

Syndrome spotter

Syndrome spotter

- Definition
- Resources
- Grouped by aetiology
- Grouped by
 - Ear
 - Nose
 - Throat

Syndrome spotter

- Definition
 - “a collection of traits, health problems, and/or birth defects in an individual which usually has a single underlying cause”
 - eg gene defect such as Downs
 - Syn + Dramien “to run together”
 - **Sequence** Single cause with multiple cascading effects
 - Eg Pierre Robin
 - **Association** recognizable pattern without single cause (yet!)
 - Eg CHARGE, VATERS

Syndrome spotter

- Resources
 - Smiths - recognisable patterns of human malformation
 - London dysmorphology database www.lmdatabases.com
 - Medline search
 - Google search
 - www.emedicine.com
 - European Surveillance of Congenital Abnormalities
<http://www.eurocat.ulster.ac.uk/pdf/Ester/EUROCAT%20Guide%206%20Version%203.pdf>

Grouped by site

- Ear
 - Abnormal pinnae eg: Treacher Collins
 - Deafness eg: Wardenburgs
- Nose
 - Abnormal external nose eg: Cranio metaphyseal dysplasia, Hallerman Streif
 - Choanal atresia eg: CHARGE
- Throat
 - Palate eg: Pierre Robin, VCF
 - Airway obstruction eg: Prader-Willi

Listed alphabetically

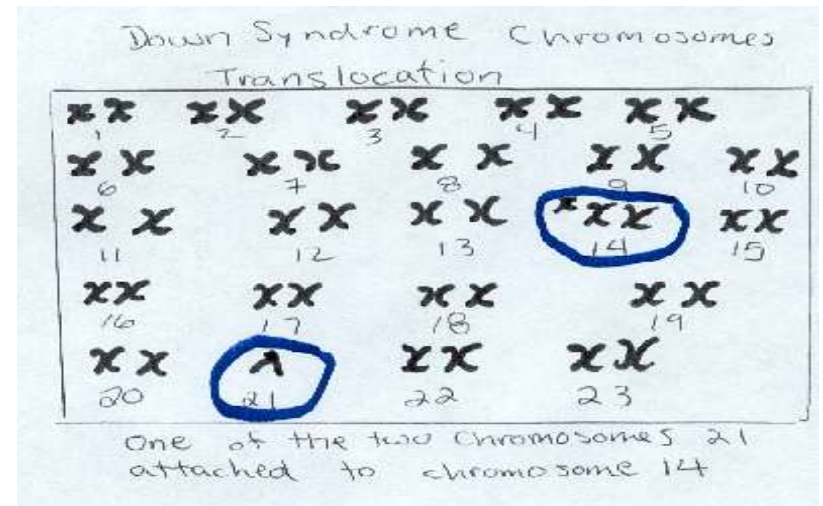
- [Achondroplasia](#)
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- [Pendreds](#)
- [Pierre Robin](#)
- [Prader Willi](#)
- [Pfeiffers](#)
- [Refsum's](#)
- [Saethre Chotzen](#)
- [Stickler](#)
- [Toxoplasmosis](#)
- [Treacher Collins](#)
- [Turners](#)
- [Usher's](#)
- [VATERS](#)
- [VCF](#)
- [Waardenburg's](#)

Chromosomal Anomalies- Downs

- Trisomy 21
 - Translocation 2%
 - Mosaicism 2%
- 1866, John Langdon Down
- 1:800 to 1,000 live births.
- increased risk in women aged over 35
 - 35 year old 1: 400
 - 40 year old 1: 110
 - 45 year old 1: 35.
- Antenatal diagnosis
 - CVS
 - Nuchal thickness

“The face is flat and broad, and destitute of prominence. The cheeks are roundish, and extended laterally. The eyes are obliquely placed, and the internal canthi more than normally distant from one another.

The palpebral fissure is very narrow. The forehead is wrinkled transversely, from the constant assistance which the levatores pebrarum derive from the occipito-frontalis muscle in the opening of the eyes. The lips are large and thick, with transverse fissures. The tongue is long, thick and is much roughened. The nose is small. The skin has a slight dirty-yellowish tinge, and is deficient in elasticity, giving the appearance of being too large of the body “

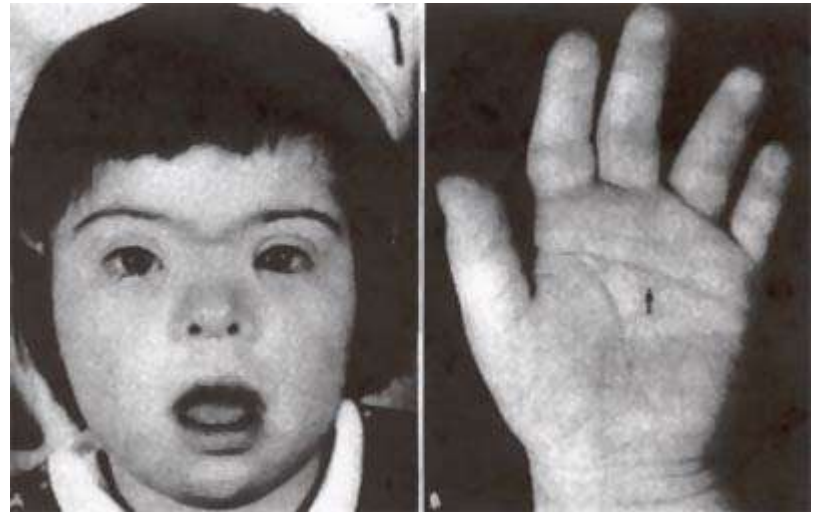


Chromosomal Anomalies- Downs

- Women with Downs have 50 percent chance that their child will have Down syndrome.
- Men with Down syndrome are believed to be sterile.

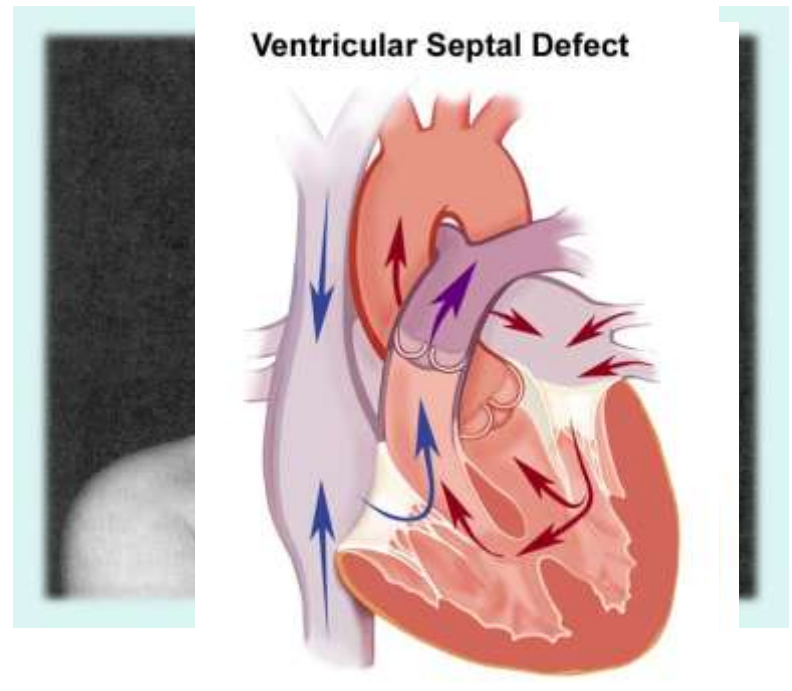
Chromosomal Anomalies - Downs

- General Features
 - Simian crease, a single deep crease across the center of the palm
 - Oblique palpebral fissures
 - Muscle hypotonia
 - Hyperflexibility
 - Most of these features also occur in general population



Chromosomal Anomalies - Downs

- **Epicanthal folds** small skin folds on the inner corner of the eyes
- Flat facial profile
 - depressed nasal bridge
 - small nose
- Cardiac anomalies
- IQ - variable
- Low immunity
- Unstable neck
 - Atlanto-occipital joint 15%
 - [PM:2527213](#)
- Subglottic stenosis



Chromosomal Anomalies - Downs

- ENT features <http://www.emedicine.com/ped/topic615.htm>
 - External ears
 - Small canals
 - Middle ears
 - Increased incidence of glue ear (age related)
 - Otoacoustic emissions often non-reproducible, even in patients with normal hearing abilities
 - ? Abnormal ossicles
 - Mixed deafness 7%
 - Sensorineural deafness 8%
 - Airway obstruction from small PNS with large tonsils and adenoids
 - Macroglossia

Chromosomal Anomalies

- Abnormal 5p
 - cri du chat
 - Partial atresia larynx
 - <http://www.emedicine.com/ped/topic504.htm>

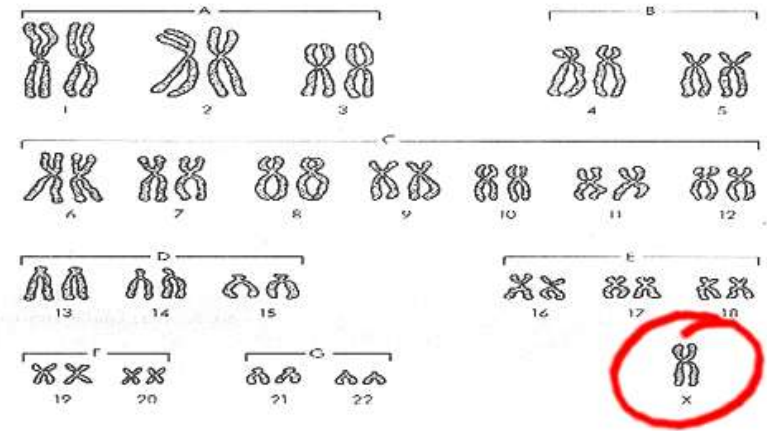
Chromosomal Anomalies - Turners

- General

- XO
- Short stature
- Ovarian dysgenesis
- Variable IQ
- Increased carrying angle

- ENT features

- Increased incidence glue ear
- Sensorineural deafness
- <http://www.emedicine.com/ped/topic2330.htm>



Craniofacial Syndromes

- Crouzons - craniosynostosis

<http://www.emedicine.com/ped/topic511.htm>

- Aperts - with syndactyly

- Pfeiffers - broad short thumbs
- oversized toes

Craniofacial Syndromes - Aperts

- First described 1906
- Single gene Mutation chromosome 10q
- Spontaneous 1:120,000
- Autosomal dominant pattern
- <http://www.emedicine.com/ped/topic122.htm>

Craniofacial Syndromes - Aperts

Craniosynostosis with syndactyly

- General features
 - Craniosynostosis
 - Syndactyly
 - Hypertelorism
 - Proptosis
- ENT features
 - Airway obstruction
 - Abnormal ear
 - Hearing loss
 - Complete cartilage rings



Craniofacial syndromes – Hearing loss

- **Pinna abnormalities** include low set, small or posteriorly rotated ears, such as those seen in our Apert's, Pfeiffer's and Saethre-Chotzen patients. A prominent antihelical fold is frequently seen in patients with Saethre-Chotzen.
- **External canal atresia** is also a feature of craniosynostosis syndromes. It was found in 13% of patients with Crouzon's syndrome and is also reported to be quite common with Pfeiffer's syndrome.
- **Middle ear abnormalities** consist of both congenital ossicular fixation and eustachian tube dysfunction.
 - **Ossicular fixation** is also a feature of other craniosynostosis syndromes, including Crouzon's, in which lateral chain abnormalities may be found.
 - **Stapes fixation** is the most classically described malformation in patients with Apert's syndrome. Bergstrom reported a perilymph gusher during stapedectomy in one patient operated on for stapes fixation. Because of this complication and the frequency of middle ear effusion and infection, the performance of stapedectomy has been condemned by a number of authors, while other simply warn that it should be approached with caution.
 - **Eustachian tube dysfunction** leading to effusions, perforation, and cholesteatoma is thought to be secondary to altered nasopharyngeal and skull base anatomy and is extremely common. Significantly, as these patients grow, the relative hypoplasia of the skull base is often accentuated and middle ear pathology frequently persists into adulthood.
- **Inner ear pathology** is poorly characterized in these patients, although there is an increased incidence of sensorineural hearing loss.

Craniofacial Syndromes - Pfeiffers

Craniosynostosis with short broad thumbs

- Craniosynostosis syndrome resulting from premature fusion of the sutures of the skull resulting in skull deformity.
- Abnormal skull growth, which results in a pointed or conical head, is also responsible for underdevelopment of the mid-face (upper jaw bone), high arched palate and prominent lower jaw are characteristic.
- Eyes are wide set and bulge.
- Teeth erupt in improper positions.
- Mild hearing loss due to a defect in the middle ear may be present.
- Thumbs are short and broad; toes are oversized.
- Hands and feet may be webbed.
- Autosomal dominant
- <http://www.emedicine.com/derm/topic325.htm>

Cleft syndromes

SYNDROME	Locus	Inheritance	FEATURES
Stickler	6p21.3	AD	cleft palate, micrognathia, glossoptosis, severe myopia, flat facies, dental anomalies, deafness
Osmed		AR	saddle nose, cleft palate, progressive deafness
Shprintzen-Goldberg		AD	craniosynostosis, microcephaly, maxillary and mandibular hypoplasia, palatal shelf soft tissue hypertrophy, cleft palate, prominent nose, narrow palpebral fissures
Simpson dysmorphia	Xq26	X	disproportionately large head, coarse facies, large protruding jaw, wide nasal bridge, upturned nasal tip, large mouth, thickened lips, central cleft of lower lip, midline groove of tongue and inferior alveolar ridge, enlarged tongue, short neck
Phenylketonuria	12q24.1	AR	microcephaly, occasional cleft palate, long simple philtrum, thin upper lip, flattened nasal bridge, epicanthus, upturned nose
Retinoblastoma	13q14.1-14.2	AD	cleft palate, high forehead, prominent eyebrows, broad nasal bridge, bulbous tip of the nose, large mouth with thin upper lip, long philtrum, prominent earlobes
Holoprosencephaly, type 3	7q36	AD	cyclopia, ocular hypotelorism, proboscis, midface hypoplasia, single nostril, midline cleft upper lip, premaxillary agenesis

Cleft syndromes

Crouzon craniofacial dysostosis	10q26	AD	craniosynostosis, parrot-beaked nose, short upper lip, hypoplastic maxilla, relative mandibular prognathism, shallow orbit
Jackson-Weiss		AD	craniosynostosis, midfacial hypoplasia
Apert		AD	craniosynostosis, brachysphenocephalic acrocephaly, flat facies, high narrow palate
Pfeiffer		AD	mild craniosynostosis, flat facies, acrocephaly
Beare-Stevenson cutis gyrata		AD	craniosynostosis, cloverleaf skull, cleft palate or uvula, craniofacial anomalies
Zellweger	8q21.1	AD	high forehead, dolichoturriccephaly, large fontanels, flat face, round face, hypoplastic supraorbital ridge, epicanthus, cleft palate
Diastrophic dysplasia	5q32-q33.1	AR	hypertrophic auricular cartilage, cleft palate, micrognathia
Neonatal osseous dysplasia I		AR	micrognathia, cleft palate, flat nasal bridge, mid-face hypoplasia, neonatal osseous dysplasia, lethal chondrodysplasia
Basal cell nevus (Gorlin syndrome)	9q22.3	AD	macrocephaly, broad facies, frontal and biparietal bossing, mild mandibular prognathism, odontogenic keratocysts of jaws, misshapen and/or carious teeth, cleft lip and palate, ectopic calcification of falx cerebri

Cleft syndromes

Waardenburg , type IIA	3p14.1 -p12.3	AD	wide nasal bridge, short philtrum, cleft lip or palate, deafness
Pallister-Hall		AD	short nose, flat nasal bridge, multiple buccal frenula, microglossia, micrognathia, cleft palate, malformed ears
Waardenburg, type I	2q35	AD	wide nasal bridge, short philtrum, cleft lip or palate, occasional deafness, dystopia canthorum
Campomelic dysplasia	17q24.3- q25.1	AR	small chondrocranium, large neurocranium, occasional platybasia, cleft palate, retroglossia, micrognathia, flat nasal bridge, malformed ears
Saethre-Chotzen	7p21	AD	craniosynostosis, acrocephaly, brachycephaly, flat facies, thin long pointed nose, cleft palate, cranial asymmetry, ptosis, malformed ears
DiGeorge	22q11	AD	low-set ears, short ears, small mouth, submucous or overt palatal cleft, cleft lip, bulbous nose, square nasal tip, short philtrum, micrognathia,
Velocardiofacial		AD	Pierre Robin syndrome, cleft palate, small open mouth, myopathic facies, retrognathia, prominent nose with squared-off nasal tip
Treacher Collins mandibulofacial dysostosis	5q32- q33.1	AD	malar hypoplasia, cleft palate, mandibular hypoplasia, macrostomia, malformed ears, sensorineural deafness, coloboma of lower eyelid

Velo cardio facial syndrome- General features

- Palate (Velo-)
 - Overt, submucous or occult cleft palate
 - Cleft lip (uncommon)
- Heart (Cardio-)
 - VSD
 - ASD
 - Pulm atresia
 - Teratology of fallot
 - Vascular ring
- Orofacial
 - Retrognathia
 - Assymmetric face
 - Teeth
 - Missing
 - Enamel hypoplasia
- Others
 - Learning difficulties
 - Feeding difficulties
 - Immune deficiency
- Test
 - (FISH). *fluorescent in situ hybridization*
 - FISH is a type of specialized chromosome analysis

Velo cardio facial syndrome- ENT features

- Ears

- Over folded helix
- Attached lobules
- Protruberant cup ears
- Microtia
- AOM
- Glue Ear
- SN loss
- Narrow canals



- Nasal

- Prominent bulbous nasal tip
- Narrow nares
- Upper airway obstruction
- Small adenoids

- Laryngeal

- Anterior laryngeal web
- Laryngomalacia

- <http://www.emedicine.com/ped/topic2395.htm>

Connective tissue -Mucopolysaccharidoses

Mucopolysaccharidoses (MPS) and Mucopolipidoses (ML) are genetic lysosomal storage disorders caused by the body's inability to produce specific enzymes.

The missing enzyme prevents the normal breakdown and recycling of cells resulting in the storage of these cell deposits in virtually every cell of the body

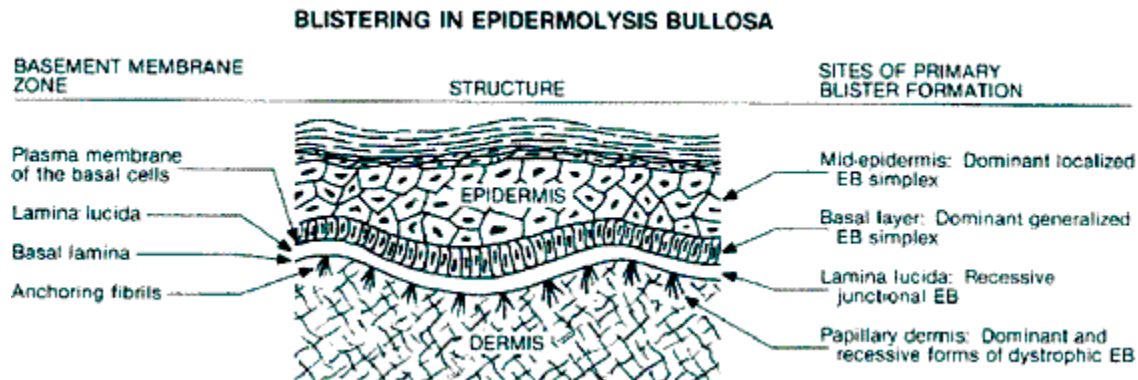
- General features
 - Coarse or rough facial features
 - Thick lips, enlarged mouth and tongue)
 - Dwarfism
 - Skeletal irregularities
 - Visceromegaly
 - Short claw-like hands,
 - Progressive joint stiffness
 - Recurring respiratory infections
 - Heart disease.
- ENT features
 - Obstructive airway disease and obstructive sleep apnea.
 - Diffuse infiltration around airway
 - Hearing loss (see below)
- http://healthlibrary.stanford.edu/resources/internet/bodysystems/metabolic_m.html

MPS

- 3 main types of type 1 MPS
 - Type HS Hurler-Scheie syndrome,
 - MPS type I H/S produces clinical features that are intermediate between types IH and IS
 - Type I H/S is milder than type IH and progresses more slowly
 - Children with this syndrome are usually healthy at birth, with onset of symptoms when aged 3-8 years
 - Survival to adulthood is common
 - Patients with type I H/S characteristically have corneal clouding, joint stiffness, dysostosis multiplex, and heart disease—cs
 - Type IH (Hurler Syndrome)
 - Type IS (Scheie Syndrome).
- Mucopolysaccharidosis II (MPS II)
 - X-linked disorder, which also has the eponym Hunter syndrome, results from the deficiency of iduronate 2-sulfatase
- MPS type III, or Sanfilippo syndrome
 - The four subgroups of MPS III are as follows: type IIIA (Sanfilippo A), type IIIB (Sanfilippo B), type IIIC (Sanfilippo C), and type IIID (Sanfilippo D)
- Morquio
 - Husler coined the term dysostosis multiplex to describe the constellation of skeletal findings specific to patients with MPS and other lysosomal storage disorders. These included a large skull with a J-shaped sella, anterior hypoplasia of the thoracic and lumbar vertebral bodies, hypoplasia of the pelvis with small femoral heads and coxa valga, oar-shaped ribs (narrow at the vertebrae and widening anteriorly), diaphyseal and metaphyseal expansion of long bones with cortical thinning, and tapering of the proximal phalanges.
- MPS VI
 - progressive connective tissue organ involvement, resulting from continuous storage of dermatan sulfate in the skeleton, heart valves, spleen, liver, and cornea.
 - Patients appear healthy at birth and have accelerated growth in the first year, followed by deceleration and short stature later in childhood. The diagnosis usually is made in early childhood when organomegaly, corneal clouding, coarse features, enlarged tongue, and joint stiffness all are apparent. Other complications include hearing loss, chronic respiratory infections, and cardiac insufficiency due to valvular disease.
- MPS VII
 - In severe cases, the condition presents as hydrops fetalis. Neonatal jaundice may be present at birth. More typically, the clinical features of the disorder become evident in the first few years of life. These early symptoms include dysostosis multiplex with dislocated hips, joint contractures, and thoracolumbar kyphoscoliosis. In many patients, a J-shaped turcica and odontoid hypoplasia also may occur. Radiographs demonstrate a flattening of the vertebral bodies termed platyspondyly.
- Many individuals have hearing loss, either conductive (in which pressure behind the ear drum causes fluid from the lining of the middle ear to build up and eventually congeal) or sensorineural.

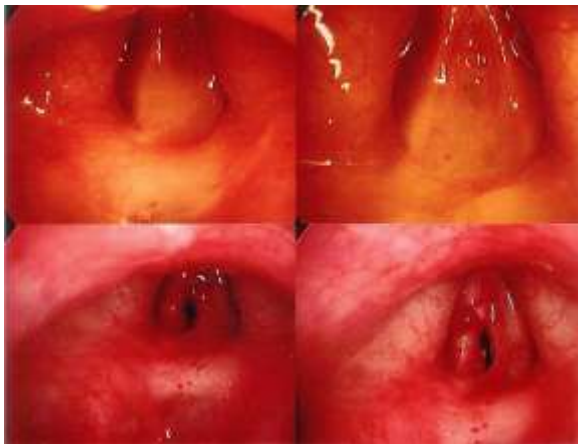
Connective tissue EB

- **EB simplex** is within the epidermis.
- **Junctional EB** is seen at the level of the lamina lucida within the basement membrane zone.
- **Dystrophic EB** or dermolytic EB is a scarring form of EB which occurs in the deeper tissue at the level the lamina densa or upper dermis.



EB- Laryngeal involvement by type

Simplex (Hand-feet)	None
Simplex (generalised)	None
Simplex (herpetiformis)	Hoarseness/weak cry
Dystrophic	Occasional
Junctional (espec lethal)	Hoarseness/weak cry Bouts of stridor Laryngeal web Death from a/w obstruction



<http://www.emedicine.com/DERM/topic124.htm>

Osteogenesis Imperfecta

- Type I
 - Commonest form
 - Autosomal dominant
 - Cells from individuals with type I OI secrete about half the normal amount of type I procollagen
 - In some families dentinogenesis imperfecta is a feature.
 - Blue sclerae
 - Tendency to fractures of the long bones, although healing occurs without deformity.
 - Hearing loss
 - Stapedectomy results
 - [PM:10962673](#)
 - [PM:15612382](#)
 - Operative findings included fixation or thickening of the stapes footplate with normal superstructure configuration and hypervascularization of the promontory mucosa.
- <http://www.emedicine.com/PED/topic1674.htm>



Goldenhars, Auriculovertebral

- Facial asymmetry
- Microtia
- Epibulbar dermoid
- Vertebral defects



- Without eye and vertebral anomalies = hemifacial microsomia
- <http://www.whonamedit.com/synd.cfm/2300.html>

Branchio-oto-renal syndrome

- Malformations of the outer, middle, and inner ear
 - conductive, sensorineural, or mixed hearing impairment
- Branchial fistulae and cysts;
- Renal malformations,
 - mild renal hypoplasia to bilateral renal agenesis.
- EYA1 gene mutations in approximately 40%
- Autosomal dominant.
- Extreme clinical variability can be observed in the same family.
- Prenatal testing is clinically available.
- <http://www.boystownhospital.org/Hearing/info/genetics/syndromes/bor.asp>

Obesity – Prader Willi

Morbid obesity with developmental delay, hypogonadism and dwarfism

- A disorder of chromosome 15
- Hypothalamic dysfunction:
 - Hyperphagia
 - Morbid obesity
 - Hypogonadism
 - Cognitive impairment
 - Difficult behaviour
 - Growth failure
 - Hypotonia



- **Due to a few recent fatalities reported in individuals with PWS who were on growth hormone therapy (GH) some physicians have also added this as an additional risk factor.** One possibility (that is currently unproven) is that GH could increase the growth of lymphoid tissue in the airway thus worsening already existing hypoventilation or OSA. Nonetheless, it must be emphasized that there are currently no definitive data demonstrating GH causes or worsens sleep disordered breathing.
- <http://www.prader-willi.org/Prader-Willi%20Overview.htm>

Obesity; Beckwith-Wiedemann Syndrome

Morbid obesity with macroglossia

- Overgrowth disorder.
 - First recognized in 1963
 - Usually sporadic, occ AD
 - Risk of hypoglycemia
 - Incidence 1:15,000 births.
 - **Macroglossia**
 - **Abdominal Wall Defects**
 - **Increased Growth**
 - Birth Weight and Length usually above average.
 - Visceromegaly:
 - Hemihypertrophy:
 - **Typical facial features**
 - Earlobe creases : or pits behind the upper ear.
 - Prominent occiput: enlarged back of the skull.
 - Nevus Flammeus: a strawberry mark commonly found on the forehead and eyelids.
- http://www.bws-support.org.uk/html/what_is_bws.html



Foetal Alcohol

Abnormal face with hearing loss

- Short palpebral fissures, abnormal philtrum, thin upper lip, hypoplastic midface
- Neurodevelopment disorder (more than one may be identified, but not all conditions must be present)
- Head circumference < 10th percentile
- Intellectual impairment
- Memory problems
- Delayed development
- Attachment concerns
- Attention deficit disorder
- Impaired motor skills
- Hyperactivity
- **Neurosensory hearing loss**
- Problems with reasoning and judgment
- Learning disabilities
- Inability to appreciate consequences
- Impaired visual/spatial skills
- <http://www.emedicine.com/ped/topic767.htm>



Fetal warfarin

- Head and neck:
 - Microcephaly and **midfacial hypoplasia**.
 - Eyes: Optic atrophy, corneal opacity, and cataracts.
 - **Nose: Hypoplastic nose with low nasal bridge and choanal atresia.**
- Thorax: Widely spaced nipples.
- Hand and foot: Hypoplasia and shortening of digits.
- Muscles: Hypotonia. Bones and joints:
- Punctate epiphyses, calcification disorders with stippling of the epiphyses, and bone defects similar to those in chondrodysplasia punctata.
- Nervous system:
 - Brain agenesis, hydrocephalus, agenesis of corpus callosum, meningoencephalocele, and seizures.
- Cardiovascular system:
 - Patent ductus arteriosus, pulmonic stenosis, transposition of the great vessels, and anomalous pulmonary veins.
- Respiratory system: **Airway obstruction.**
- Growth and development:
 - Growth and mental retardation.
 - Behaviour and performance:
 - **Deafness,**
 - **Feeding difficulty, and failure to thrive.**
- <http://www.emedicine.com/emerg/topic872.htm>

Congenital Rubella

- Sensorineural deafness, which can progress after birth;
- Ophthalmic defects such as cataracts;
- Cardiovascular defects;
- Brain damage, that only occurs after infection between the 3rd and 16th week of gestation, causing mild to severe mental retardation with microcephaly and spastic diplegia
- Major structural malformations are rare.
- In France, systematic vaccination of male and female newborns was introduced in 1985 and induced a marked reduction in the incidence of CRS (from 13 to 5 cases in 100,000 livebirths).
- <http://www.emedicine.com/emerg/topic388.htm>

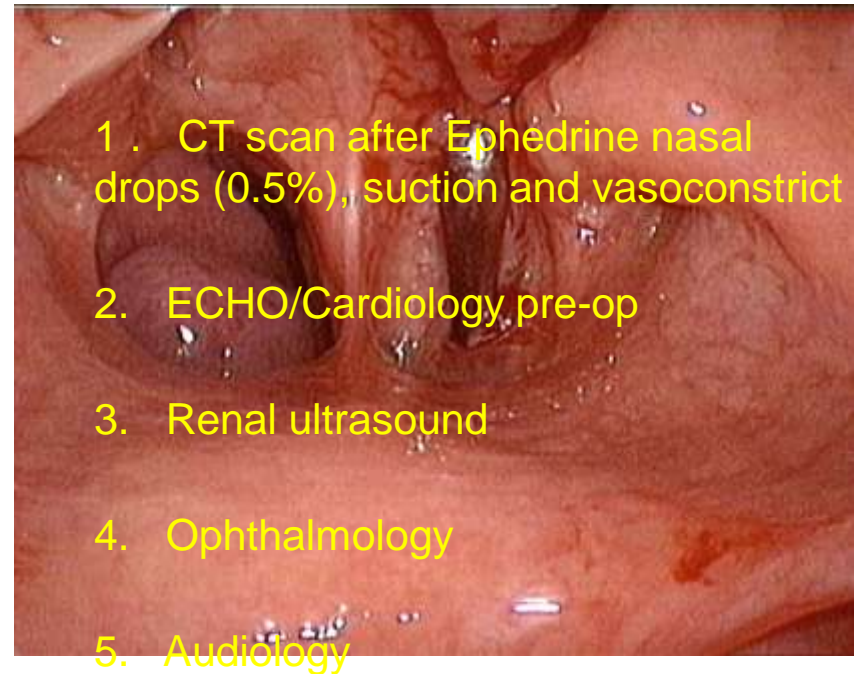
Treacher Collins syndrome

- Downslanting eyes
- Notches of the lower eyelids, most frequently on the lateral 1/3
- Mandibular hypoplasia
- Prominent nose
- Broad mouth
- Small chin with a steep angle of the lower jaw
- Microtia
- Sideburns
- Hearing loss, usually conductive.
- The nasopharynx may be narrow.
- Also
 - Cleft lip, with or without cleft palate
 - Heart defects
 - Strabismus
- <http://www.emedicine.com/ped/topic1364.htm>



CHARGE

- Location 2p14? ;7q21;2q33?
- Coloboma (iris or retina)
- Heart (any defect)
- Atresia Choanae
- Retardation (growth and development)
- Genital (hypoplasia)
- Ear (microtia)
- (protocol for pts with Choanal atresia)
- <http://www.emedicine.com/ped/topic367.htm>



Cornelia De lange

Abnormal face, feeding difficulties and reflux

- Low-pitched weak cry
- Initial hypertonicity (100%)
- Respiratory and feeding difficulties in newborn period and infancy (71%)
 - failure to thrive.
 - gastroesophageal reflux
 - Developmental delay and mental retardation
 - Severe speech delay is typical.
 - mild-to-moderate mental retardation.
- Behavioral manifestations
 - Hyperactivity.
 - diminished ability to relate.
- Ophthalmologic manifestations (50%)
- Short stature
- Microcephaly (98%)
- Facial features
 - Confluent eyebrows
 - Long curly eyelashes
 - Low anterior and posterior hairline
 - Underdeveloped orbital arches
 - Neat, well-defined, and arched eyebrows
 - Long philtrum
 - Anteverted nares
 - Down-turned angles of the mouth
 - Thin lip (especially upper vermilion border)
 - Low-set ears
 - Depressed nasal bridge
 - High arched palate
 - Late eruption of widely spaced teeth
 - Micrognathia
 - Short neck

Hallerman Streiff

Characteristic beak shaped nose

- short stature,
- Small beak shaped nose
- bird like face,
- atrophy of skin
- mandibular hypoplasia
- Microstomia
- Difficult intubation
- natal teeth
- cataract
- <http://children.webmd.com/Hallermann-Str>



Noonan

Turner-like syndrome of males (and females) with webbing of the neck

- Autosomal dominant manner.
- Gene *PTPN11*, was discovered in 2001.
- Frequently seen abnormalities include
 - webbing of the neck,
 - changes in the sternum
 - facial abnormalities
 - low-set or abnormally shaped ears,
 - ptosis
 - hypertelorism
 - epicanthal folds
 - micrognathia
 - congenital heart disease
 - Mild mental retardation
 - Hearing loss varies.
 - Puberty is usually delayed, and males may have undescended testicles and a small penis.
 - Adult height is usually decreased.

- <http://www.emedicine.com/PED/topic1616.htm>

-

Opitz G

Hypertelorism with laryngeal cleft

- Hypertelorism
- Hypospadias
- Cryptorchidism
- Dysphagia
- Imperforate anus
- Clefts
 - Lip
 - Palate
 - Uvula
 - Esophagus
 - larynx
 - Trachea
- Agenesis of the corpus callosum
- The hairline may come to a point in the front on the forehead ("widow's peak")
- Hypertelorism
- The ears may be small and/or low-set
- Flat nasal bridge
- Dysphagia
- Aspiration (cleft larynx)
- Tracheomalacia
- sensorineural deafness.
- <http://www.emedicine.com/ped/topic2117.htm>

Moebius syndrome

Impassive face and strabismus due to congenital VI and VII palsy.

- Also
 - delayed crawling and/or walking due to low muscle tone
 - respiratory illnesses due to low muscle tone
 - speech problems
 - hearing problems – glue ear
 - limited movement of the tongue
 - sensitivity to loud sounds
 - sensitivity to bright light
- Surgery
 - Strabismus surgery.
 - Nerve and muscle transfers.
- <http://www.emedicine.com/neuro/topic612.htm>

Fraser

Hidden eyes with possible abnormal ears and laryngeal stenosis

- Cryptophthalmos
 - Orofacial defects,
 - Urogenital malformations,
 - Syndactyly, decreased number of digits
 - Bilateral or unilateral renal dysplasia, renal agenesis.
 - Nose broad, with a flat bridge
 - External ear
 - Microtia, low-set.
 - meatal stenosis
 - Laryngeal stenosis
 - Mental retardation occurs in 80% of survivors
- Important as may be deaf/blind
- <http://www.whonamedit.com/synd.cfm/2010.html>



Waardenburg's

- Petrus Johannes, Dutch ophthalmologist (1886-1979)
- A wide bridge of the nose;
- Pigmentary disturbances
 - Heterochromia iridium
 - White forelock and eyelashes
 - Premature graying of the hair
- Type I is characterized by displacement of the fold of the eyelid and hypertelorism
- Type II higher frequency of deafness.
- Cochlear deafness
 - 25-70% type I
 - 50-88% type II
- Autosomal dominant
- (Pax3 mouse gene) on chromosome 2
- <http://www.emedicine.com/derm/topic690.htm>

Larsen

Cartilage abnormalities with tracheomalacia, cleft palate and hearing loss

- Abnormalities of the growth centres and length of the bones
- Short stature
- Scoliosis
- Short stubby fingers
- Broad thumbs
- Short metacarpals
- Cervical kyphosis
- Spina-bifida
- Cleft lip and/or palate
- Tracheomalacia
- Feeding difficulties
- Mixed hearing loss
- <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=150250>

Ectrodactyly, ectodermal dysplasia and cleft lip/palate

- EEC syndrome
- Ectrodactyly
 - Missing or irregular digits
- Ectodermal dysplasia
- Cleft lip/palate
- Chromosome 19,
 - region defined by D19S894
 - <http://www.nfed.org/EEC.htm>



Chondrodysplasia Punctata

- Skeletal abnormality
 - Punctate calcification of the cartilage of the epiphyses, larynx and trachea.
 - Growth retardation,
 - Shortening of limbs,
 - Cataracts,
 - Dry and scaly skin affects ears
-
- Conradi-hunermann (X-linked dominant form)
 - <http://www.hon.ch/HONselect/RareDiseases/EN/C05.116.099.708.195.html>

Osteopetrosis

- Recessive form more severe
- Sclerotic bones
- Long bones may have longitudinal striations
- Macrocephaly
- Square-shaped head
- Frontal bossing
- Ptosis
- Strabismus
- Progressive pressure on cranial nerves leads to
 - Optic atrophy
 - Deafness and
 - Facial palsy
- The teeth are abnormal and decay easily
- <http://www.emedicine.com/med/topic1692.htm>

Craniometaphyseal dysplasia

Cranial nerve compression and nasal obstruction with facial deformity

- Dysplastic disease
 - Either autosomal dominant or autosomal recessive
 - Facial deformity
 - Cranial hyperostosis
 - Failure of tubular bones to undergo normal modelling
 - Optic nerve atrophy
 - Compression of the brain stem.

 - Radiographic features include progressive sclerosis about the cranial sutures and base of the skull and **obliteration of the paranasal sinuses**.
- Facial deformity
 - Malocclusion of teeth
 - Nasal obstruction
 - Facial paralysis
 - Deafness
 - Optic nerve atrophy
 - <http://www.medterms.com/script/main/art.asp?articlekey=17537>

Achondroplasia

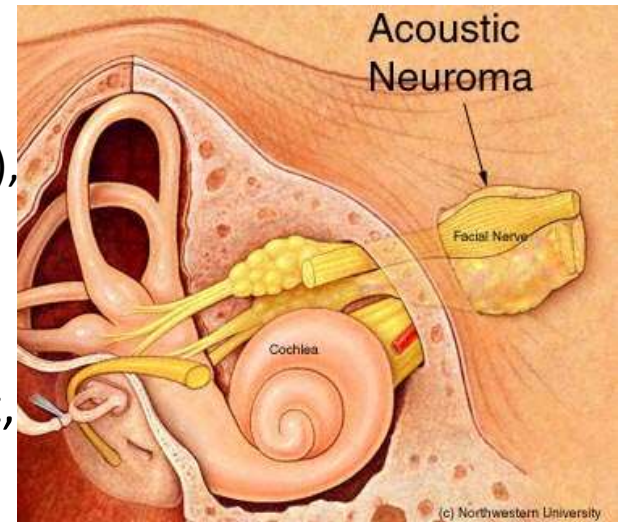
- Short stature
- Rhizomelic (proximal) shortening of the arms and legs with redundant skin folds on limbs
- Limitation of elbow extension
- Trident configuration of the hands
- Genu varum (bow legs)
- Thoracolumbar gibbus in infancy
- Exaggerated lumbar lordosis, which develops when walking begins
- Large head with frontal bossing
- Midface hypoplasia
- Obstructive apnea or central apnea
 - adenotonsillar hypertrophy
 - hypotonicity
 - Narrow pns
- Frequent otitis media
- Sensorineural hearing loss
- "towering" petrous ridges
 - [PMID: 8456822](#)
- <http://www.emedicine.com/ped/topic12.htm>

NF type 1

- Autosomal dominant
- 1 in 3000 individuals.
- Cafe au lait patches (more than six greater than 1.5 cms in diameter)
- Peripheral neurofibromata.
- Macrocephaly
- Short stature
- Hypertelorism, and
- Thorax abnormalities
- Cardiac malformations
- Hypertension due to renal artery stenosis
- Pheochromocytoma
- Neurofibrosarcomas
- Meningiomas
- Variable sensorineural deafness
- (Acoustic neuromas) probably not
- <http://www.emedicine.com/ped/topic2418.htm>

NF type 2

- 'Central' form of neurofibromatosis (NF)
- The average age of onset is in the early twenties
- Presenting symptoms :
 - vestibular schwannoma (acoustic neuroma “AN”),
 - cranial meningioma
 - spinal tumour.
- Bilateral AN’s
- Cafe au lait patches may occasionally be present, but are not as numerous as in NF1
- 5-10% of patients with AN have NF2
- The gene has been mapped to 22q
- <http://www.emedicine.com/radio/topic475.htm>



VATER

- V: Vertebral dysgenesis
- A: Anal atresia
- C: Cardiac anomalies
- T-E: Fistula +/- esophageal atresia
- R: Renal or Radius anomalies
- L: Limb anomalies
- S: Single Umbilical artery
- <http://children.webmd.com/VACTERL-Association>

McCune-Albright syndrome

- At least 2 of the triad
 - polyostotic fibrous dysplasia
 - café au lait skin pigmentation
 - autonomous endocrine hyperfunction
- Cushing syndrome generally results in growth failure and hypertension in infancy.
- The adrenal glands are bilaterally enlarged
- Bone changes in the skull can lead to blindness or **deafness**
- <http://www.emedicine.com/ped/topic1386.htm>

Deafness

- Patho-emryology
- Classification of Childhood Hearing Loss
 - Congenital without organ involvement
 - With Associated Organ involvement
 - Waardenburg
 - LEOPARD
 - Skeletal Dysplasia
 - Klippel-Feil Syndrome
 - Pierre Robin Syndrome
 - Van der Hoeve's Syndrome (Osteogenesis imperfecta)
 - Craniofacial Anomalies
 - Treacher-Collins Syndrome (Mandibulofacial dysostosis)
 - Goldenhar's Syndrome (Oculoauriculovertebral dysplasia)
 - Crouzon's Syndrome (Craniofacial dysostosis)
 - Apert's Syndrome (Acrocephalysyndactyly)
 - Ocular Abnormalities
 - Usher's Syndrome
 - Alstrom's Syndrome
 - Refsum's Disease
 - Cardiac Abnormalities
 - Jervell and Lange-Nielsen Syndrome
 - Renal Abnormalities
 - Alport's Syndrome
 - Endocrine Dysfunction
 - Pendred's Syndrome
 - Metabolic Storage Diseases
 - Chromosomal - trisomy21
- Acquired
 - Prenatal
 - Maternal ingestion of teratogens/ototoxins
 - Intrauterine infection
 - Rubella
 - CMV
 - Toxoplasmosis
 - Influenza
 - Herpes 1 and 2
 - Syphilis
 - Postnatal
 - Prematurity
 - Anoxia
 - Kernicterus

Pathoembryology

- A. Inner ear has separate development (otic placode) at a different time (4th-20th week gestation) from external and middle ear, however inner ear abnormalities do occur in 15-20% of cases of external canal atresia (SNHL in only 6%).
- B. Auricle (1st and 2nd branchial arches) is formed early from 6th-12th week gestation and malformation of auricle implies malformation of middle ear, mastoid, VII nerve.
 - Normal auricle with external canal (1st branchial groove) atresia indicates abnormal development during 28th week gestation by which time ossicles and middle ear already formed.
 - Ossicles: 1st arch derivatives--malleus head, incus short process and body; 2nd arch derivatives--manubrium of malleus, incus long process, stapes.
- C. Histopathology of Congenital SNHL
 - 1. Abnormal bony labyrinth
 - a. occurs rarely
 - b. due to faulty induction of inner ear (bony labyrinth inductor = developing CNS); fetus with abnormal brain development will often have abnormal bony labyrinth
 - c. abnormal bony labyrinth seen on radiographic exam of inner ear- -suspect CNS abnormality
 - 2. Abnormal neuroepithelium
 - a. occurs more frequently--predominant histopathology in most congenital and postnatal SNHL
 - b. usually absence of organ of Corti + abnormal surrounding membranous structures
 - c. thought to be secondary to premature cell death (degeneration) rather than lack of development
 - d. with abnormal bony labyrinth, neuroepithelium is often normal
 - e. with loss of organ of Corti and sound deprivation, normal development of CNS may be impaired; some of the CNS changes (with subsequent behavioral deficits) may be ameliorated by early use of sound stimulation--early detection of hearing loss is imperative

Genetic deafness

- Of all congenital deafness,
 - 50% is secondary to acquired disease
 - 50% is inherited
- Of the inherited congenital deafness
 - 75-88% is autosomal recessive (AR),
 - 12-24% is autosomal dominant (AD),
 - 1% is X-linked
- Majority of hereditary congenital HL is clinically undifferentiated (not part of recognizable syndrome and does not affect other organ systems)
- Conductive autosomal recessive HL always exists as part of a syndrome; clinically undifferentiated conductive HL is therefore autosomal dominant
- Autosomal recessive is usually stable; autosomal dominant tends toward progression

Inner Ear Aplasia

- 1. General
 - a. inner ear deformity can occur alone or in association with a recognized syndrome
 - b. more accurately thought of as a spectrum
- 2. Classification
 - a. Michel Aplasia (1) most severe form (2) complete failure of bony and membranous labyrinth development (3) no residual hearing
 - b. Mondini Aplasia
 - (1) incomplete formation of bony and membranous labyrinth, often asymmetrical
 - (2) middle and apical turns of cochlea occupy common bony space (cloaca)
 - (3) cochlea represented by single curved tube with 1 1/2 instead of 2 3/4 turns
 - (4) vestibular structures also underdeveloped
 - (5) 2nd most common, (autosomal dominant)
 - c. Scheibe Aplasia
 - (1) most common, (autosomal recessive)
 - (2) membranous aplasia of pars inferior (cochlea/sacculle)
 - (3) bony labyrinth normal (no radiographic abnormality)
 - (4) Audio--profound SNHL with residual low frequency hearing
 - d. Alexander Aplasia
 - (1) least severe
 - (2) partial aplasia of cochlear duct (basal turn)
 - (3) high frequency HL

Associated Organ System Involvement

- a. Waardenburg Syndrome
 - (1) autosomal dominant-variable penetrance
 - (2) most frequently diagnosed hereditary deafness syndrome (1-2% of all congenital deafness)
 - (3) 6 predominant features:
 - 1. widely spaced medial canthi with shortening of palpebral fissures;
 - 2. prominent, broad nasal route;
 - 3. hypertrichosis of eyebrows;
 - 4. white forelock;
 - 5. heterochromia of irides;
 - 6. SNHL (total or subtotal) in 20% of cases
 - (4) other features: cleft lip/palate, high arched palate, areas of depigmentation, absent vestibular response
 - (5) Diagnosis: observing stigmata in patient or family (dystrophic canthi and increased intercanthal distance are most common expressions of syndrome)
- b. LEOPARD Syndrome
 - (1) autosomal dominant
 - (2) lentigines, EKG abnormality, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, bilateral sensorineural deafness (25% affected)

Skeletal Dysplasia

- a. Klippel-Feil Syndrome
 - (1) autosomal recessive; females > males
 - (2) severe progressive SNHL with middle ear anomalies (conductive component), short neck due to fused cervical vertebrae, spina bifida, EAC atresia
- b. Pierre Robin Syndrome Sequence
 - (1) autosomal dominant
 - (2) main features: cleft palate (50%), micrognathia, glossoptosis
 - (3) mixed hearing loss, malformed auricles, mental retardation, hypoplastic mandible, aspiration--common cause of death
- c. Van der Hoeve's Syndrome (Osteogenesis imperfecta)
 - (1) autosomal dominant
 - (2) bone fragility, blue sclera, progressive deafness--conductive, sensorineural, or mixed beginning in childhood (50% affected)

Craniofacial Anomalies

- a. Treacher-Collins Syndrome (Mandibulofacial dysostosis)
 - (1) autosomal dominant
 - (2) auricle malformed and small; preauricular fistulas; EAC atresia
 - (3) mandibular and malar hypoplasia--fishmouth
 - (4) usually bilateral involvement
 - (5) down sloping palpebral fissures; notched lower lids
 - (6) CHL due to malformed malleus/incus (stapes normal)--30% have significant HL
- b. Goldenhar's Syndrome (Oculoauriculovertebral dysplasia)
 - (1) autosomal dominant or autosomal recessive
 - (2) 1st and 2nd arch abnormality
 - (3) often unilateral (hemifacial microsomia)
 - (4) malformed auricles/microtia; malformed middle ear/ossicles; possible underdeveloped inner ear
 - (5) mostly CHL--40% affected
 - (6) upper lid colobomas, epibulbar dermoids, hypoplasia of mandible/ maxilla, cleft palate, spinal anomalies
- c. Crouzon's Syndrome (Craniofacial dysostosis)
 - (1) autosomal dominant
 - (2) CHL due to EAC atresia or middle ear malformations--30% affected
 - (3) premature closure of cranial suture lines, midface hypoplasia, bulging eyes--"frog face"
- d. Apert's Syndrome (Acrocephalysyndactyly)
 - (1) autosomal dominant
 - (2) facial morphology similar to Crouzon's syndrome, but also syndactyly of hands and feet
 - (3) mental retardation common

Ocular Abnormalities

- a. Usher's Syndrome
 - (1) autosomal recessive
 - (2) 4% of congenital deafness
 - (3) characteristics: congenital SNHL, progressive retinitis pigmentosa, night blindness and tunnel vision, cataracts, mental retardation, psychosis, spinocerebellar ataxia
 - (4) vestibular dysfunction--almost all will have no vestibular response to caloric test or ice water calorics; helps in diagnosis when etiology unknown
 - (5) usually born deaf due to atrophy of organ of Corti with progressive vision loss from retinitis pigmentosa; night blindness is 1st retinal sign (before age 10) with 50% patients having decreased visual acuity by 2nd decade
 - (6) retinal findings: granular accumulation of pigment beginning at fundus and extending to periphery
 - (7) Diagnosis: ophthalmoscopy or electroretinography--perform in infant born with SNHL of unknown etiology; may need routine fundoscopic exams during first 2 decades; important to determine if vision will be lost because if deaf patient loses vision, must initiate special habilitative intervention; important for parents to know if they carry the gene; test family members (audio, electroretinography) to identify heterozygote carriers
- b. Alstrom's Syndrome
 - (1) autosomal recessive
 - (2) progressive SNHL beginning in childhood, obesity, diabetes, retinal pigmentation
- c. Refsum's Disease
 - (1) autosomal recessive
 - (2) progressive asymmetric SNHL (50%), neurologic dysfunction, retinitis pigmentosa, ichthyosis beginning late childhood
 - (3) absence of enzyme for phytanic acid metabolism (from chlorophyll) (
 - 4) Dx.: high phytanic acid plasma level
 - (5) Rx.: eliminate phytanic acid from diet

Cardiac Abnormalities

- a. Jervell and Lange-Nielsen Syndrome
 - (1) autosomal recessive
 - (2) characteristics: profound bilateral SNHL (high frequency worst), recurrent syncope (prominent feature), usually terminates in sudden death--early detection important to preserve life
 - (3) suspect with family history of SIDS
 - (4) EKG abnormalities: large T waves, prolonged QT interval
 - (5) syncopal episodes usually begin 2nd or 3rd decade, last 5-10 minutes, frequency variable (EKG--asystole followed by V. tach)
 - (6) 50% die before age 15 w/o treatment (7) Treatment: 1. propranolol +/- phenobarbital 2. implant cardioverter defibrillator when refractory to drugs
 - (8) Diagnosis: all patients with idiopathic SNHL should have at least 1 EKG; attempt to identify carriers in family members with EKG (note: EKG may normalize in young adults)
 - (9) cardiac histopathology: hypertrophy of intima of artery to SA node, infarction of SA node, abnormal Purkinje fibers and AV node

Renal Abnormalities

- a. Alport's Syndrome
 - (1) autosomal dominant
 - (2) most common progressive inherited cause of SNHL in children
 - (3) characteristics: progressive SNHL usually beginning age 10, progressive nephritis with hematuria and proteinuria beginning 1st or 2nd decade
 - (4) males more severely affected--if untreated usually die by 3rd decade; females often have normal life span with toxemia during pregnancy
 - (5) Diagnosis: consider Alport's in any child with SNHL of recent onset; UA -- >3 RBCs/HPF, >5 WBCs/HPF, proteinuria; serum Cr/BUN abnormal; IVP--atrophy or lobulated kidney with advanced disease
 - (6) HL usually progresses with age, predominant in HF, affects 50%, correlation between HL severity and renal disease severity; seldom more than severe HL--helped significantly with hearing aid; possible improvement in HL after renal dialysis or renal transplant
 - (7) ocular abnormality may also occur and is important because of possible impairment of 2 sensory modalities (similar to Usher's Syndrome and Congenital Rubella); occurs in 23% with lens most commonly involved
 - (8) histopathology: degeneration of organ of Corti, atrophy of spiral ganglion, thickening of glomerular basement membrane, focal sclerosis, interstitial fibrosis, foam cells

Endocrine Dysfunction

- a. Pendred's Syndrome
 - (1) autosomal recessive
 - (2) variable bilateral SNHL (atrophy of organ of Corti) -- usually severe to profound, especially high frequency
 - (3) develop goiter which usually apparent before age 8; usually euthyroid; no association with cancer; perchlorate test - - abnormal organification of nonorganic iodine
 - (4) comprise 1-7% severe to profoundly deaf children
 - (5) U-shaped audiogram, vestibular response variable
 - (6) Treatment: exogenous thyroid hormone; total or partial thyroidectomy is contraindicated -- goiter returns

Metabolic Storage Diseases

- a. Mucopolysaccharidoses
- (1) ie., Hurler's Syndrome (Gargoylism); Hunter's Syndrome is same but X-linked
- (2) characterized by excessive urinary excretion of glycosaminoglycans
- (3) abnormal mucopolysaccharides are deposited in tissues
- (4) all autosomal recessive (except Hunter's)
- (5) hearing loss is conductive or mixed with air-bone gap in high frequencies
- (6) dwarfism, forehead prominence, low set ears, mental retardation, hepatosplenomegaly, coarsening of facial features, corneal opacities
- (7) death in early adolescence

Chromosomal Abnormalities

- a. Trisomy 13 and 18
 - lethal in infancy
 - mixed hearing loss
- Trisomy 21
 - Mixed hearing loss important to recognize because the sensory deprivation may be significant burden for Down's children)

Acquired Congenital Deafness

- A. Maternal ingestion of teratogens/ototoxins
 - 1. Thalidomide
 - 2. Streptomycin
 - 3. Quinine, Chloroquine phosphate
- B. Intrauterine infection (note: often no signs/symptoms of maternal infection)
 - 1. Rubella
 - a. most common cause of acquired congenital SNHL
 - b. earlier in intrauterine life--more severe effects, 5-10% of mothers with rubella in 1st trimester give birth to children with deafness
 - c. clinical presentation: (after 1 week of inapparent viral infection) -- posterior cervical and retroauricular adenopathy followed by mild URI, then rash which begins on face and disappears rapidly in 72 hrs.
 - d. Diagnosis: physical exam +immunologic techniques, maternal rash or exposure history
 - e. Findings: pigmentary retinitis ("salt and pepper")-- most common and consistent finding; congenital cataracts, microcephaly (mental retardation), cardiovascular anomalies, IUGR, jaundice, long bone lesions
 - f. suggested that all pregnant women have rubella titers drawn at beginning of pregnancy and follow-up titers later
 - g. Titer: diagnosis based on rubella specific IgM in cord blood or mother/infant serum in 1st 6mos.; older children--more difficult diagnosis (vaccination, infection with wild type virus); titer should be obtained from all patients and mothers when etiology of SNHL unknown (unless child has been immunized)
 - h. severe to profound SNHL, may be assymetric, may be progressive; may have CHL--fixed stapes or CSOM secondary to high arched palate, therefore audiometric + impedance monitoring for progressive HL or CHL is important
 - i. there is an increased incidence of SNHL caused by rubella in families with genetic predisposition to SNHL (possibly predisposition increased by presence of both factors)

Acquired Congenital Deafness

– 2. Cytomegalic inclusion disease

- a. CMV--very ubiquitous viral infection, nearly always without signs/ symptoms of maternal illness;55-72% pregnant women have positive CMV titers--10% of their offspring have CMV infection; majority of CMV infected infants appear normal but 10-15% develop disabilities from CNS damage (developmental delay, learning difficulties); neonates with symptoms at birth (less common) have more severe form and HL is common (1 in 3000 live births)
- b. CMV can infect neonate when mother has a primary or subsequent infection (consecutive pregnancies with infected children); children infected during mother's primary infection have more severe morbidity
- c. Teratogenic action variable with lower incidence of pathologic change than rubella--HL of variable severity, can be progressive
- d. Stigmata: microcephaly, hydrocephaly, mental retardation, palatal abnormalities, intracerebral calcifications, prematurity, low birth weight, chorioretinitis, jaundice with hepatosplenomegaly, petechiae
- e. Diagnosis: positive titers (CMV specific IgM) from mother and child (sometimes deceiving), stigmata (may not be present), positive CMV urine cultures (very helpful in **early** infancy); No established means of prevention or treatment

Other Intrauterine Infections

- a. Toxoplasmosis--parasitic disease causing fever, lymphadenopathy, pulmonary lesions and calcific foci in mother
- b. Influenza--maternal fever, lymphadenopathy, URI, arthralgias, myalgias
- c. Herpes 1 and 2--history of labial or vaginal lesions
- d. Syphilis--25-38% of patients with congenital syphilis have HL
 - (1) early (infantile) form--severe, bilateral SNHL, usually multisystem involvement with fatal outcome
 - (2) late (tardive) form--onset in early childhood with bilateral, severe, sudden SNHL associated with vestibular symptoms (similar to Meniere's disease); may have later onset (as late as 5th decade)--mild HL with severe episodic vertigo; one ear affected first followed by the other ear (
 - 3) Histopath: osteitis, obliterative endarteritis, endolymphatic hydrops
 - (4) Signs: Hennebert's--positive fistula test with no clinical evidence of middle ear or mastoid disease or fistula (fibrous bands between footplate and vestibular membranous labyrinth or excessively mobile footplate); Tullio's phenomenon--vertigo and nystagmus with high intensity sound
 - (5) Treatment: penicillin + steroids

Perinatal Causes

- 1. Prematurity
 - a. most common cause due to factors including: anoxia, kernicterus, ototoxic medication, labyrinthitis, meningitis, temporal bone fractures
 - b. prematurity as a factor in SNHL--10%
 - c. 2% children less than 1.36 kg (3 lbs.) have significant SNHL
 - d. premature infant has 20x greater chance of deafness than normal birth weight child
 - e. usually severe SNHL especially HF f. 68% of premature children with SNHL have multiple handicaps (aphasia, MR, visual pathology, emotional disturbance) and this must be considered in planning rehab program
- 2. Anoxia
 - a. most important factor in SNHL of premature infant; asphyxia likely with cord blood pH <7.25, 5 minute Apgar <5
 - b. pathologic lesion probably lies in cochlear nucleus and other portions of CNS (not cochlea)
 - c. high rate of other CNS handicaps
- 3. Kernicterus
 - a. many are also premature
 - b. few cases of RH incompatibility, but ABO and other blood group incompatibilities assoc. with kernicterus + SNHL
 - c. hearing loss--bilateral HF SNHL with little loss of speech discrimination; 22% have severe SNHL correlating with severity of hemolytic disease
 - d. Histopath: abnormal CNS with greatest nerve cell injury in ventral cochlear nucleus
 - e. exchange transfusion --if serum bilirubin >20mg/dl