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## Genetic Hearing Loss Associated with Craniofacial Abnormalities

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### 1. Introduction

It is estimated that hereditary hearing loss accounts for 60% of deafness in the developed countries. About 30% of hereditary hearing impairment is syndromic which involves other presenting abnormalities along with deafness. There are more than 400 syndromes which include various degrees of hearing impairment with different phenotypes. (Barlow Stewart et al., 2007; Berrettini et al., 2008). Abnormalities of different systems or suggestive clinical findings have been associated with syndromic hearing loss. These include craniofacial malformations, dental abnormalities, ocular abnormalities, renal defects, cardiac abnormalities, endocrine dysfunction, neurologic dysfunction, skeletal abnormalities, integumentary abnormalities, metabolic disease, chromosomal abnormalities.

Treacher Collins, Goldenhar and Charge syndrome, Pierre Robin sequence, Stickler, Apert, Crouzon, Pfeiffer and velocardiofacial syndrome are just few conditions in which hearing loss is associated with craniofacial abnormalities. Most of these conditions are related to first and second branchial arches development abnormalities. The first and second branchial arches contribute to the development of skeletal (e.g. mandibula, maxilla, middle ear ossicles), muscular (facial muscles) and nervous (e.g. facial nerve) structures of the face. That explains why, due to the abnormal development of first and second branchial arches, midface malformations are usually the typical findings in these patients. (Gorlin et al., 1995; Johnson et al., 2011)

We describe some of these disorders underlining the main characteristic impairments and the observed hearing loss. We also report our observations on some clinical cases seen at Neonatology Unity of Santa Chiara University Hospital of Pisa (Table 2).

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## 2. Clinical syndromes

### 2.1 Goldenhar syndrome

Hemifacial microsomia (or Goldenhar syndrome or oculo-auricular-vertebral syndrome) is usually a sporadic disorder even if there is evidence of familial transmission. In some cases autosomal recessive and autosomal dominant inheritance have also been described. The incidence of Goldenhar syndrome is reported to be approximately 1 in 5,000-25,000 live births (Editorial Team Orphanet, 2005). Genetic heterogeneity is frequently observed. Kelberman et al performed a genome search for linkage in two families with features of hemifacial microsomia and identified data highly suggestive of linkage to a region of approximately 10.7 cM on chromosome 14q32 for one family (Kelberman et al., 2001).

During embryogenesis the correct development of the 1st or the 2nd branchial arches are hypothesized to be interrupted resulting in Goldenhar Syndrome. Clinical features mainly consist of a hemifacial microsomia. Maxillary, temporal, malar and skull bones can also be involved. Auricular malformations range from mild abnormalities in the external ears (such as preauricular tags or pinnae hypoplasia of various degrees) to anotia. Vertebrae abnormalities (e.g. hemivertebrae and fused vertebrae) as well as facial cleft or ocular abnormalities (epibulbar dermoid, eyelid coloboma, microphtalmia, retinal anomalies) are described. Mouth opening can be modified by mandibular hypoplasia. Congenital heart diseases of various degrees (e.g. ventricular septal defect of Tetralogy of Fallot) or a wide range of CNS malformations can be associated too. Bony involvement can cause weakness of cranial nerves. Mental retardation is described in 5-15% patients. Kidney, pulmonary or gastrointestinal abnormalities can also be associated less frequently. (OMIM 164210; Toriello et al., 2004)

**Hearing loss** in Goldenhar syndrome usually ranges from mild to moderate conductive impairment and severe to profound sensorineural hearing loss (Skarzynski et al., 2009). Deformity of the auricle, external auditory canal atresia and malformation of the tympanic cavity or ossicles may be the main cause of conductive hearing impairment. Abnormalities of the stria vascularis and the semicircular canals have also been reported (Scholtz et al., 2001). Sensorineural hearing loss and facial nerve disfunction is often underestimated. In the study by Carvalho et al (Carvalho et al., 1999) 11% of the patients with Hemifacial microsomia had sensorineural hearing loss.

### 2.2 Charge syndrome

In 1981 Pagon et al. first introduced the acronym "CHARGE" to define a nonrandom association of the following features: **C**oloboma, **H**eart defect, **A**tresia choanae, **R**etarded growth and development, **G**enital hypoplasia and **E**ar anomalies/deafness.

Charge syndrome (OMIM 214800) is a rare disorder with an incidence of about 1 in every 8500-10000 births (Issekutz et al., 2005). CHARGE syndrome is an autosomal dominant disorder. Mutations in *CHD7* have been detected in more than 75% of CHARGE patients. *CHD7* belongs to the gene family coding for ChromodomainHelicase DNA binding proteins. During early human development, *CHD7* is expressed in the undifferentiated neuroepithelium and in mesenchyme of neural crest origin. It is thought to play a role in regulating the expression of important developmental genes in mesenchymal cells derived from the cephalic neural crest, by chromatin remodeling. The phenotype of CHARGE

syndrome can also be caused by mutation in the semaphorin-3E gene. (Michelucci et al., 2010). Patients with Charge syndrome have a typical square-flattened face, usually asymmetric, with a bulbous nasal tip, long philtrum, low-set and dysplastic ears, antimongoloid slant of palpebral fissures, anteverted nares and malar hypoplasia. Ptosis and cleft lip or palate can also be associated findings. (OMIM 214800). Based on Blake et al definition, individuals with all four major characteristics (the classical 4C's: Choanal atresia, Coloboma, Characteristic ears and Cranial nerve anomalies) or three major and three minor characteristics (Cardiovascular malformations, Genital hypoplasia, Cleft lip/palate, Tracheoesophageal fistula, Distinctive CHARGE facies, Growth deficiency, Developmental delay) are highly likely to have CHARGE syndrome. Nevertheless any infant with one or two major criteria and several minor characteristics is highly suspected to have CHARGE. (Blake et al). Based on Verloes criteria the presence of three major findings (Coloboma of the iris or choroid, with or without microphthalmia, Atresia of Choanae, Hypoplastic semi-circular Canals) are necessary and sufficient to make a diagnosis of CHARGE, even if no other features are present. Patients with "borderline phenotypes" are classified in two groups: partial (or incomplete) CHARGE and atypical CHARGE. Partial CHARGE are those individuals who have two major signs but only one minor sign (minor signs for Verloes are Rhombencephalic dysfunction, Hypothalamo-hypophyseal dysfunction, Abnormal middle or external ear, Malformation of mediastinal organs, Mental retardation), whereas individuals with atypical CHARGE are those who have two major signs and no minor sign, or one major sign and at least three minor signs of CHARGE. (Verloes et al., 2005) Coloboma is uni-lateral or bilateral, involving iris, retina and/or disc.

Heart defects in CHARGE syndrome are mainly conotruncal defects or aortic arch anomalies. Urinary defects range from abnormalities of kidney (or genitourinary tract) size or position to renal agenesis, genital hypoplasia, which is typically recognized only in males (micropenis/cryptorchidism). Almost every part of the audiological system can be involved in Charge association. External ears are typically low-set and malformed. Unusually shaped and floppy external Pinnae can cause difficulties in placing behind-ear- hearing aids. Ear canals may be stenotic. The most common audiological features are severe-to-profound asymmetric mixed losses. (Edwards et al., 2002). Ossicular anomalies (eg stapes or incus abnormalities), absence of oval window or absence of the stapedium muscle and middle ear effusion (eustachian tube dysfunction from craniofacial malformation is a common finding) cause conductive hearing loss which is often asymmetrical and fluctuating in nature, usually greater on low frequencies. (Dhooge et al., 1998) . Cochlear malformations such as Mondini's Displasia can contribute to hearing loss. Cochlear involvement is greatest for high frequencies (Thelin et al., 1986). Abnormalities of the semicircular canals can be found in most patients (Morimoto et al., 2006). Auditory neural pathway abnormalities (such as hypoplasia or absence of the auditory nerve) may be involved as well.

### 2.3 Pierre Robin sequence

This condition is commonly defined Pierre Robin "sequence" instead of "syndrome" because the major clinical features have a common origin. The mandibular hypoplasia starts being evident in the first period of gestation and causes an anomalous position of the tongue. This prevents the correct development of the palate. At birth micrognathia, glossoptosis and cleft palate are the main signs. Consequently, respiratory, feeding and swallowing problems are the major problems in these patients. (Evans et al., 2011)

Pierre Robin sequence is usually a sporadic event with an estimated prevalence of about 1/10,000. In about 10% of patients a familial transmission has been described although the involved genes have not been identified.

**Hearing loss** is typically conductive and bilateral patients with Pierre Robin sequence. In Middle ear effusion is a finding in most patients. Therefore the use of tympanostomy (ventilation) tubes is the therapy of choice in patients with Pierre Robin Sequence. In a study by Handzic et al the mean hearing loss at speech frequencies was 24.5 dB (Handzić J et al., 1995, 1996). Pierre Robin Sequence is also a risk factor for sensorineural Hearing Loss: the 30% of the Pierre Robin patients in a study (Medard et al., 1999) had congenital permanent sensorineural evolutive hearing loss.

Another study revealed multiple architectural anomalies involving the entire ear such as abnormal auricles or ossicles, aplasia of the lateral semicircular canals or a large vestibular aqueduct (Gruen et al., 2005).

## 2.4 Stickler syndrome

Stickler syndrome affects about 1 in every 7,500/9,000 newborns. Mutations in the *COL2A1*, *COL9A1*, *COL11A1*, and *COL11A2* genes impairing collagen production have been identified as the cause of this disorder. Except for *COL9A1* mutations which are transmitted in an autosomal recessive fashion, the syndrome is autosomal dominantly inherited. The affected patients show a typical long and flat face with malar and mandibular hypoplasia (midface hypoplasia). The nose is small with a depressed nasal bridge and anteverted nares. The flatness of the face gives the appearance of large eyes. Vision is altered: myopia, cataracts, glaucoma and retinal detachment can be some of the associated findings. Cleft palate, bifid uvula and macroglossia may also occur.

Joint problems are presented by the patients from an early age. This involves arthritis which causes joint pain and stiffness. Flattened vertebrae and spine deformity such as scoliosis or kyphosis vertebral may also be present. Additionally, the prevalence of mitral valve prolapse in this syndrome has been reported to be higher than that in the general population.

**Hearing loss** can be both sensorineural and conductive. The conductive hearing loss in Stickler syndrome type I (*COL2A1*) can be due to the stapedial fixation. It can therefore be improved by stapes surgery. (Baijens et al., 2004)

Mutations in the fibrillar collagen genes *COL11A1* and *COL11A2* can cause sensorineural hearing loss probably due to the essential role these two genes have in the function of the basilar or tectorial membranes. There seems to be a correlation of hearing loss severity, onset, progression and affected frequencies with the underlying mutated collagen gene (Shpargel et al, 2004). In the study by Admiraal et al the mean sensorineural hearing threshold in Stickler patients with *COL11A2* mutation was about 40 dB HL and was liable to increase at the highest frequencies. (Admiraal et al., 2000)

In the study conducted by Szymko-Bennett (Szymko-Bennett et al., 2001) most of the 46 adults with Stickler syndrome had a sensorineural hearing loss, affecting high frequencies. Additionally, hearing loss was not more progressive as compared to age-related hearing loss.

## 2.5 Brachio-Oto-renal (BOR) syndrome

Branchio-oto-renal syndrome (OMIM 113650) is a genetic condition with a prevalence of 1/40,000 births and has an autosomal dominant mode of inheritance. *EYA1*, *SIX1*, and *SIX5* are three genes which are known to be mutated in this syndrome. The syndrome is called "Branchio-oto-renal" because malformations of the second branchial arch are associated with ears and renal abnormalities. The face is typically long and narrow with a constricted palate. (Alkis et al., 2002) Kidney and urinary tract show various degree of involvement. Shape or position abnormalities can be isolated or associated with an impaired renal function. Abnormalities in the development of the second branchial arch lead to neck malformations such as branchial cleft, cysts or fistulae.

**Auditory system** involvement ranges from pinnae abnormalities such as microtia, abnormally shaped ears, pre-auricular tags or pits to inner ear or middle ear malformations leading to sensorineural, conductive or mixed hearing loss. Hearing impairment occurs in 75%-93% of patients with BOR syndrome and ranges from mild to profound. Age of onset varies from early childhood to adult age. Younger patients manifest greater threshold fluctuation. Inner and middle ear anomalies ranges from cochlear hypoplasia, semicircular canals hypoplasia, ossicular anomalies, external auditory canal stenosis or atresia, vestibular dysplasia, enlarged aqueductus or endolymphatic sac (the last seems to predispose to more severe hearing impairment), absence of stapedium muscle or Eustachian tube dilation and cochlear nerve deficiency. (Huang et al., 2011; Kemperman et al., 2004)

## 2.6 Treacher-Collins syndrome

Treacher Collins syndrome (TCS) is an autosomal dominant disorder of craniofacial development with an incidence of 1 in 50,000 live births. It shows genetic heterogeneity: Treacher Collins syndrome-1 (TCS-1) (OMIM 154500) is caused by a heterozygous mutation in *TCOF-1* located on chromosome 5q32 (Wise et al., 1997). Treacher Collins syndrome-2 (OMIM 613717) is caused by a heterozygous mutation in *POLR1D* on chromosome 5q32.13q12.2, while TCS-3 (OMIM 248390) is caused by a heterozygous mutation in the *POLR1C* gene on chromosome 6. However, about 60% of TCS patients have *de novo* gene mutations. Some authors hypothesize that these genetic mutations lead to an aberrant expression of a nuclear protein critically required during human craniofacial development.

Facial abnormalities are usually bilateral in TCS. They involve facial bones showing zygomatic arches hypoplasia, hypoplasia of supraorbital rims and micrognathia. The face is narrow with an antimongoloid slant of the eyes and hypertelorism. Coloboma of the lower lid can be present with deficiency of cilia medial to the coloboma. Ophthalmologic defects such as vision loss or refractive errors require specialistic evaluation: Preauricular hair displacement is a typical finding.

External ear show abnormalities ranging from various degree of pinnae malformations to microtia. About 40-50% of the patients with Treacher Collins have conductive **hearing loss** (often compounded by a high-frequency sensory component) mainly caused by hypoplasia of the middle ear or malformations of the ossicles. Inner ear is usually normal. Pron et al. reported on the hearing loss and computerized tomography (CT) assessments of ear malformations in a large pediatric series of patients with Treacher Collins. Of the 23 subjects assessed the external ear abnormalities were largely symmetric, with a stenotic

atresic canal. In most cases, the middle ear cavity was hypoplastic and dysmorphic with aberrant ossicles while inner ear structures were normal. The majority of patients had asymmetric conductive hearing loss of various degrees. Hearing loss was bilateral and mixed in three patients. (Pron et al., 1993; Jahrsdoerfer et al., 1995).

## 2.7 Apert syndrome

Apert syndrome (or Acrocephalosyndactyly) (OMIM 101200) occurs in about 1 every 65,000-88,000 newborns. It is usually sporadic but some familial cases with an autosomal dominant way of inheritance have been observed. Mutations in *FGFR2* (fibroblast growth factor receptor-2) increase the number of precursor cells involved in the osteogenic process leading to increased subperiosteal bone matrix and premature ossification. Consequent premature skull bone ossification leads to craniosynostosis (especially affecting the coronal sutures) which is the main clinical pattern in Apert syndrome (Rice et al., 2008). Patients with this condition have a typical back to front flat skull with frontal bossing which is longer than usual. Eyes are wide set and the midface is typically hypoplastic with a retrusion of supraorbital wings which make proptosis evident, eyebrows interruption, a beaked nose and a small upper jaw causing crowded upper teeth projecting back to the lower teeth.

Cranial abnormalities are quite directly related to brain development: mental status ranges from normal intelligence to various degree of mental retardation. Hydrocephalus and malformations of corpus callosum or septum pellucidum are common findings. Craniofacial abnormalities are associated to finger or toes webbing: syndactyly of at least three finger or three toes typically involves bones structure. When vertebral abnormalities occur, C5-C6 fusion is typically observed. Hyperhidrosis is frequently reported as is also skin with acne.

Vision and auditory problems are usual findings in Apert syndrome.

**Hearing loss** is a common diagnosis in these patients. The conductive hearing loss, usually bilateral, may be due to ossicular chain fixation or otitis media with effusion. Hearing loss is rarely present at birth. In about 50% of the cases hearing loss is acquired by the age of 20. It ranges from mild to moderate, predominantly affecting the lower frequencies. The incidence of congenital hearing loss is low (3-6%) (Rajenderkumar et al., 2005).

In a study by Zhou et al. hearing loss was found in 90% of the 20 pediatric patients with Apert syndrome and 80% of them had conductive hearing loss. Air-bone gaps were found at all frequencies, maximum at the low ones. Inner ear anomalies were found in all patients at CT scans of the temporal bones. The most frequent anomalies were dilated vestibule, malformed lateral semicircular canal and cochlear dysplasia (Zhou et al., 2009)

## 2.8 Crouzon syndrome

Crouzon syndrome (OMIM 123500) was first described in 1912 by Crouzon. It is a condition which is inherited in an autosomal dominant way. In Europe it occurs in 1 child every 50,000 live births. The syndrome is caused by mutation in the fibroblast growth factor receptor 2. Mutations in this gene lead to the production of an abnormal protein which overstimulates immature cells to form mature bone cells. The premature fusion of skull sutures causes the typical synostosis which begins in the first year of life and is completed

by 2-3 years from birth. Different patterns of skull growth depend on which suture is mainly involved (Harroop et al., 2006; Kirman et al., 2005). Increased intracranial pressure can occur, mainly when treatment is delayed.

The face is typically huge with a high forehead, proptosis which causes external strabismus, hypertelorism, prognathism and hypoplastic upper jaw which leads to dental problems. The nose is usually beak shaped. Cleft lips or palate have sometimes been observed.

**Hearing loss** is mainly conductive and is due to auditory canal abnormalities such as middle ear effusions, intratympanic bony masses, ossicular or oval window malformations. Sensorineural hearing loss may rarely occur.

In the study by De Jong et al. mild or moderate hearing loss (mostly conductive) was found in 28.5% of patients with Crouzon syndrome (De Jong et al., 2011).

In the study by Orvidas et al 8 of the 19 patients with Crouzon syndrome had ear anomalies ranging from pinna malformations to auditory canal atresia while 10 had proper hearing impairment: in 4 of them conductive hearing loss was found (mainly due to ossicular fixation and otitis media) in 4 of them hearing loss was sensorineural while in 2 was mixed (Orvidas et al., 1999)

A particular variant of Crouzon syndrome caused by a mutation in *FGFR3* has been described in association to Acanthosis Nigrigans. In these patients hydrocephalus, coanal stenosis or atresia and Chiari malformation have been described. (Arnaud-López et al., 2007)

## 2.9 Pfeiffer syndrome

Crouzon syndrome and Pfeiffer syndrome (OMIM 101600) are allelic disorders with overlapping features. Pfeiffer syndrome is an autosomal dominant condition which occurs in 1 every 100.000 live births. It is caused by mutations in *FGFR1* or *FGFR2* which cause prolonged signaling which over stimulates premature cells in the developing embryo. This causes the premature fusion of skull bones. Early fusion of the coronal and lambdoid sutures and occasionally of the sagittal sutures leads to an abnormal skull shape.

The face is usually broad with midface hypoplasia, prognathism, high forehead, flat occiput, hypertelorism and swallowing orbits which cause proptosis. Upperways obstruction can follow midface hypoplasia and nasal obstruction (Vogels et al., 2006).

Skull malformation is associated to limb abnormalities such as short and broad deviating thumbs, big toes and syndactyly of the second and third fingers.

Three different subtypes of this condition have been described. In type 1 patients, mild skull and facial abnormalities such as brachycephaly and midface hypoplasia are associated with fingers and toes malformations while neurological development is usually normal. In type 2 patients trilobated skull deformity is associated with neurological problems such as underdeveloped brain or increased intracranial pressure. Proptosis is evident and causes visual problems. Other limb defects such as elbow ankylosis are associated to fingers and toes abnormalities. Kidney malformations can also occur. Type 3 patients are similar to type 2 patients without cloverleaf skull.

Otologic malformations and **hearing loss** are common features in Pfeiffer syndrome. They are mainly due to external auditory canal or middle ear malformation. For example atresic or stenotic auditory canal, hypoplastic ossicles or fixed ossicular chain, hypoplastic or enlarged middle ear cavity can be common findings. The inner ear is usually normal though an enlarged internal acoustic meatus may be present. (Cremers et al., 1981)

In a study by Vallino et al. hearing loss, mostly moderate to severe, was present in eight of the nine patients with Pfeiffer syndrome. Seven patients had conductive hearing loss and one had mixed loss (Vallino-Napoli et al., 1996).

Sensorineural hearing loss is less common and may be related to the effect of *FGFR* mutations on cranial nerve or inner-ear development. (Desai et al., 2010)

### 2.10 Saethre-Chotzen syndrome

This is a genetic condition with an incidence which ranges from 1:25.000 to 1:50.000 births (OMIM 101400). It is inherited in an autosomal dominant way and it is caused by mutation of *TWIST1*. Patients with Saethre-Chotzen syndrome typically show an abnormal fusion in the skull's bones causing the typical appearance: brachycephaly, low frontal hair line, flattened nasofrontal angle with a beaked nose, widely spaced eyes, ptosis, facial asymmetry. Fingers and Toes defects such as mild syndactyly and a broad or duplicated thumb or hallux are typical; vertebral anomalies and short stature can also be associated.

Mild external ear anomalies can be additional findings. The hearing defect is usually conductive (Clauser et al., 2004) and can be due to stapes ankylosis, fixed ossicular chain, microtia or enlarged vestibules (sometimes associated to a small epitympanum and small or even absent mastoids) (Ensink et al., 1996). Mixed hearing loss due to brain stem anomalies has also been described (Lamonica et al., 2010).

### 2.11 Townes-Brocks syndrome

Townes-Brocks syndrome (OMIM 107480) is a genetic condition showing an incidence of about 1 in 250.000 live births. It is caused by mutations in *SALL1* causing abnormal production of transcription factors. It is inherited in an autosomal dominant pattern. Patients with this syndrome typically show the triad: anus imperforatus (in about the 82% of the patients) with rectovaginal or rectoperineal fistula, external ear anomalies (85%) usually associated with thumbs malformation (89%) such as thumb duplication or hypoplasia.

In 65% of cases sensorineural or conductive hearing loss are part of the clinical presentation. External ear anomalies range from overfolded superior helices which cause the typical satyr form, to microtia, preauricular tags or pits and can be associated to middle ear anomalies (e.g. ossicular abnormalities, hypoplastic malleus head and abnormally shaped oval window and incus). (Toriello et al., 2004; Powell et al., 1999). The hearing loss is predominantly sensorineural and slowly progressive (from mild during early childhood to moderate in early adulthood), it affects high-frequency thresholds more than the low-frequency ones and has a variable, but usually small, conductive component. (Rossmiller et al., 1994)

Renal and genitourinary abnormalities, congenital heart disease, foot malformation and mental retardation have also been described in Townes-Brocks syndrome.

### 2.12 Miller syndrome

Miller syndrome or postaxial acrofacial dysostosis (OMIM 263750) is a rare condition which affects fewer than 1 in 1 million of newborns. It has an autosomal recessive mode of inheritance. Mutations in *DHODH* cause this syndrome disrupting the development of the first and second pharyngeal arch. Patients with this syndrome typically show craniofacial abnormalities such as malar hypoplasia, micrognathia, down-slanting eyes with drooping of the lower eyelids (which becomes more evident with age) and coloboma, cleft palate, long philtrum and small, protruding "cup-shaped" ears.

Craniofacial abnormalities are associated with limb defects such as syndactyly, hypoplasia or absence of fingers or toes (eg the fifth digits), hypoplasia of forearms or lower legs.

Extra nipples, vertebrae or ribs deformities have been described while abnormalities of the heart, kidneys, genitalia, or gastrointestinal tract are less common.

**Hearing loss** is usually caused by defects in the middle ear (various degree conductive hearing loss). (Toriello et al., 2004)

### 2.13 Nager acrofacial dysostosis

Nager syndrome (OMIM 154400) is a rare condition (about 70 cases have been described) and the involved genes are unknown. Both autosomal and recessive cases have been described. Facial malformation is associated with limbs abnormalities. The face shows maxillar hypoplasia and micrognathia. The eyes have typical downslanting fissures with ptosis of the upper lids, lack or absence of the lower eyelashes and occasionally coloboma of the lower lids.

Ears can show various degree of malformations which range from abnormal positioning to microtia. Auditory canal or middle ear can be involved leading to conductive **hearing loss**. Otitis media is a common problem. In a study by Herrmann et al. 8 over 10 patients with Nager syndrome had pure conductive hearing loss (> 30 db HL in 90% of cases, between 55 and 70 dB HL in 40% of patients) while in 2 cases hearing impairment was mixed. In the last two cases the sensorineural deficit was progressive and developed later in childhood. A Cholesteatoma has been described in some cases.

Limb malformations consist of hypoplasia or absence of radius, radioulnar synostosis, and hypoplasia or absence of the thumbs. Phocomelia is rare. Renal and genital abnormalities occasionally occur. (Opitz et al., 2003)

Syndrome	Main Clinical Features	Genetics	Hearing loss
<b>Goldenhar syndrome</b>	<ul style="list-style-type: none"> <li>• Hemifacial microsomia</li> <li>• Auricular malformations</li> <li>• Vertebrae abnormalities</li> <li>• Facial cleft</li> <li>• Ocular abnormalities</li> <li>• Congenital heart diseases</li> </ul>	Genetic heterogeneity	Ranges from mild to moderate conductive impairment and severe to profound sensorineural hearing loss

Syndrome	Main Clinical Features	Genetics	Hearing loss
<b>Charge syndrome</b>	<ul style="list-style-type: none"> <li>• Choanal atresia</li> <li>• Coloboma</li> <li>• Characteristic ears</li> <li>• Cranial nerve anomalies</li> <li>• Cardiovascular malformations</li> <li>• Genital hypoplasia</li> <li>• Cleft lip/palate</li> <li>• Tracheoesophageal fistula</li> <li>• Growth deficiency</li> <li>• Developmental delay</li> </ul>	Mutations in <i>CHD7</i> are detected in more than 75% of CHARGE patients	Severe-to-profound asymmetrical mixed losses.
<b>Pierre Robin Sequence</b>	<ul style="list-style-type: none"> <li>• Micrognathia</li> <li>• Glossoptosis</li> <li>• Cleft palate</li> </ul>	Genetic heterogeneity	Typically conductive and bilateral
<b>Stickler syndrome</b>	<ul style="list-style-type: none"> <li>• Long and flat face</li> <li>• Malar and mandibular hypoplasia</li> <li>• Small nose with a depressed nasal bridge and anteverted nares</li> <li>• Altered vision</li> <li>• Joint problems</li> </ul>	Mutations in <i>COL2A1</i> , <i>COL9A1</i> , <i>COL11A1</i> , and <i>COL11A2</i> genes	Both sensorineural and conductive
<b>BOR syndrome</b>	<ul style="list-style-type: none"> <li>• Branchial cleft, cysts or fistulae</li> <li>• Ear abnormalities</li> <li>• Kidney abnormalities</li> </ul>	<i>EYA1</i> , <i>SIX1</i> , and <i>SIX5</i> mutations	Sensorineural, conductive or mixed hearing loss
<b>Treacher-Collins syndrome</b>	<ul style="list-style-type: none"> <li>• Zygomatic arches hypoplasia</li> <li>• Hypoplasia of supraorbital rims</li> <li>• Micrognathia</li> <li>• Narrow face</li> <li>• Antimongoloid slant of the eyes and hypertelorism</li> <li>• Coloboma of the lower lid with deficiency of cilia medial to the coloboma</li> <li>• Large nose is with hypoplastic alae</li> <li>• Down-turning mouth</li> <li>• Cleft palate</li> <li>• External ear abnormalities</li> </ul>	Genetic heterogeneity: TCS-1, TCS-2 and TCS-3 have been related to mutations in <i>TCOF-1</i> , <i>POLR1D</i> and <i>POLR1C</i> respectively	About 40-50% of patients with Treacher Collins have conductive hearing loss. Few cases of mixed hearing loss have been described.
<b>Apert syndrome</b>	<ul style="list-style-type: none"> <li>• Craniosynostosis</li> <li>• Frontal bossing</li> <li>• Wide set eyes</li> <li>• Hypoplastic midface</li> </ul>	<i>FGFR2</i> mutations	Mild to moderate conductive hearing loss

Syndrome	Main Clinical Features	Genetics	Hearing loss
	<ul style="list-style-type: none"> <li>• Proptosis</li> <li>• Small upper jaw</li> <li>• Syndactyly</li> </ul>		
<b>Crouzon syndrome</b>	<ul style="list-style-type: none"> <li>• Synostosis</li> <li>• High forehead</li> <li>• Proptosis</li> <li>• External strabismus</li> <li>• Hypertelorism</li> <li>• Prognathism</li> <li>• Hypoplastic upper jaw</li> </ul>	<i>FGFR2</i>	Conductive hearing loss
<b>Saethre-Chotzen syndrome</b>	<ul style="list-style-type: none"> <li>• Brachycephaly</li> <li>• Low frontal hair line</li> <li>• Flattened nasofrontal angle</li> <li>• Widely spaced eyes</li> <li>• Ptosis</li> <li>• Facial asymmetry</li> <li>• Syndactyly</li> <li>• Broad or duplicated thumb or hallux</li> </ul>	<i>TWIST1</i>	Conductive or mixed
<b>Pfeiffer syndrome</b>	<ul style="list-style-type: none"> <li>• Broad face is midface hypoplasia</li> <li>• Prognathism</li> <li>• High forehead, flat occiput, hypertelorism</li> <li>• Swallowing orbits which cause proptosis</li> <li>• Skull malformation</li> <li>• Limb abnormalities</li> </ul>	<i>FGFR1 &amp; FGFR2</i>	Conductive
<b>Townes-Brock syndrome</b>	<ul style="list-style-type: none"> <li>• Anus imperforatus</li> <li>• Rectovaginal</li> <li>• Rectoperineal fistula</li> <li>• External ear anomalies</li> <li>• Thumbs malformation</li> </ul>	It is caused by mutations in <i>SALL1</i>	Sensorineural or conductive hearing loss
<b>Miller syndrome</b>	<ul style="list-style-type: none"> <li>• Malar hypoplasia</li> <li>• Micrognathia</li> <li>• Down-slanting eyes</li> <li>• Coloboma</li> <li>• Cleft palate</li> <li>• Limb defects</li> </ul>	<i>DHODH</i>	Conductive hearing loss-mainly due to anomalies of middle ear
<b>Nager syndrome</b>	<ul style="list-style-type: none"> <li>• Limbs abnormalities</li> <li>• Maxillar hypoplasia</li> <li>• Micrognathia</li> </ul>	Not known	Conductive or mixed hearing loss

Table 1. Main craniofacial syndromes associated with hearing loss

### 3. Imaging

Imaging studies of middle and inner ear are required for better management of the craniofacial syndromes. They are necessary for a correct diagnosis of anatomical aberrations and for the planning of the surgical intervention.

MRI is the first-choice of imaging technique for craniofacial syndromes, midface masses and brain abnormalities; it is important in showing the anatomy of the brain and the soft tissue structures and in detecting any associated cerebral malformations.

	Case 1	Case 2	Case 3	Case 4
<b>Gender</b>	M	M	F	F
<b>Family History</b>	First son of a non-consanguineous gypsy couple. The mother was 17-yrs old and father was 18. Un-remarkable family history.	Unremarkable family history. Non-consanguineous parents.	Unremarkable family history. Non-consanguineous parents.	High percentage of in-utero deaths in mother's family history.
<b>Gravidic History</b>	No exposure to known teratogens during pregnancy. Gravidic history was unremarkable until 34 weeks of GA when a spontaneous vaginal delivery occurred	Pregnancy was complicated by polyhydramnios	Unremarkable gravidic history	Unremarkable gravidic history
<b>Neonatal Outcome</b>	Soon after the delivery, the newborn required ventilation support because of bradycardia, irregular breathing, hypotonia, and hyporeactivity	Term delivery at 42 weeks of gestational age (GA)	Spontaneous vaginal delivery at 41 weeks of GA. At birth ventilation support was required because of bradycardia and irregular breathing.	Spontaneous vaginal delivery at 41 weeks of GA
<b>Physical Examination</b>	The weight at birth was 2035 g (10th-25th percentile), length was 46,5 cm (50th -75th ),	Birth Weight 3400 g (10th-50th percentile); Birth length 50 cm (10th-50th ). He had bilateral	At birth she weighed 2680 g (3th-10th centile), length was 47 cm (3th-10th), and her head circumference was 33.5 cm (10th-50th). She was pale and had petechiae at	At birth she weighed 2670 g (3 <sup>th</sup> -10 <sup>th</sup> percentile). She showed hyperemic and

	Case 1	Case 2	Case 3	Case 4
<b>Gender</b>	M	M	F	F
	and head circumference was 29.5 cm (3th percentile). He had microcephaly and trigonocephaly, prominent forehead, flat occiput, narrow palpebral fissures, big and rounded nose with hypoplastic alae, small mouth, with the inferior dental arch lying behind the superior one, low-set ears, micropenis, talipes and metatarsus varus. A single umbilical artery was found.	coloboma, atresia of the right choana, characteristic external ears and hypoplasia of the cochlea. Characteristic facial features with square-shaped facies, narrow bifrontal diameter, broad nasal bridge, small mouth and inverted V-shaped upper lip. He had bilateral cryptorchidism, hypoplastic genitalia and orofacial cleft	upper limbs, neck, head, axillae and inguinal region. She showed mild hypotonia and characteristic facial features: plagiocephaly, with flat occiput, frontal bossing, head bent to the left, left eyelid ptosis; thin upper lip with long filtrum and short tongue frenulum. Clinodactily of the fifth fingers. Bilateral shortness of ulna and radius with carpal bones relatively longer than fore-arm. Mild enlargement of cardiac profile.	edematous eyelids and atresia of the left choana, Characteristic facial features: hypertelorism, bilateral frontal bossing, large anterior fontanel, bilateral hypoplastic elix and low-set ears, right eye ptosis, rounded nose with flat origin, hypoplastic alae and micrognatia. The fifth finger was bilateral curved with nails abnormalities.
<b>Main problems</b>	Breathing problems and chronic tirage due to laryngomalacia was found. Feeding difficulties (poor sucking, gastric stagnation, regurgitation, vomiting) with subsequent failure to thrive due to gastro-oesophageal reflux and hypertrophic pyloric stenosis surgically	Transposition of the great arteries surgically corrected during the first week of life. At 21 months growth deficiency was apparent. He showed delayed motor milestones, hypotonia, and delayed development of social and emotional skills. He was fed via percutaneous endoscopic	Low platelets count (16.000/mmc). Cranial USS showed mild dilation of lateral ventricles, hyperechogenic areas in the basal ganglia and candelabrum-like appearance of the thalamus. Echocardiography showed mild increasing pulmonary transvalvular gradient and atrial septum defect (ostium secundum). Growth deficiency with delayed motor milestones and delayed development of social and emotional skills	Growth deficiency with delayed motor milestones and delayed development of social and emotional skills were apparent

	Case 1	Case 2	Case 3	Case 4
<b>Gender</b>	M	M	F	F
	treated at 7 months of age. Echocardiogram showed pulmonary valve stenosis. Brain magnetic resonance imaging (BMRI) revealed dysmature brain in a trigonocephalic skull.	gastrostomy (PEG) from the age of 4 months and required surgery for gastroesophageal reflux. He also required a tracheostomy between ages of 2 and 5 months.		
<b>Hearing Loss</b>	Bilateral sensorineural hypoacusia: average threshold of 50 dB HL on the right side and 70 dB HL on the left side (2000-4000 Hz)	Moderate bilateral sensorineural hypoacusia (bilateral average threshold of 55 dB on the left and 45 dB HL on the right at 2000-4000 Hz).	Profound bilateral sensorineural hypoacusia (bilateral average threshold above 80 dB at 2000-4000 Hz)	Sensorineural bilateral hypoacusia (bilateral average threshold above 90 dB on the left and 75 dB HL on the right at 2000-4000 Hz). Partially corrected by a Cochlear implant.
<b>Genetic Findings</b>	High resolution chromosome analysis on PHA-cultured lymphocyte pointed out a male karyotype with a partial 5q duplication and pericentric inversion of chromosome 9 (46,XY, inv9qh, dup(5)(q11.2-q13). Parents did not authorize any cytogenetic studies on themselves	The patient met all the four major and six minor Blake criteria for CHARGE syndrome. Direct sequencing of exon 2 of CHD7 gene revealed the presence of a nonsense mutation: a C→T transition at the nucleotide 925 (c.925C>T) causing a premature stop codon (p.Q309X).	Chromosome analysis revealed a female karyotype with a chromosome deriving from a paternal traslocation: 46XX-11,+der11t(6;11)(11pter→11q24.2::6p22.3→6pter). CGH array revealed a microduplication at region 6pter → 6p22.3 in the short arm of chromosome 6 and a microdeletion at the region 11q24.2 →11qter in the long arm of chromosome 11.	Genetic studies showed a female Karyotype with an interstitial deletion at the long arm of chromosome 9. CGH-Array and FISH pointed out a 10 Mb de novo interstitial deletion in the regionq31.1-9q31.3.

Table 2. Some clinical cases observed at Neonatology Unity of Santa Chiara University Hospital of Pisa

CT (best of all three dimensional CT) is the referral technique for studying syndromes of the first and second branchial arch: the resolution provided by this technique for the fine bony craniofacial structures is unmatched by other modalities. It is useful for example in diagnosing early suture fusion and in detecting any underlying abnormality of the brain. It is also useful when choanal stenosis or pyriform cavity or nasolacrimal ductus abnormalities are present as well as when anomalies of the temporal bone, osseous labyrinth, or internal and external acoustic canal are involved. The choice between techniques depends on the anatomical or functional damage which causes the hearing loss but often only the combined use of MRI and CT is able to give a complete imaging of craniofacial malformations. (Lowe et al., 2000; Johnson et al., 2001; Tokumaru et al., 2006)

#### 4. Conclusion

The knowledge of clinical characteristics of syndromes is still the first and most important step for reaching a correct diagnosis. The clinical appearance leads the clinician to suggest various genetic tests to make a definitive diagnosis. Although many syndromes with craniofacial malformations and hearing loss are known, there are many patients with craniofacial abnormalities and deafness whose disorder cannot be currently classified into any syndrome (Table 2). These patients may have detectable genetic aberrations (e.g. chromosomal abnormalities such as deletions or duplications). The imaging aid to the diagnosis and for intervention in hearing loss associated with these syndromes is certain. The choice between CT or MRI depends on the anatomical/functional damage which causes the hearing.

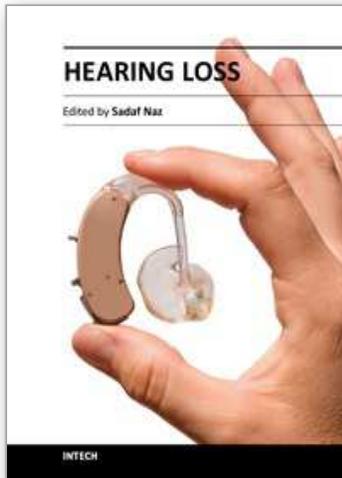
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## **Hearing Loss**

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Authored by 17 international researchers and research teams, the book provides up-to-date insights on topics in five different research areas related to normal hearing and deafness. Techniques for assessment of hearing and the appropriateness of the Mongolian gerbil as a model for age-dependent hearing loss in humans are presented. Parental attitudes to childhood deafness and role of early intervention for better treatment of hearing loss are also discussed. Comprehensive details are provided on the role of different environmental insults including injuries in causing deafness. Additionally, many genes involved in hearing loss are reviewed and the genetics of recessively inherited moderate to severe and progressive deafness is covered for the first time. The book also details established and evolving therapies for treatment of deafness.

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