Branchio-oto-renal syndrome is estimated to occur in 2% of children with congenital hearing impairment.

b) Seventy-five percent of patients with branchio-oto-renal syndrome have significant hearing loss.

Treacher Collins Syndrome

i. Conductive hearing loss is present 30% of the time, but sensorineural hearing loss and vestibular dysfunction can also be present.

ii. Ossicular malformations are common in these patients.

iii. The syndrome is transmitted autosomal dominant with high penetrance gene located on 5q-32-q33.1, TREACLE

Neurofibromatosis

a. Mental retardation, blindness, and sensorineural hearing loss can result from central nervous system tumors.

b. Neurofibromatosis is classified as types 1 and 2.

c. Autosomal dominant 22q12.2.

d. NF2 is a tumor supressor gene

e. Acoustic neuromas are usually unilateral and occur in only 5% of affected patients.

f. Neurofibromatosis type 2, which is a genetically distinct disorder, is characterized by bilateral acoustic neuromas.

g. Bilateral acoustic neuromas are present in 95% of affected patients and are usually asymptomatic until early adulthood.

Ushers syndrome

a. Usher's syndrome has a prevalence of 3.5 per 100,000 populations.

b. Sensorineural hearing loss and retinitis pigmentosa characterize the syndrome.

i. Usher type 1 patients have congenital bilateral profound hearing loss and absent vestibular function

ii. Type 2 patients have moderate losses and normal vestibular function.

iii. Type 3 demonstrate progressive hearing loss and variable vestibular dysfunction and are found primarily in the Norwegian population.

Pendred Syndrome

i. Pendred's syndrome includes thyroid goiter and profound sensorineural hearing loss.

ii. Hearing loss is progressive in about 15% of patients.

iii. The majority of patient present with bilateral moderate to severe sensorineural hearing impairment, with some residual hearing in the low frequencies.

Otopalatodigital Syndrome

a. Otopalatodigital syndrome includes hypertelorism, craniofacial deformity involving supraorbital area, flat midface, small nose, and cleft palate.

b. Patients are short statured with broad fingers and toes that vary in length, with an excessively wide space between the first and second toe.

c. Conductive hearing loss is seen due to ossicular malformations. Affected males manifest the full spectrum of the disorder and females may show mild involvement.

d. The gene has been found to be located on chromosome Xq28.

Wildervaank Syndrome

i. Wildervaank's syndrome is comprised of the Klippel-Feil sign involving fused cervical vertebrae, sensorineural hearing or mixed hearing impairment, and cranial nerve 6 paralysis causing retraction of the eye on lateral gaze.

ii. This syndrome is seen most commonly in female because of the high mortality associated with the X-linked dominant form in males. Isolated Klippel-Feil sequence includes hearing impairment in about one third of cases.

iii. The hearing impairment is related to bony malformations of the inner ear.

Jervell and Lange-Neilsen Syndrome

a. Jervell and Lange-Neilsen syndrome is a rare syndrome that consists of profound sensorineural hearing loss and syncopal episodes resulting from a cardiac conduction defect.

b. Genetic studies attribute one form of Jervell and Lange-Neilsen syndrome to homozygosity for mutations affecting a potassium channel gene (KVLQT 1) on chromosome 11p15.5, which are thought to result in delayed myocellular repolarization in the heart. The gene KCNE1 has also been shown to be responsible for the disorder.

Hereditary Meniere's syndrome

a. Recurrent severe unilateral headaches

b. variable results of vestibular function tests

How to cite this article: Genetic Hearing Loss- Syndromes. Glob J Oto 2017; 5(3): 555665. DOI: 10.19080/GJO.2017.05.5556665.

c. Vertigo and vomiting

Audiological finings- fluctuating SNHL

Unilateral or bilateral

Assymetrical and progressively deteriorates

Mild to severe HL

Autosomal recessive transmission

Charge

a. Coloboma, Heart anomalies, Atresia, Choanae, Retarded growth and development, Genital hypoplasia and ear anomalies

b. Autosomal dominant inheritance

c. CHL, SNHL or mixed, trough shaped configuration and vestibular anomalies

Symptoms

a. CNS impairment

b. Brain malformation

c. Facial paresis

d. Facial assymetry

e. Microcephaly

f. Low set posteriorly rotated ears

g. Micrognathia

h. Nasal root

i. Semicircular canal

j. Hypoplasia

k. Heart anomalies

l. Tracheoesophageal fistula

m. Genital anomalies

n. Scoliosis

o. Short neck

Crouzon syndrome (Craniofacial dyostosis)

a. Mutation of single gene FGFR2 located on the long arm of chromosome 10 at 10 q 26

b. Autosomal dominant inheritance with variable expression

c. CHL common. Mild to moderate stenosis of EAC, chronic middle ear disorder and ossicular anomalies

Symptoms

i. Maxillary hypoplasia

ii. Malocclusion

iii. Soft tissue hypertrophy of hard palate

iv. Cognitive impairment

v. Increased intracranial pressure

vi. Bulging eyes

vii. Dental crowding

viii. Abnormality of cranial and facial bones

ix. Cleft palate

x. synostosis

Down Syndrome

a) Trisomy of the 21st chromosome.

b) Gene located on 21q22.3

c) CHL, SNHL or mixed, chronic middle ear infection, serous otitis media and middle ear effusion, ET dysfunction, structural abnormalities of cochlea and decreased length

Symptoms

a. CNS impairment

b. Mental retardation

c. Alzheimer's disease

d. Hypotonia

e. Cerebral and cerebellar hypoplasia

f. Brachycephaly

g. Microcephaly

h. Macroglossia

i. Small ears, stature

j. Obesity

k. Small fingers

l. Branchydactyly

Hunter syndrome

a. X- linked recessive inheritance. Gene mapped to Xq 28 and is labelled as IDS

b. CHL, Chronic middle ear disorder, glue ear, progressive HL

Symptoms

a) Short stature,

b) cognitive defects,

c) Thick lips,

d) alveolar ridge hypertrophy,

 How to cite this article: Genetic Hearing Loss- Syndromes. Glob J Oto 2017; 5(3): 555665.. DOI: 10.19080/GJO.2017.05.555665.

e) thickening of palate,

f) abnormal retinal pigmentation,

g) retinal degenration,

h) corneal opacities,

i) Heart, liver and spleen problems.

DOI: 10.19080/GJO.2017.05.555665

How to cite this article: Genetic Hearing Loss- Syndromes. Glob J Oto 2017; 5(3): 555665. DOI: 10.19080/GJO.2017.05.5556665.