

**TITLE: COMMON OTOLARYNGOLOGICAL CONGENITAL ABNORMALITIES:**

**Visual Synopsis of Classic Syndromes and Features**

**SOURCE: Grand Rounds Presentation, UTMB, Dept. of Otolaryngology**

**DATE: November 22, 2010**

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**\* Special gratitude goes to Lewis Hutchinson, M.D. for his assistance and contribution.\***

## **INTRODUCTION**

Many children will present to the otolaryngology practice with congenital abnormalities, and it is important that he or she be familiar with characteristics affiliated with a number of these syndromes. There may be times when one may be the first to encounter an affected individual and suggest the diagnosis, but awareness of otolaryngologically related features and subsequent treatment is vital in managing such patients. (Author's note: This manuscript is best used as a supplement to its accompanying PowerPoint presentation, which is designed to visually highlight the classic presentation of commonly encountered syndromes from an otolaryngological perspective.)

## **DOWN SYNDROME**

Considered the most common cause of intellectual disability today, Down syndrome was first described in 1866 by John Langdon Down but its etiology was not discovered until 1959 by Jerome Lejeune and Patricia Jacobs. The genetic basis for this condition is the inheritance of a third chromosome 21 leading to its other eponym, Trisomy 21, which commonly occurs from a nondisjunction in gamete formation during meiosis. Down syndrome is notable for presenting with genetic mosaicism, where there are two cell populations reside within the same person, leading to a high degree of phenotypical variability among affected individuals. This syndrome can also arise from a Robertsonian translocation, typically when the long arm of chromosome 21 attaches to another chromosome (usually chromosome 14) during gamete formation. While the parent would remain phenotypically normal, there is a significantly higher chance of passing an extra chromosome 21 to the offspring. There also appears to be an increased risk of Down syndrome with advanced maternal age.

Characteristic head and neck physical exam findings include brachycephaly that typically manifests with a flat occiput and nasal bridge along with a hypoplastic maxilla resulting in a “round” appearing face. Ears are oftentimes low-set and microtic with an over-folded helical fold. Affected individuals may demonstrate macroglossia and glossoptosis, which may be more pronounced in the presence of microgenia. Aggregations of connective tissue, known as Brushfield spots, can lead to a “speckled” appearance on irises. While some individuals in the normal population may have natural mild upslanting palepebral fissures, they are more pronounced in those with Down syndrome. In a similar manner, epicanthal folds may be present in unaffected people but are more noticeable in Down syndrome as to cover a significant portion of their medial canthi.

Although they involve organ systems that are not primarily evaluated by otolaryngologists, children with Down syndrome have been observed to exhibit a Simian crease within the palms of their hands and a widened gap between their first and second toes, often referred to as a sandal gap deformity. There is also a high incidence of atrioventricular cardiac septal defects, gastroesophageal reflux, duodenal stenosis or atresia, and Hirschsprung disease or celiac disease. Figure 1 presents a number of these findings.

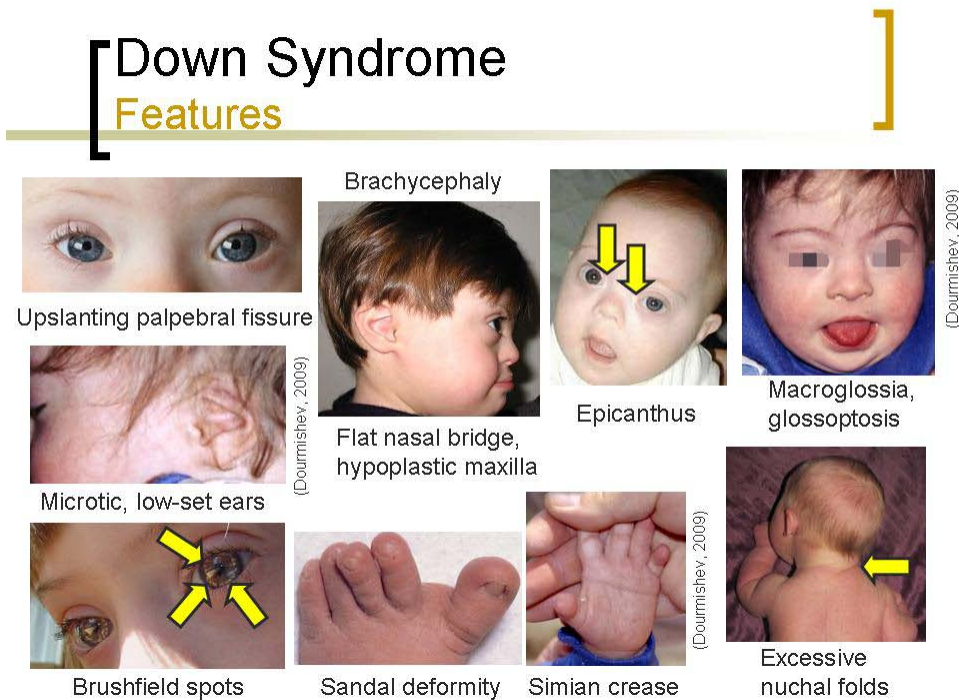


Figure 1. Some typical features of Down syndrome.

The first physical finding suggestive of Down syndrome can actually be discovered by the obstetrician with the discovery of absent or hypoplastic nasal bones on prenatal ultrasonography. The risk is greatest if no nasal bones are appreciated in the first trimester, while this risk

decreases, but still remains elevated, with the presence of hypoplastic nasal bones or observing these anomalies in the second trimester.

From an otolaryngological perspective, affected children are typically referred for placement of tympanostomy tubes secondary to recurrent otitis media and conductive hearing loss (CHL) stemming from persistent middle ear effusions. Otolaryngologists may also be asked to evaluate for obstructive sleep apnea (OSA) secondary to upper airway obstruction from adenotonsillar hypertrophy and glossoptosis. In more complex cases, children may present with tracheoesophageal fistulas warranting prompt surgical repair. Throughout their lives, individuals with Down syndrome should be monitored for signs of hypothyroidism, often from Hashimoto's thyroiditis, and hematopoietic malignancies including acute lymphoblastic leukemia and transient myeloproliferative disorder.

Special surgical consideration comes about from a high incidence of atlantoaxial instability of the cervical spine, usually from laxity of the transverse ligament between the odontoid process of the C2 vertebra and the posterior aspect of the anterior arch of the C1 vertebra. The clinical consequence of this is the anterior subluxation of C1 against C2 resulting in spinal cord compression. Most studies of this phenomenon reported greater dislocation with neck flexion, but a combination of extension and head "lifting"—a movement commonly incurred during laryngoscopy—may produce the same result especially when compounded with head rotation. This can be further exacerbated by bony cervical anomalies that may be present in Down syndrome individuals. Consequently, a thorough history and physical examination is crucial to identifying those with suspected cervical cord compression prior to undergoing surgical procedures.

## **CROUZON SYNDROME**

Crouzon syndrome is well-known for its striking craniofacial malformations. First described in 1912 by the French physician, Octave Crouzon, the genetic defect appears to emanate from an autosomal dominant mutation of fibroblast growth factor receptor II (FGFR2) on chromosome 10. The result is an abnormal first branchial arch during embryological development, affecting the maxilla and mandibular precursors with an early fusion of facial and skull bones during fetal development.

Craniosynostosis is commonly encountered, which should be expected considering the premature fusion of the craniofacial skeleton. The maxilla is often hypoplastic and results in the appearance of mandibular prognathism, although the mandible itself may also be subject to bony abnormalities. Affected individuals typically exhibit some degree of ocular malformations including hypertelorism, strabismus, and exophthalmos. The external appearance of the nose may demonstrate psittichorhina, a beak-like appearance. Mental retardation is not a hallmark feature unless premature closure of the cranial suture lines impairs brain development. These findings are presented in Figure 2.

## Crouzon Syndrome

### Features

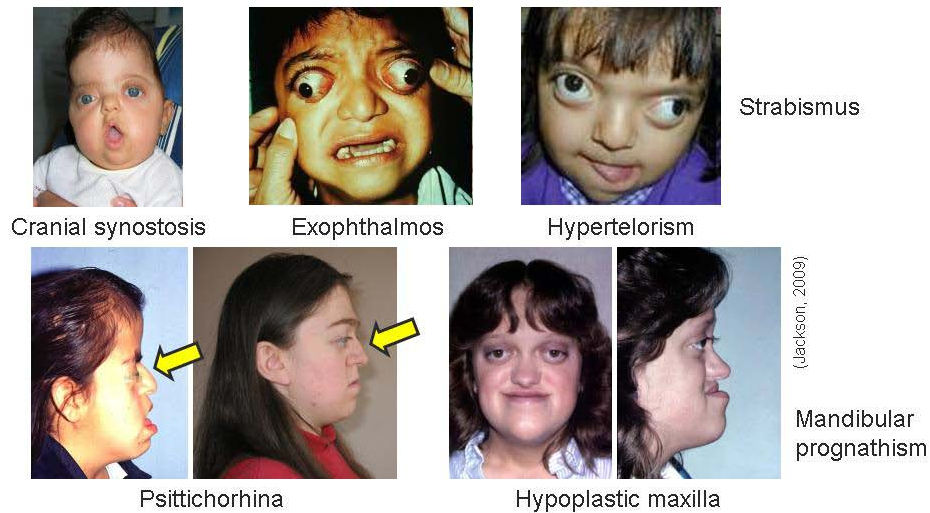


Figure 2. Some typical features of Crouzon syndrome.

Approximately one-third of patients with Crouzon syndrome suffer from hearing loss. While some may experience sensorineural hearing loss (SNHL) or mixed hearing loss, the majority are conductive in nature due to auricular misalignment, ossicular fixation, or persistent serous otitis media. Surgical craniofacial reconstruction may be undertaken for functional and cosmetic purposes.

### APERT SYNDROME

Named after the French physician who first described it in 1906, Eugene Apert, individuals with this condition share similar craniofacial features as Crouzon syndrome, which is not surprising since it also involves the same *FGFR2* mutation. In addition, Apert syndrome is distinguished by the presence of syndactyly secondary to a keratinocyte growth factor receptor (*KGFR*) mutation. Although regarded as an autosomal dominant condition, affected parents have been noted to pass it on to their offspring only 50% of the time whereas the majority of cases occur via sporadic mutations.

Although similar in pathophysiology and external appearance to Crouzon, individuals with Apert syndrome exhibit a few differences aside from syndactyly. Patients do share some degree of craniofacial dysostosis and maxilla hypoplasia, but they tend to manifest a prominent frontal region. Exophthalmos and hypertelorism are also present, and while the nose can also demonstrate some deformity, it is usually more along the lines of a depressed nasal bridge.

Palatal and dental anomalies are common, including cleft palate and high-arched palate, in addition to crowding of teeth and ectopic eruption leading to malocclusion. Some of these features are displayed in Figure 3.

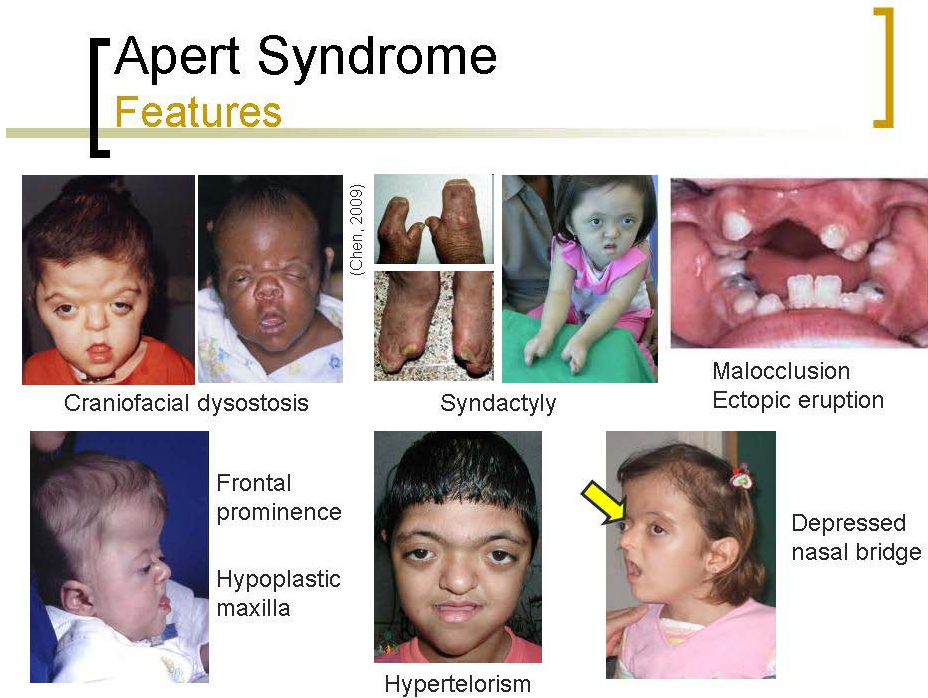


Figure 3. Some typical features of Apert syndrome.

Hearing preservation is often the primary objective for the otolaryngologist as many individuals experience some degree of CHL due to chronic otitis media and even stapes fixation. Despite these middle ear abnormalities, the cochlear aqueduct is usually patent. Craniofacial reconstruction can also be performed in a similar manner as with Crouzon syndrome.

### TREACHER COLLINS SYNDROME

Named after Edward Treacher Collins, the British ophthalmologist who described the essential features to this disorder in 1900, aspects of Treacher Collins syndrome were likely first described by Thomson and Toynbee in the mid-1840's and later by Berry in 1889. Mandibulofacial dysostosis is another eponym while it is oftentimes referred to as Franceschetti-Zwahlen-Klein syndrome in Europe. The primary etiology is a mutation of the TCOF1 gene on the long arm of chromosome 5, but sporadic mutations have been reported to occur in up to 60% of cases. There is complete penetrance with this autosomal dominant condition, but expression of the syndrome varies. Furthermore, there have been cases of recessive forms of this syndrome.

The craniofacial anomalies can be best summarized as a result of maldevelopment of the first and second embryological pharyngeal arches, grooves, and pouches. In general, there is a characteristic facial dysmorphism that incorporates downward slanting palpebral fissures, hypoplastic supraorbital rims, malar and mandibular hypoplasia. The mandible often demonstrates a hypoplastic condyle, short ramus and body, and an anteriorly displaced temporomandibular joint (TMJ). The nose is usually of normal size but appears large due to the surrounding facial hypoplasia. However, affected individuals can demonstrate a flatter nasofrontal angle and underdeveloped lower nasal cartilage.

From a soft-tissue perspective, children with Treacher Collins syndrome often demonstrate bilateral colobomas involving the lateral one-third of the lower eyelids. There are scant lower eyelashes, but those that are present are always lateral to the coloboma. In conjunction with a partial or complete absence of the zygomatic arches, this results in the appearance of “tear drop”-shaped orbits. More severe cases will exhibit clefting of the lateral wall and floor of the orbits with extension into the inferior orbital fissures. Cleft palate may also occur in one-third of affected children. Figure 4 presents a number of these findings.

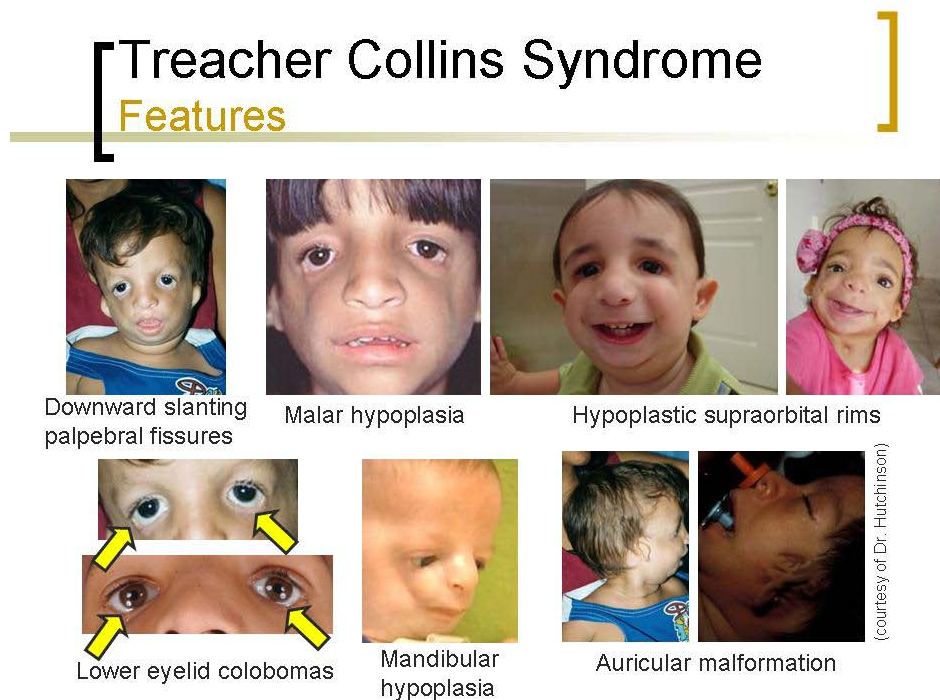


Figure 4. Some typical features of Treacher Collins syndrome.

Otolaryngologists are often asked to manage hearing loss, which can occur in approximately 30%. While there can be some SNHL with or without associated vestibular dysfunction, the majority of cases are conductive in nature stemming from microtia, external auditory canal atresia, or ossicular malformation. Despite such middle ear abnormalities, the stapes is usually

normal although it may be discontinuous with the incus or exhibit an ankylosed footplate. Functional and cosmetic craniofacial reconstruction is another therapeutic endeavor, as is cleft palate repair if one is present. Of more immediate concern is placement of a tracheostomy if the degree of dysostosis results in significant upper airway obstruction.

## **GOLDENHAR SYNDROME**

Famous for its key feature of hemifacial hypoplasia, Goldenhar syndrome has not been associated with a single genetic locus. There are been a variety of explanations, and two more common ones include the presence of *in utero* vascular disruptions with subsequent hematoma formation preventing normal embryological development and a disturbance of neural crest cells at 30-45 days of gestation. An autosomal dominant familial pattern has been described in 1-2% of families. While affecting the first and second branchial arches, Goldenhar syndrome can also engender musculoskeletal abnormalities, particularly the spine, leading to its other eponym, oculoauriculovertebral dysplasia. Cardiac, pulmonary, renal, and gastrointestinal defects may be present. The term, hemifacial microsomia, is designated when the affected individual has no internal organ or vertebral disruption.

Hypoplasia of one-half of the head and face is the hallmark characteristic, which is probably most commonly noted with unilateral mandibular hypoplasia resulting in microstomia. Aside from potentially being malpositioned or smaller in size, the eyes may demonstrate epibulbar lipodermoids. Eyelid colobomas may also be present, but in stark contrast with those found in Treacher Collins, they affect the upper eyelid and are usually unilateral. The parotid gland on the affected side is often displaced or has even undergone some degree of aplasia. Microtia is typically present and may be associated with preauricular tags that can appear in clusters and even be located just lateral to the oral commissure. While vertebral anomalies are common, congenital heart defects may be discovered in just over half of affected children. These features are displayed in Figure 5.

## Goldenhar Syndrome Features

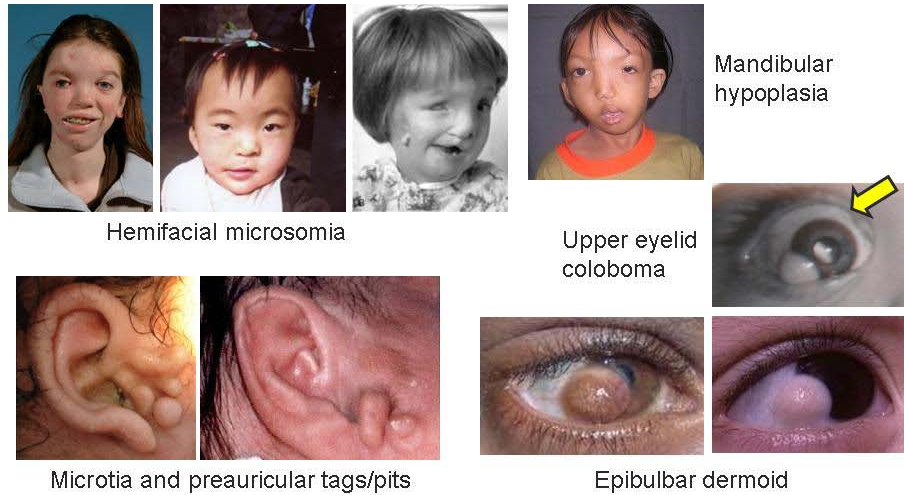


Figure 5. Some typical features of Goldenhar syndrome.

A classification scheme used to describe the various manifestations of Goldenhar syndrome and their severity is summarized with the OMENS acronym: Orbital distortion; Mandibular hypoplasia; Ear anomaly; Nerve (facial nerve) involvement; and Soft-tissue deficiency. The term, “plus,” denotes the presence of anomalies of other organ systems. The orbital distortion is designated with an increasing number from 0 to 3, correlating to a smaller size orbit, a displaced one inferiorly or superiorly, or one that has experienced both, respectively. The degree of facial nerve dysfunction essentially follows the same classification where an increasing number describes paresis of the upper facial nerve branches, the lower ones, or all of them, respectively. A similar schema is used for the ear and soft-tissue deficiency with a progressively larger number to implicate a more severe degree of microtia and tissue agenesis.

Describing the severity of mandibular hypoplasia also fits within the same structure but with a few subtle alterations. A type I mandible refers to one that is of smaller size but with clearly identifiable landmarks. Type II encompasses those with an abnormally shaped but functional TMJ alongside an abnormal glenoid fossa. This is further categorized to Type IIA, where the glenoid fossa is situated in an acceptable position, and Type IIB, where the abnormal TMJ cannot be incorporated into any prospective surgical reconstruction. Finally, Type III signifies the most severe case of mandibular dysmorphia where the ramus is absent and the glenoid fossa is nonexistent.

Ossicular malformations may also manifest in addition to microtia, and consequently, the otolaryngologist is typically asked to evaluate and rectify CHL, although SNHL may sometimes be present. Of particular note, any surgeon operating in the mastoid region should be aware that the area may be poorly pneumatized and the facial nerve may demonstrate an aberrant course. Craniofacial reconstruction typically involves rectifying the mandibular hypoplasia.

## **PIERRE ROBIN SYNDROME**

The first discussion of this condition was with the description of two patients exhibiting micrognathia, cleft palate, and retroglossoptosis by Odilon Lannelongue and Maxime Menard in 1891. However, it was Pierre Robin who published a case of an infant with the complete syndrome in 1926. The name, Pierre Robin Syndrome, can be considered a misnomer in that it is actually a sequence of micrognathia, glossoptosis, and cleft palate. The designation, “syndrome,” is reserved for cases when there are multiple malformations attributed to a single etiology. Unfortunately, there is a substantial amount of confusion regarding classifying Pierre Robin as a Pubmed literature review will reveal 14 different definitions with 15 different opinions regarding this particular sequence.

Virtually all theorists agree that Pierre Robin sequence is a consequence of an arrest in intrauterine development. Some have speculated on a neurological maturation theory, citing electromyography results of the tongue, pharyngeal pillars, and palate of affected individuals. In particular, there has been a measurable delay in hypoglossal nerve conduction. This is further supported by the observation of a spontaneous correction in the majority of cases with age. The rhombencephalic dysneurulation theory is one that suggests that a major disorder in ontogenesis disrupts the motor and regulatory organization of the embryologic rhombencephalus.

The most accepted theory is the mechanical one, which believes that mandibular hypoplasia occurring between 7 and 11 weeks of gestation serves as the triggering event. The hypoplasia is attributed to the mandible getting temporarily caught between the clavicle and sternum during development. This causes the tongue to remain high in the oral cavity, preventing closure of the palatal shelves and resulting in a cleft palate. Oligohydramnios may also contribute to this picture by further deforming the mandible and impacting the tongue between the palatal shelves.

Children with Pierre Robin sequence exhibit the triad of cleft palate, glossoptosis, and micrognathia. The cleft palate is U-shaped in 80% of cases and V-shaped for the rest. Despite palatal involvement, it should be noted that cleft lip usually does not occur. While it is important for the clinician to clearly define between micrognathia (a small mandible) and retrognathia (posterior displacement of the mandible), both findings may be simultaneously present. Macroglossia and ankyloglossia occur in a minority of affected children. Figure 6 summarizes the findings associated with this condition.

## Pierre Robin Syndrome

### Features

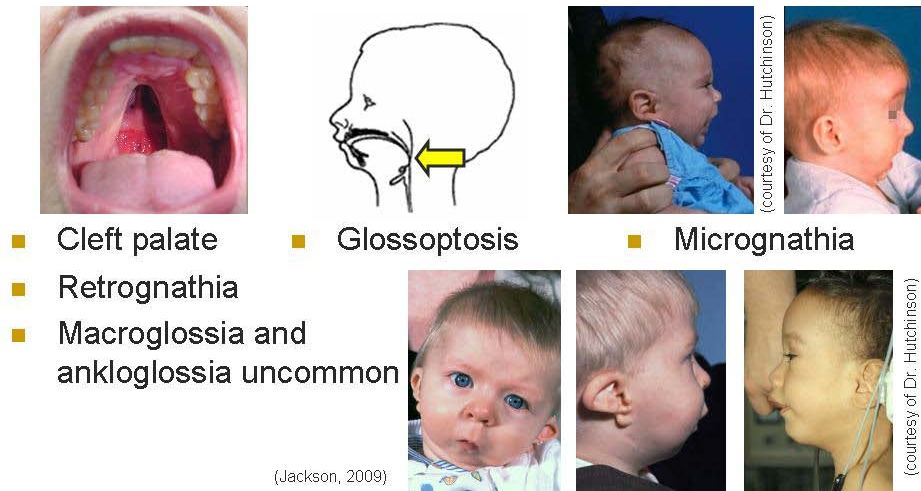


Figure 6. Some typical features of Pierre Robin syndrome.

The hallmark features of Pierre Robin may be severe enough to preclude a stable airway. Significant obstruction may lead to OSA or even necessitate tracheostomy placement in more acute settings, and subglottic stenosis has been reported in some children. Feeding is often hampered, usually by the presence of cleft palate, and the distorted anatomy may even contribute to aspiration. Otolaryngologists may also be requested to manage hearing loss, which is often conductive in nature secondary to chronic otitis media and likely exacerbated by cleft palate. Auricular malformation and mixed hearing loss may also be present. Craniofacial reconstruction revolves around mandibular distraction osteogenesis.

Physicians need to be aware that mandibular “catch up” is possible only if micrognathia is a component of Pierre Robin sequence. Parents of affected children must not be mistakenly reassured that the hypoplastic mandible will eventually grow to an age-appropriate size if the classic triad is in conjunction with associated syndromes. Different studies have reported Pierre Robin occurs as an isolated sequence at an average between 20-40% although one report has published a rate as high as 74%. The most common syndrome associated with Pierre Robin sequence is Stickler syndrome, followed by velocardiofacial syndrome and Treacher Collins syndrome.

## STICKLER SYNDROME

Gunnar Stickler described in 1965 a family that demonstrated a set of syndromic features including myopia, clefting, and hearing loss among five generations. Further investigation would lead to the discovery of the congenital syndrome named after him, which is essentially a disorder affecting connective tissue leading to craniofacial, ocular, and arthropathic features. In particular, type II and XI collagen appear to be involved with autosomal dominant mutations of the COL2A1 gene on chromosome 12, and COL11A1 and COL11A2 genes on chromosome 6. Chromosome 6 has also been reported to house the COL9A1 gene that is thought to lead to a rare autosomal recessive variant.

The orofacial presentation of Stickler syndrome is generally subtle where affected individuals tend to demonstrate a “flattened” face. This may manifest with midfacial hypoplasia, micrognathia, a short upturned nose, and a long philtrum. Cleft palate is often present. Some of the orofacial features of this condition are presented in Figure 7. There are various ocular findings such as myopia, glaucoma, retinal detachment, and cataracts. Similarly, children with Stickler syndrome may exhibit a range of musculoskeletal features including osteoarthritis, joint hypermobility, abnormal epiphyseal development, and vertebral abnormalities, usually scoliosis. A classic clinical history incorporates the combination of a cleft palate with a family history of osteoarthritis.

**Stickler Syndrome**  
**Features**

- “Flattened” face
- Ocular findings
- Musculoskeletal abnormalities
- Cleft palate



(courtesy of Dr. Hutchinson via Maria Blazo, M.D.)

Figure 7. Some typical features of Stickler syndrome.

Martin Snead and John Yates proposed criteria to make the diagnosis of Stickler syndrome that encompasses the myriad of physical findings. Children were felt to be affected if they demonstrated a congenital vitreous anomaly in conjunction with three of the following: myopia before six years of age; rhegmatogenous retinal detachment; paravascular pigmented lattice degeneration; joint hypermobility; SNHL; or midline clefting.

The otolaryngologist's role usually involves hearing preservation as mild to moderate SNHL will be present in 80%, while 15% may experience significant SNHL or even a mixed hearing loss. Most components of CHL are secondary to eustachian tube dysfunction as a consequence of cleft palate, although ossicular abnormalities may be present. In light that it is the most common syndrome associated with Pierre Robin sequence, attention may also be drawn to manage upper airway obstruction.

### **WAARDENBURG SYNDROME**

The Dutch ophthalmologist, Petrus Johannes Waardenburg, first described a patient who presented with hearing loss, dystopia canthorum, and retinal pigmentary differences in 1947. Upon identifying additional people with similar symptoms, he defined the syndrome associated with these characteristic features in 1951.

Hypopigmentation is one of the hallmark findings of this condition, most commonly manifesting in the hair and eyes. Patients will often exhibit a white forelock and either heterochromia irides or isohypochromia irides. Heterochromia irides describes the presence of two different colored irises on the same person while isohypochromia irides will often result in the appearance of striking sapphire-colored irises. Some individuals will also present with vitiligo and premature graying. Another characteristic finding is the lateral displacement of the medial canthi, referred to as dystopia canthorum. This phenomenon can produce the appearance of telecanthus and also be associated with dystopia of the lacrimal puncta and blepharophimosis. From a craniofacial perspective, affected children may demonstrate a flat nasal root with hypoplastic nasal alae and confluence of the medial eyebrows, often referred to as synophrys, while approximately 10% may present with cleft lip and palate. Figure 8 displays many of these findings.

## Waardenburg Syndrome

### Features

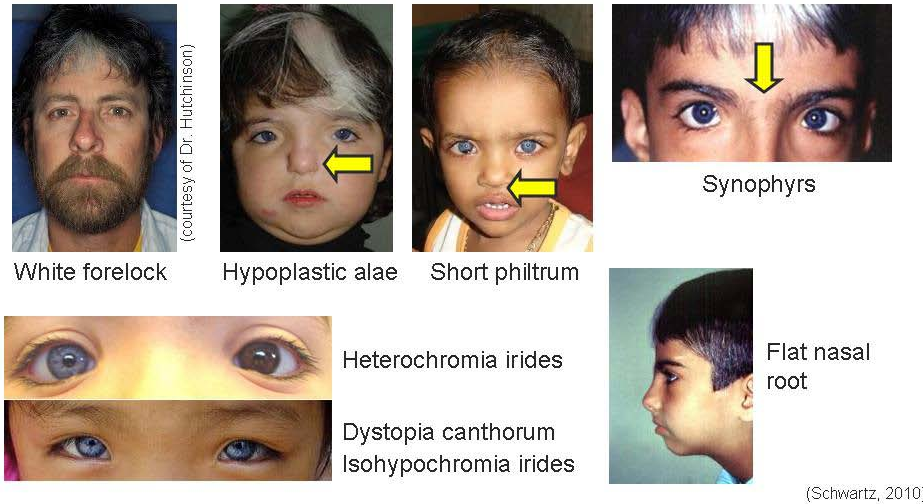


Figure 8. Some typical features of Waardenburg syndrome.

The classic findings of Waardenburg syndrome can be divided into major and minor diagnostic criteria. Hallmark pigmentation anomalies such as heterochromia irides and a white forelock, dystopia canthorum, congenital SNHL, and a positive family history comprise major features. Those involving the nasal structure, synophrys, and congenital leucoderma are considered minor ones. The diagnosis of Waardenburg syndrome can be made if two major criteria or one major with two minor ones are present.

Since its initial discovery, many genes leading to four distinct subtypes of Waardenburg syndrome have been identified. These genes are regarded to be related to melanocyte differentiation, which has been attributed to the various pigmentary abnormalities. This has also been hypothesized to be the basis for the high prevalence of SNHL as melanocytes are thought to be required in the stria vascularis for normal cochlear function.

Autosomal dominant mutations in the PAX3 gene on chromosome 2 have led to types 1 and 3. Type 1 Waardenburg syndrome is the hallmark presentation of this disorder, presenting with the full symptomatology in addition to the presence of facial asymmetry and dysmorphic facies in some children. These same features are also found in type 3 with the addition of mental retardation and musculoskeletal abnormalities including rib aplasia, amyoplasia, cystic changes of the sacrum, and cutaneous syndactyly. Dystopia canthorum is not present and the white forelock rarely so in type 2, which is caused by mutations of the MITF and SNAI2 genes on chromosomes 3 and 8, respectively. Affected individuals will usually demonstrate

heterochromia irides and SNHL. Type 4 is a notable variant in that it is engendered by autosomal recessive mutations of EDN3 (chromosome 20), EDNRB (chromosome 13), and SOX10 (chromosome 22) genes resulting in an association with Hirschsprung's disease.

The primary role of otolaryngologists is hearing preservation as many children will experience congenital SNHL. This is usually not progressive and can usually be satisfactorily managed with hearing amplification or cochlear implantation. In addition to diminished hearing, up to 75% may suffer from some degree of vestibular dysfunction. Cleft lip and palate may also be repaired if present, and it is possible for some individuals to request cosmetic surgical intervention usually related to their hypopigmentation or nasal features.

### **BECKWITH-WIEDEMANN SYNDROME**

Hans-Rudolf Wiedemann first reported a familial form of omphalocele and macroglossia in Germany in 1964, and Bruce Beckwith described a similar set of patients in California in 1969. Together, they identified the most common overgrowth syndrome in infancy. While most cases occur sporadically, there is an autosomal dominant familial inheritance pattern in 15% that appears to be related to an imprinting defect at chromosome 11p15.

The five most common features of Beckwith-Wiedemann syndrome are macroglossia, macrosomia, ear pits or creases, a midline abdominal wall defect, and neonatal hypoglycemia. The severity of the abdominal defect can vary, ranging from an umbilical hernia to an omphalocele. Most ear pits will occur along the helical rim while ear creases are located near the anti-tragus or lobule regions. These features are shown in Figure 9. In concordance with the pathophysiology of overgrowth, affected individuals may also present with an enlargement or abnormalities of visceral organs, especially the renal and adrenal systems. Of particular note, the diagnosis may be delayed in some children whose manifestations may present with hemihyperplasia.

## Beckwith-Wiedemann Features

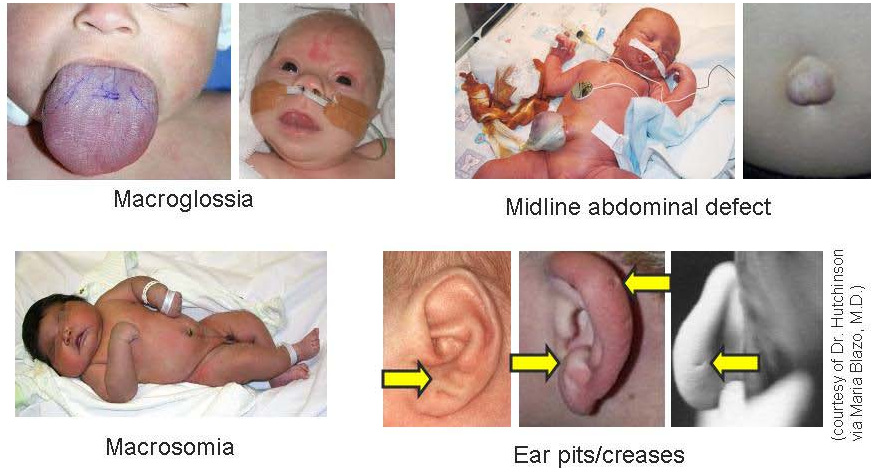


Figure 9. Some typical features of Beckwith Wiedemann syndrome.

There are a few minor findings associated with Beckwith-Wiedemann syndrome including neonatal hypoglycemia, polyhydramnios, prematurity, facial nevus flammeus, hemangiomas, dysmorphic facies such as midfacial hypoplasia, cardiac abnormalities, diastasis recti, and an advanced bone age. Together with the typical major findings, the diagnosis can be made with either the presence of three major features or two major features and three minor ones.

The macroglossia associated with Beckwith-Wiedemann syndrome is typically less noticeable with age, but otolaryngologists may encounter such children in more emergent situations if the degree of tongue enlargement precludes a patent upper airway. Some have even advocated surgical tongue volume reduction, although this is highly controversial with disagreement regarding the timing and amount to be removed. While often managed by other physicians, the otolaryngologist should be conscious of the increased risk of Wilms' tumor and hepatoblastoma in affected individuals. This risk is usually at its peak by four years of age and tends to decrease as children get older, but routine surveillance is necessitated with obtaining an alpha-fetoprotein level every six weeks until four years of age and an abdominal ultrasound every three months until eight years of age.

## NEUROFIBROMATOSIS

First written about in 1882 by Friedrich Daniel von Recklinghausen, the underlying process of neurofibromatosis involves the growth of nerve tissue that can cause compressive damage if it

continues to grow unimpeded. Divided into two major variants, type 1 is sometimes referred to as peripheral neurofibromatosis to describe the type of neoplasms that result. An autosomal dominant condition with variable expression, the genetic insult attributed to type 1 neurofibromatosis is a mutation of the neurofibromin gene (NF1) on chromosome 17 although up to half may arise from a *de novo* mutation.

There are a myriad of hallmark features associated with type 1 neurofibromatosis. Cutaneous neurofibromas are soft and can be pushed deeper into the dermis with palpation, known as the “button hole sign,” and they typically enlarge and increase in number with time. Multiple neurofibromas may cluster together to form a plexiform neuroma. Affected individuals may demonstrate some cutaneous pigmentary findings such as café au lait spots and freckling of the axillary or inguinal regions, sometimes referred to as a “Crowe sign.” Skeletal anomalies may be present such as tibial pseudoarthrosis and long bone bowing. Pulsatile exophthalmos may be encountered if there is sphenoid wing dysplasia. An ophthalmological examination may reveal Lisch nodules, which are hamartomas of the iris that are often asymptomatic and usually only seen with slit-lamp testing, and a higher incidence of optic gliomas. Figure 10 presents these findings.

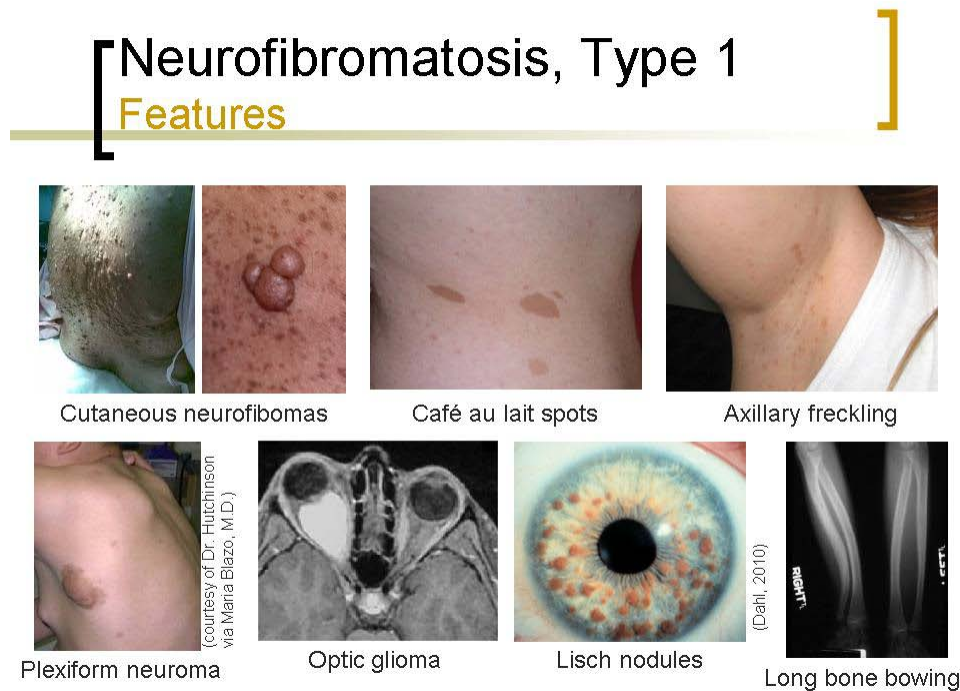


Figure 10. Some typical features of Type 1 Neurofibromatosis.

Using these characteristic findings, the diagnosis of type 1 neurofibromatosis can be made if a person fulfills at least two of the following criteria: two or more neurofibromas or a single plexiform neuroma; axillary or inguinal freckling; an optic glioma; two or more Lisch nodules; a

distinctive osseous lesion; café au lait macules; or a first-degree relative with the same condition. In regards to the café au lait lesions, they must have a diameter larger than 5mm in prepubescents or larger than 15mm in adults.

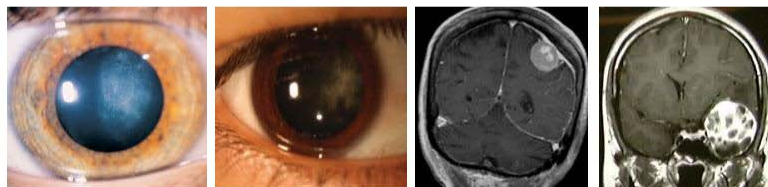
Also an autosomal dominant, type 2 neurofibromatosis affects the Merlin gene (NF2) on chromosome 22 and is sometimes regarded as central neurofibromatosis in light of the high incidence of neoplasms involving the central nervous system (CNS). There is a paucity of café au lait spots and axillary or inguinal freckling, and CNS involvement does not necessarily occur at an early age. This can make the diagnosis a difficult one, especially since type 2 neurofibromatosis only comprises approximately 10% of all individuals affected with neurofibromatosis.

The pathognomonic finding of type 2 neurofibromatosis is bilateral acoustic neuromas. Patients may also present with schwannomas affecting the spinal cord, which are often dumbbell-shaped, or other nonvestibular cranial nerves such as III, V, IX, X, and XI. Meningiomas are the most common central nervous tumor. While less in quantity compared to type 1, café au lait spots may still be present. Similarly, subcapsular cataracts are more prevalent with type 2 as opposed to the Lisch nodules and optic gliomas associated with type 1. These features are displayed in Figure 11.

## Neurofibromatosis, Type 2

### Features

- Café au lait spots
- Schwannomas
  - Bilateral acoustic neuromas
  - Spinal cord
  - Nonvestibular
- Subcapsular cataracts
- Meningiomas



Kurtz JW Jr, Roland PS, Isaacson B. Skull base, acoustic neuroma (vestibular schwannoma). *multimedia. eMedicine* 24 Sep 2009. Accessed 5 Nov 2010. <<http://emedicine.medscape.com/article/882876-media>>.

Figure 11. Some typical features of Type 2 Neurofibromatosis.

The diagnosis can be presumptive if a person presents with a unilateral vestibular schwannoma and an affected first-degree relative in addition to two of the following: meningioma, glioma, schwannoma, or a juvenile posterior subcapsular or cortical cataract. When there is no positive family history, the diagnosis can be suggestive in the presence of multiple meningiomas.

The otolaryngologist is often called upon to help in the management of the various schwannomas that may develop, but children may also present with striking facial deformities with involvement of structures in the head and neck region. While type 1 neurofibromatosis is regarded to carry a more favorable prognosis than type 2 due to its lack of CNS neoplasms, there is a higher incidence of malignant peripheral nerve sheath tumors, neurosarcomas, and gastrointestinal stromal tumors.

### **ADDITIONAL SYNDROMES**

Not all congenital syndromes will present with obvious craniofacial findings. First described in 1912 by Maurice Klippel and André Feil, the syndrome that carries their namesake encompasses the congenital fusion of cervical vertebrae. No clear etiology has been elucidated to Klippel-Feil syndrome, but there have been some reports suggestive of a familial inheritance suggestive of an autosomal dominant pattern with fusion at the C2-3 level and more of an autosomal recessive one at the C5-6 one. This condition can be categorized into three classifications. Cervical fusion occurs at a single level in type I and along multiple noncontiguous ones in type II, while type III demonstrates multiple contiguous fusion segments. Children may exhibit a short webbed neck and a low hairline. Other associated anomalies include a malformed and displaced scapula, known as a Sprengel deformity, scoliosis, renal abnormalities, and even facial asymmetry.

The hallmark feature of feature of Usher syndrome is the combination of both hearing and vision loss. A defective inner ear is the underlying process to this condition and can be divided into three main variants. Type I refers to when deafness and vestibular dysfunction are both present, which contrasts with type II where the hearing loss is nonprogressive and the vestibular system is normal. Hearing loss is progressive in type III, and the vestibular function is estimated at half of normal. Vision loss results from retinitis pigmentosa and is typically progressive. Initially affecting the rod cells of the retina, patients will often first complain of diminished night vision before eventually proceeding toward a loss of peripheral vision.

Pendred syndrome pairs the presence of SNHL and a thyroid goiter. Some affected individuals will also experience hypothyroidism. In Jervell and Lange-Neilsen syndrome, KCNQ1 and KCNE1 mutations result in defective potassium channels in the inner ear and cardiac muscle. Consequently, patients present with SNHL and potentially fatal palpitations stemming from long QT syndrome.

### **CONCLUSION**

Many congenital syndromes will warrant otolaryngological intervention. While the degree of this endeavor may range from mild to more dire in nature, a otolaryngologist can manage the

syndromic child best with a keen awareness of coexisting morbidities. On a final note, it should be noted that mental retardation is not a hallmark feature of many of these conditions. Consequently, a substantial number of these children are fully aware of the ridicule from their peers their syndrome can create. Regardless of his or her specialty, a good physician can help the affected child cope with both the medical and social implications of their disorder.

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