Congenital anomalies, Dysmorphology

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Definitions

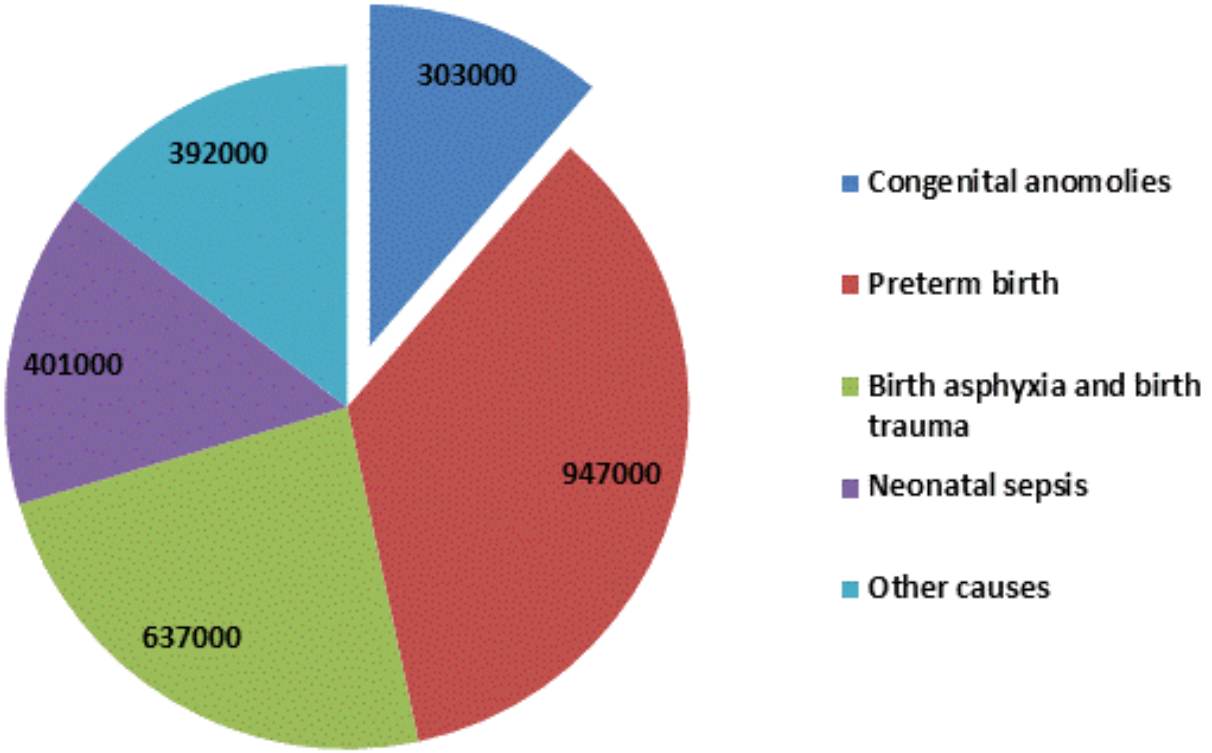
Phenotype: the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment.

Congenital anomalies: structural or functional anomalies that occur during intrauterine life and can be identified prenatally, at birth or later in life.

- Major anomalies – abnormalities that have medical, surgical, or cosmetic significance
- Minor anomalies – cosmetic significance

  = **dysmorphic features**

Causes of 2.68 million deaths during the neonatal period in 2015, worldwide



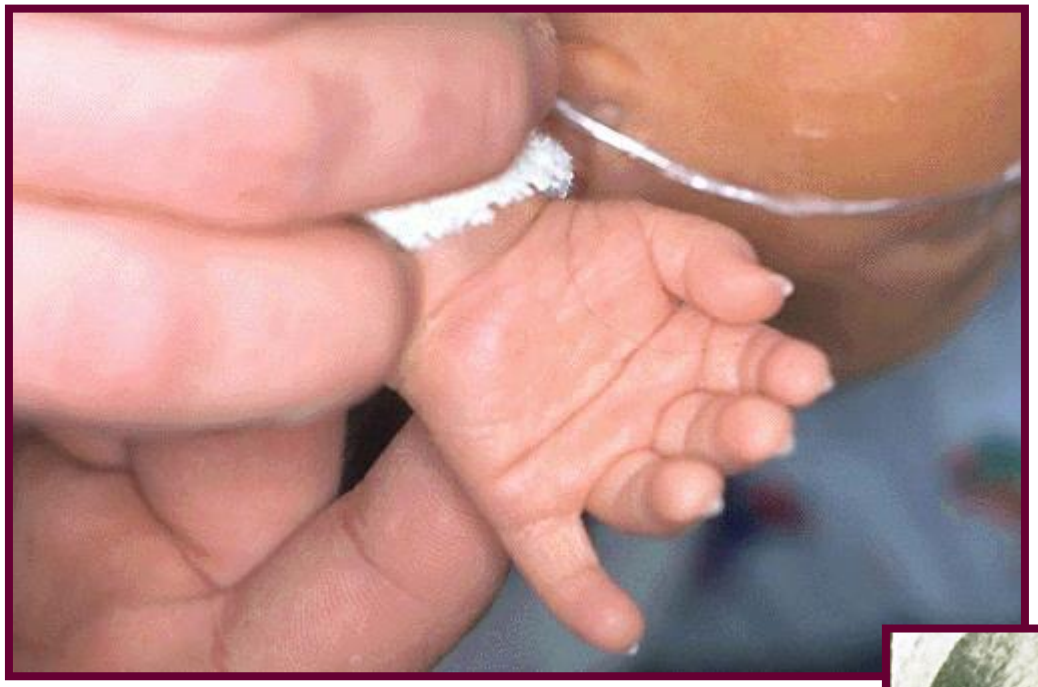
Source: adapted from WHO 2000-2015 child causes of death

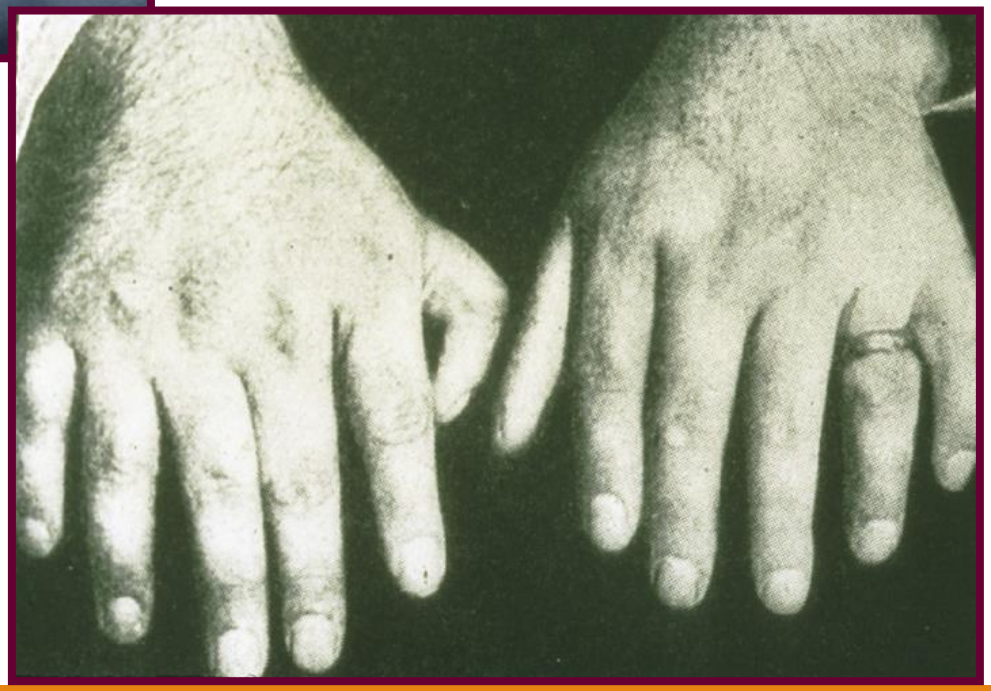
Congenital anomalies

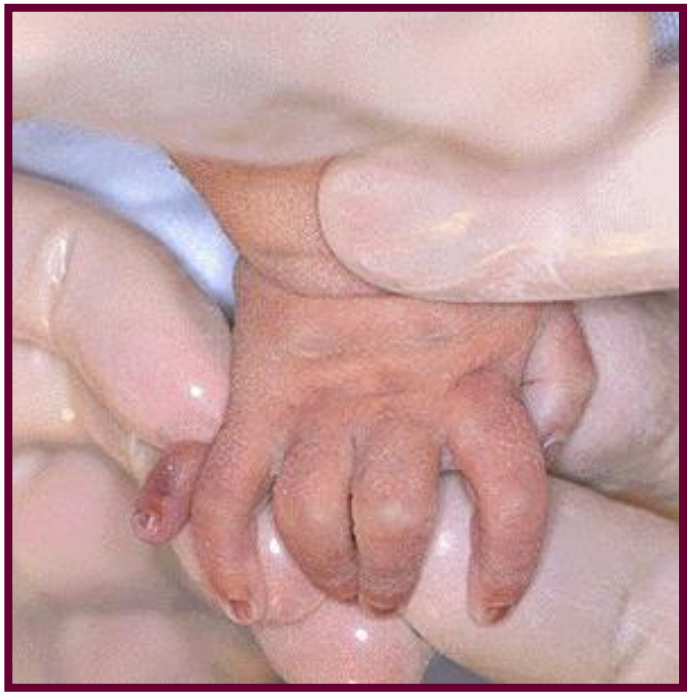
2-3% singletons have a major anomaly (e.g. heart defect)

10% have a minor anomaly (e.g. polydactyly)

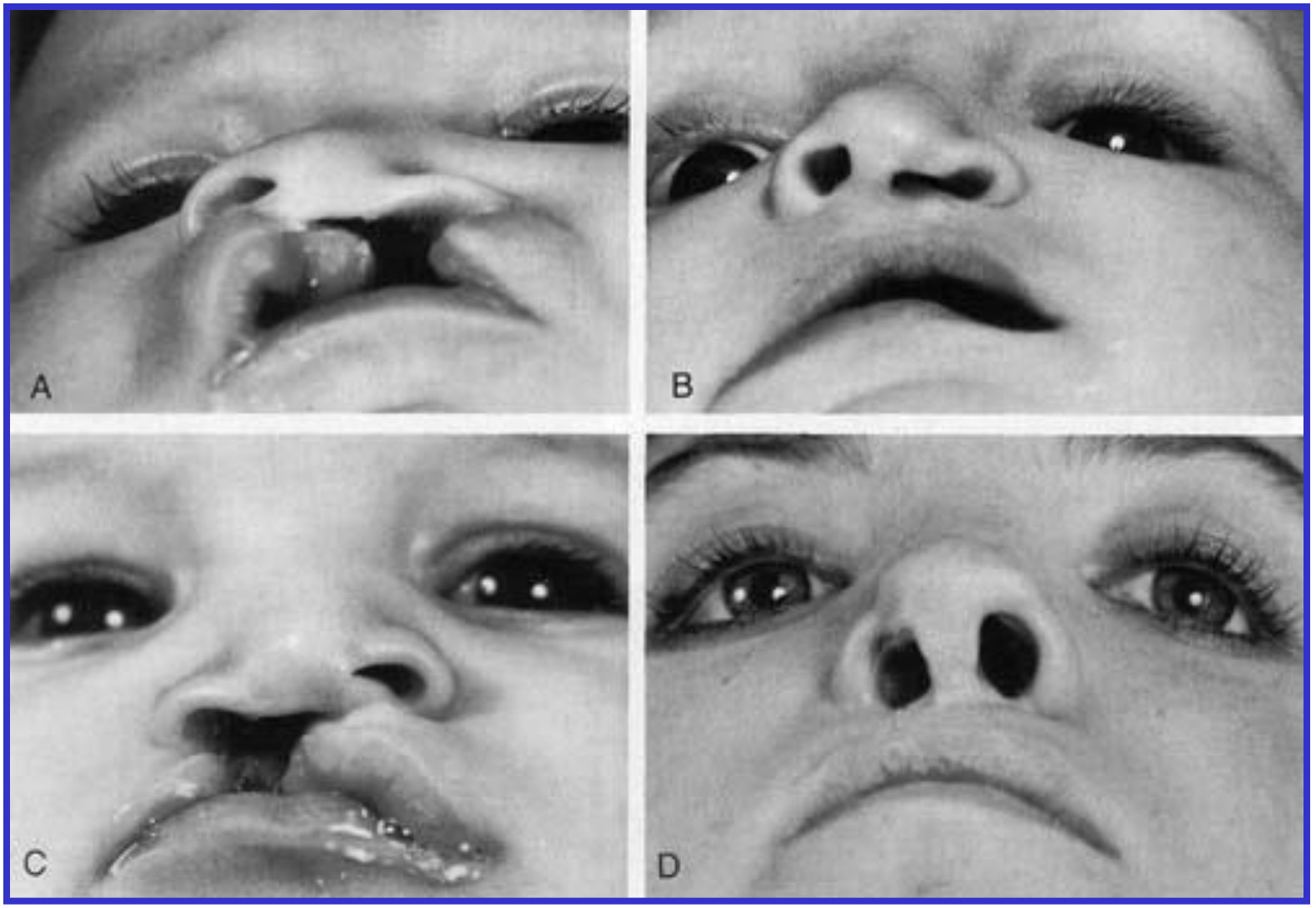
Causes: localized errors (e.g. clefts), deformation (by physical force, e.g. oligohydramnios), disruption (by destruction, e.g. amniotic bands), teratogens (e.g. FAS), germline errors (syndromes)







Polydactyly


A
B
C
D

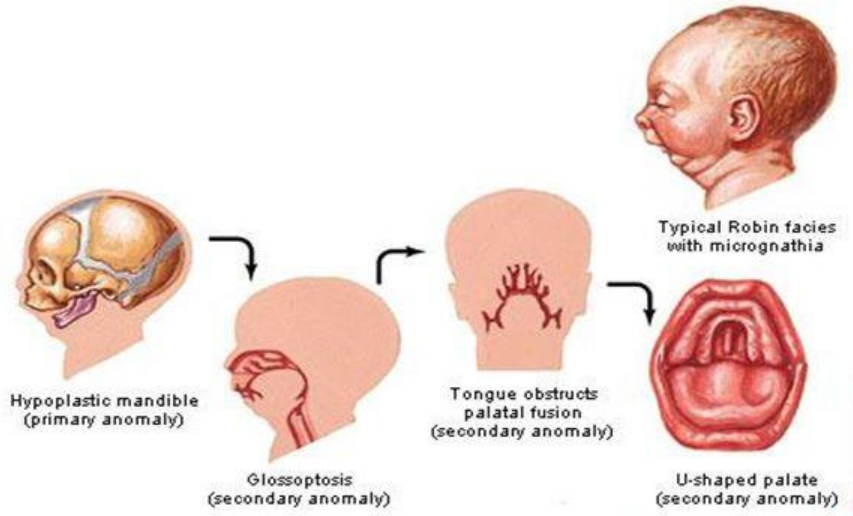
Etiologic heterogeneiety of cleft lip/palate

- Teratogens
- 22q deletion
- Primary mandibular hypoplasia
- Trisomy13
- Amniotic band syndrome
- Van der Woude syndrome

Pierre-Robin sequence

Symptoms

- Cleft soft palate
- High-arched palate
- Small opening in roof of the mouth (might cause chocking)
- Jaw that is abnormally small (Micrograthia)
- Jaw placed abnormally far back in the throat
- Downward displacement of the tongue (Glossoptosis)
- Large tongue
- Natal teeth
- Ear infections



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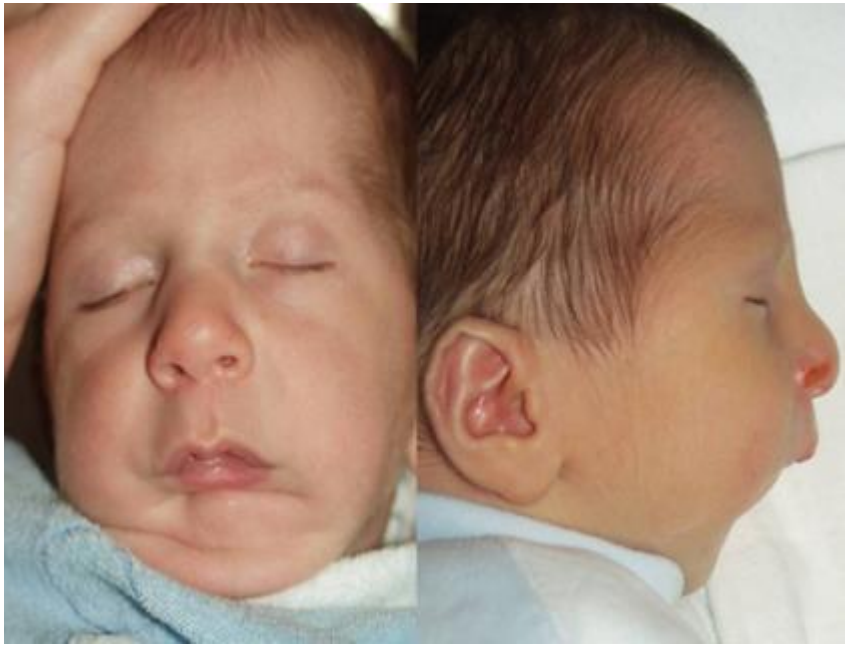
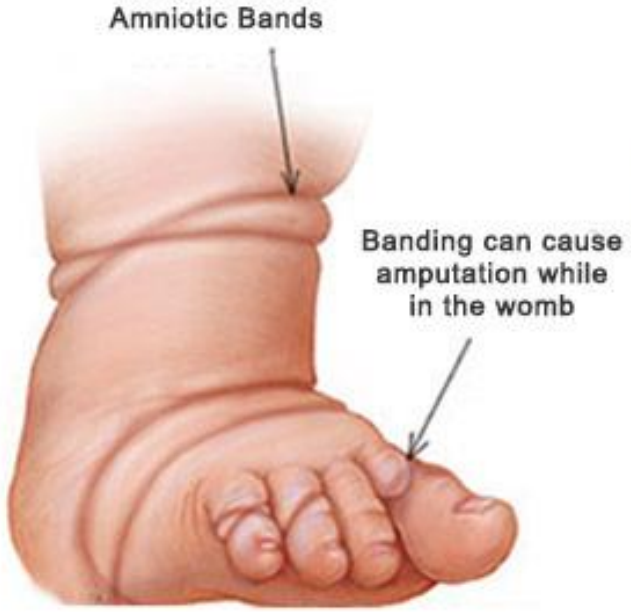
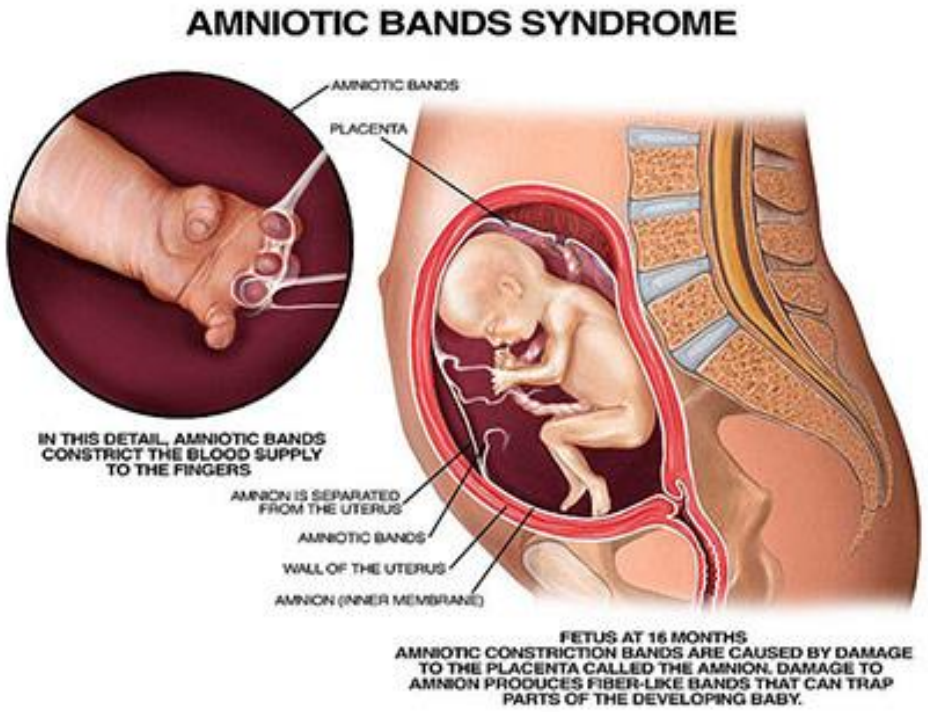


Preoperative frontal and lateral views of an infant with Pierre Robin sequence.

Sesenna *et al. Italian Journal of Pediatrics* 2012 38:7 doi:10.1186/1824-7288-38-7.





http://chicagofootcareclinic.com/footproblems/deformities/amnioticbandsyndrome.html

Causes of congenital anomalies

- Multifactorial : 20-30%
- Monogenic disorders: 10-20%
- Chromosomal aberrations: 15%
- Infection: 2.5%
- Maternal diabetes: 1.5%
- Medication: 1-2%
- Unknown etiology

Discriminating Features

Short palpebral fissures

Flat midface

Short nose

Indistinct philtrum

Thin upper lip

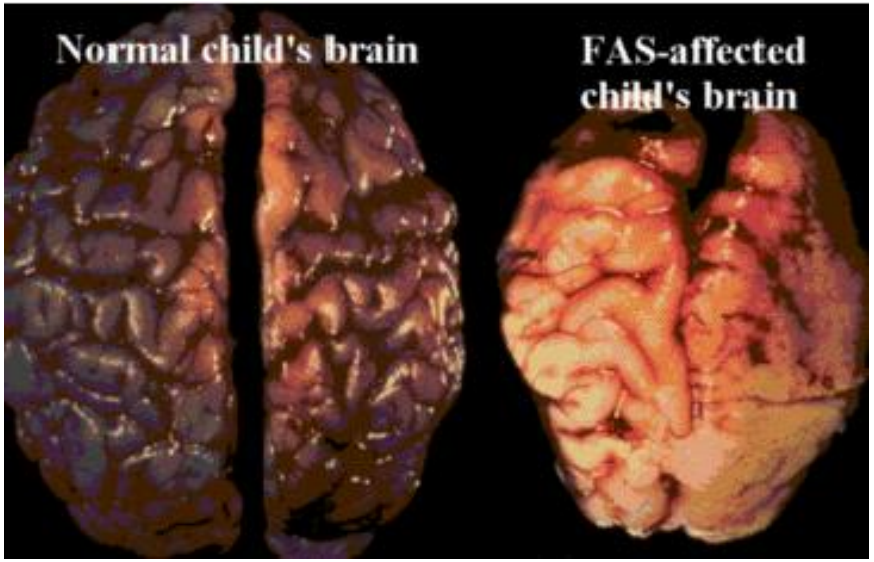
Associated Features

Epicanthal folds

Low nasal bridge

Minor ear anomalies

Micrognathia



Empiric Recurrence Risks (%) for Selected Birth Defects

Condition	**Affected Relatives(s)**		
	None	1 sib/parent	2 sibs / sib & parent
Cleft lip/palate	0.1	4	10-11
Neural Tube Defect	0.1	3	8
Heart Defect	0.3	4-5	10-11

The risk of having any one major birth defect is less than 1% but this risk increases significantly if other relatives have the same birth defect

Genetic etiology of recognized congenital disorders

Many genes: chromosomal aneuploidies

A number of genes: chromosomal microdeletions / microduplications

A single gene: monogenic disorders

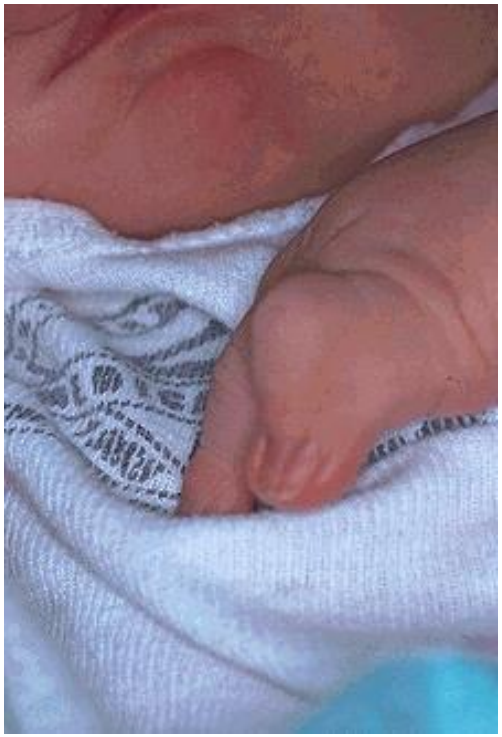
Types of morphologic abnormalities

- Malformation
- Deformation
- Disruption
- Dysplasia

Malformation

Defect of morphogenesis due to an intrinsically abnormal disorder of formation, growth, or differentiation of an organ or structure

- hypoplasia of an organ or structure (microtia), incomplete closure (NTDs, cleft palate), incomplete separation (syndactyly)

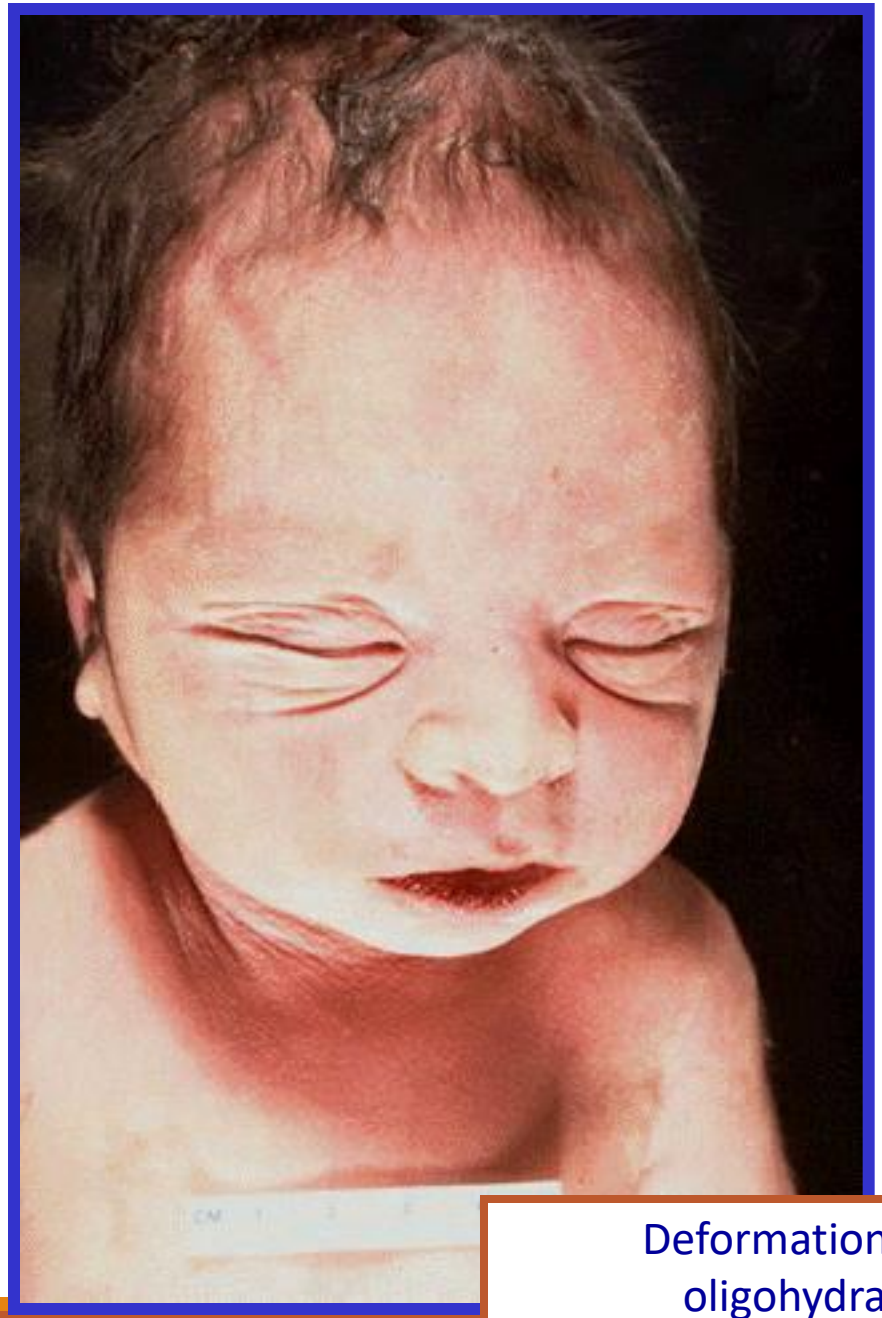


Deformation

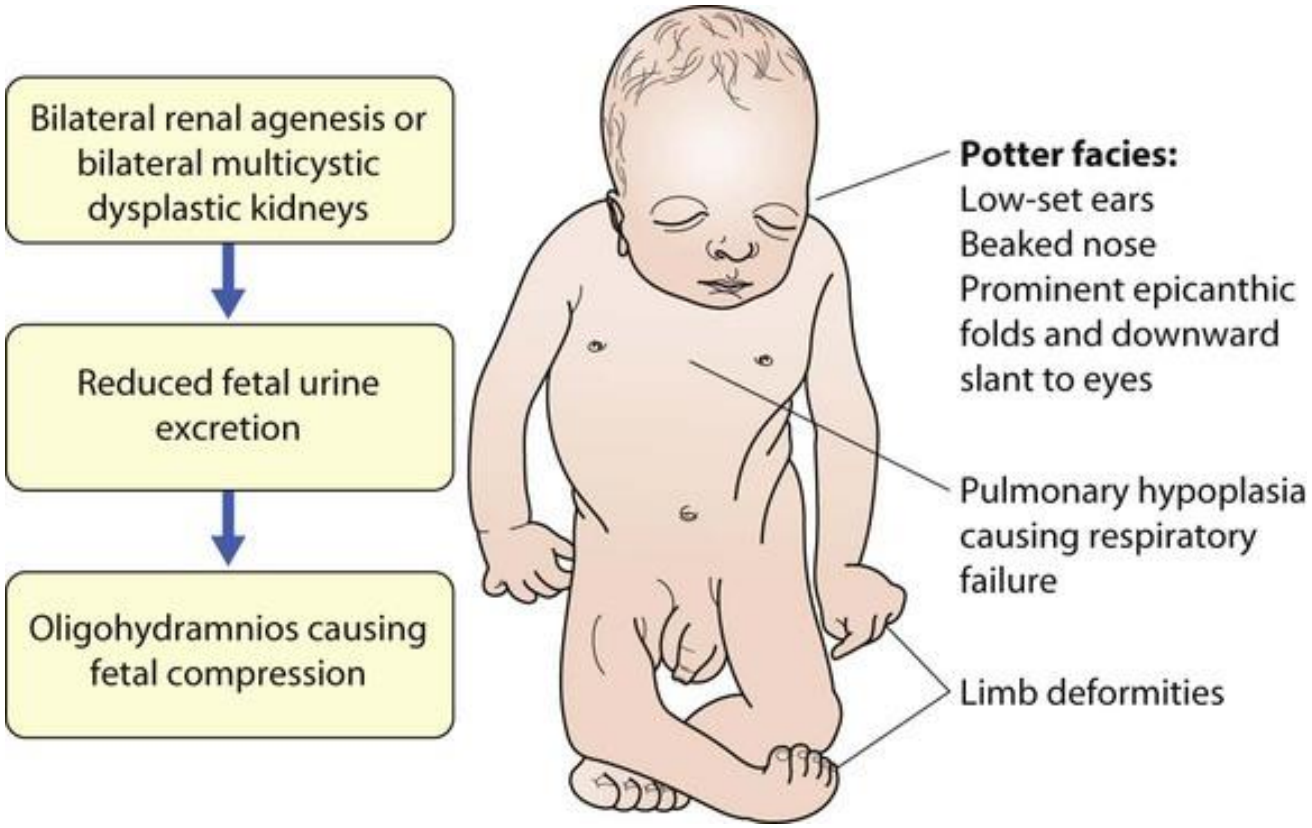
Abnormal form or position of a body or region of the body caused by extrinsic non-disruptive mechanical forces on a normally developing structure (fetal constraint)

- clubfoot, congenital hip dislocation, craniofacial asymmetry, overfolded ear

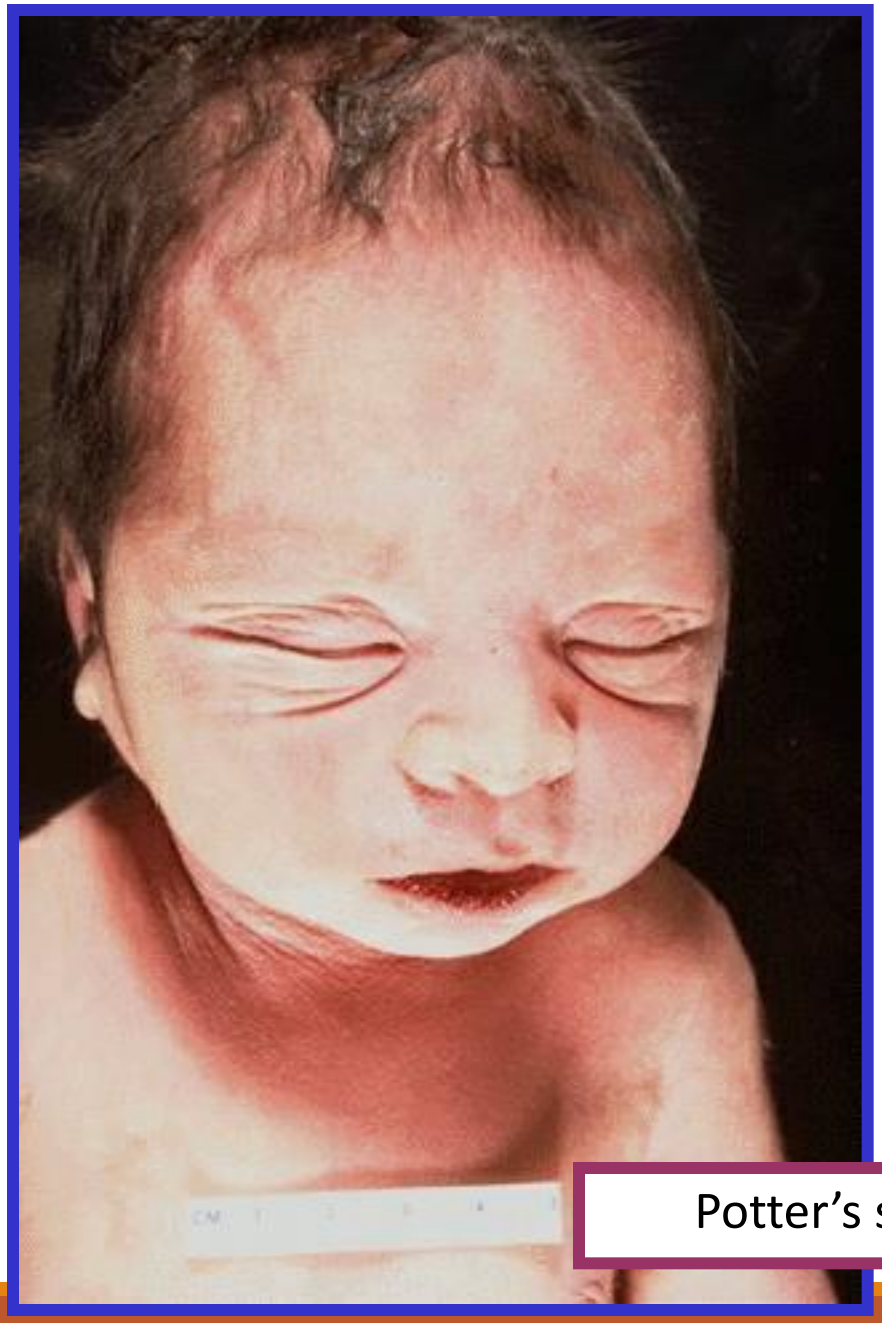
Deformity of ear helix due to uterine compression

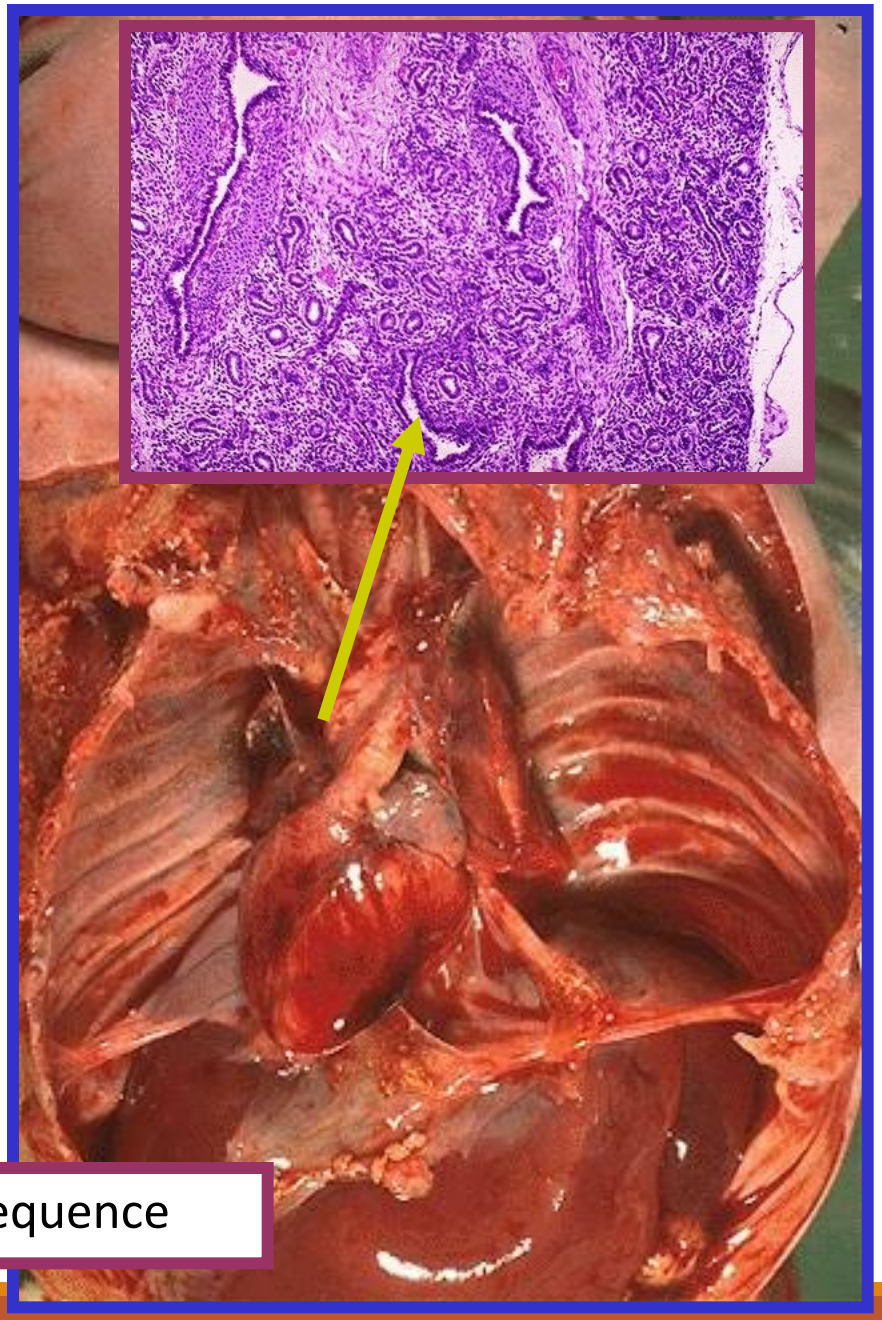


Deformations due to oligohydramnios



http://clinicalgate.com/kidney-and-urinary-tract-disorders/





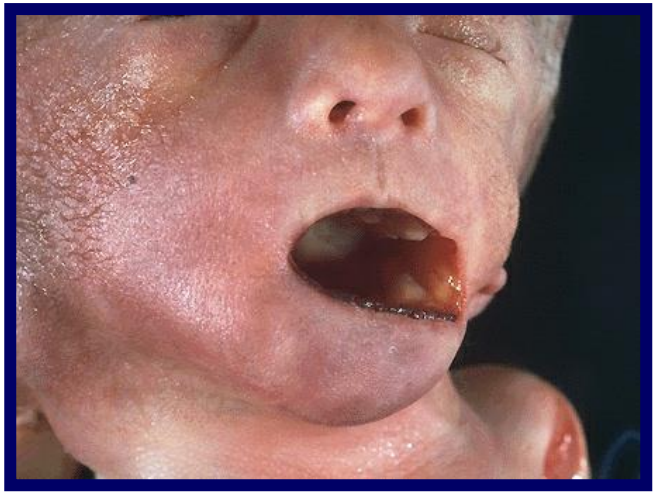
Potter’s sequence

Disruption

Defect resulting from a destructive breakdown of, or interference with, a normally developing structure resulting in death of cells or tissue destruction.

May be secondary to mechanical forces, infections, or vascular events.

- Loss of digit due to amniotic band constriction, lack of normal limb development due to intrauterine vascular disruption

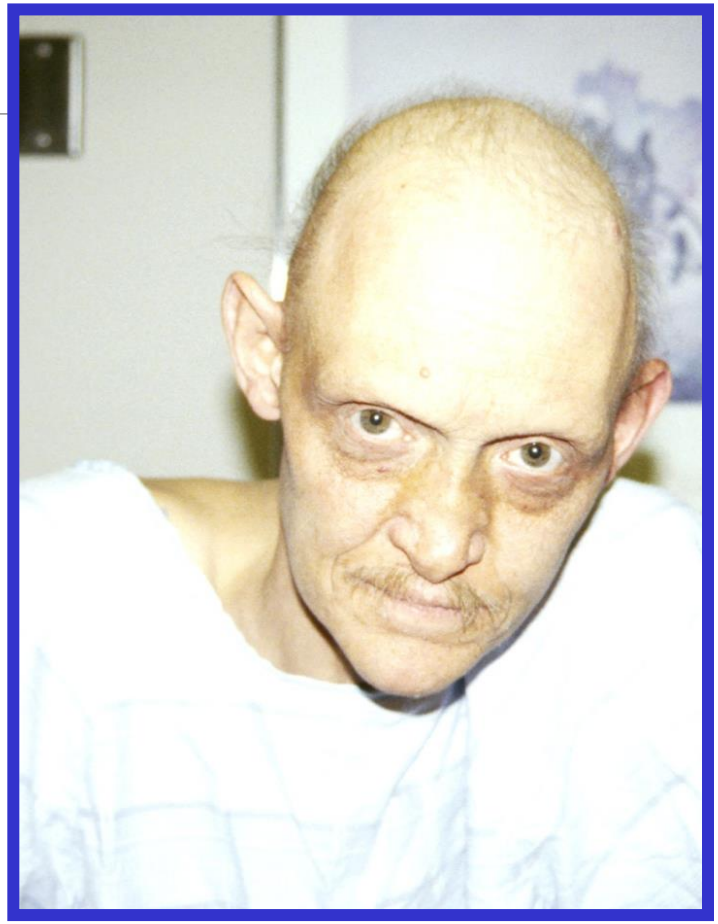


Disruption of lip formation due to amniotic bands

Dysplasia

Error of morphogenesis causing abnormal cellular organization or function in a specific type of tissue, mostly due to single gene defects

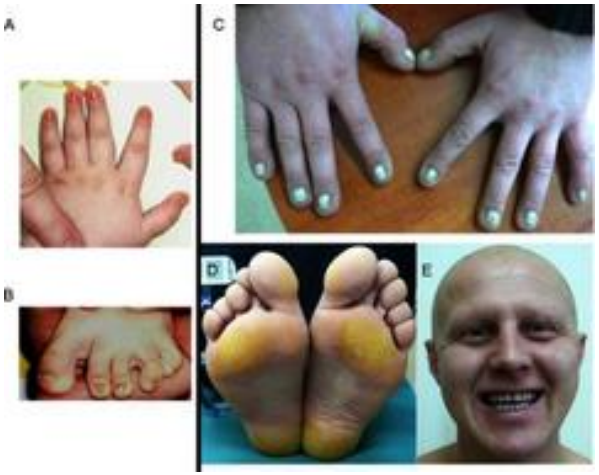
- Achrondroplasia, ectodermal dysplasia, osteogenesis imperfecta



Ectodermal dysplasia

Clouston syndrome – ectodermal dysplasia (*GJB6* gene)

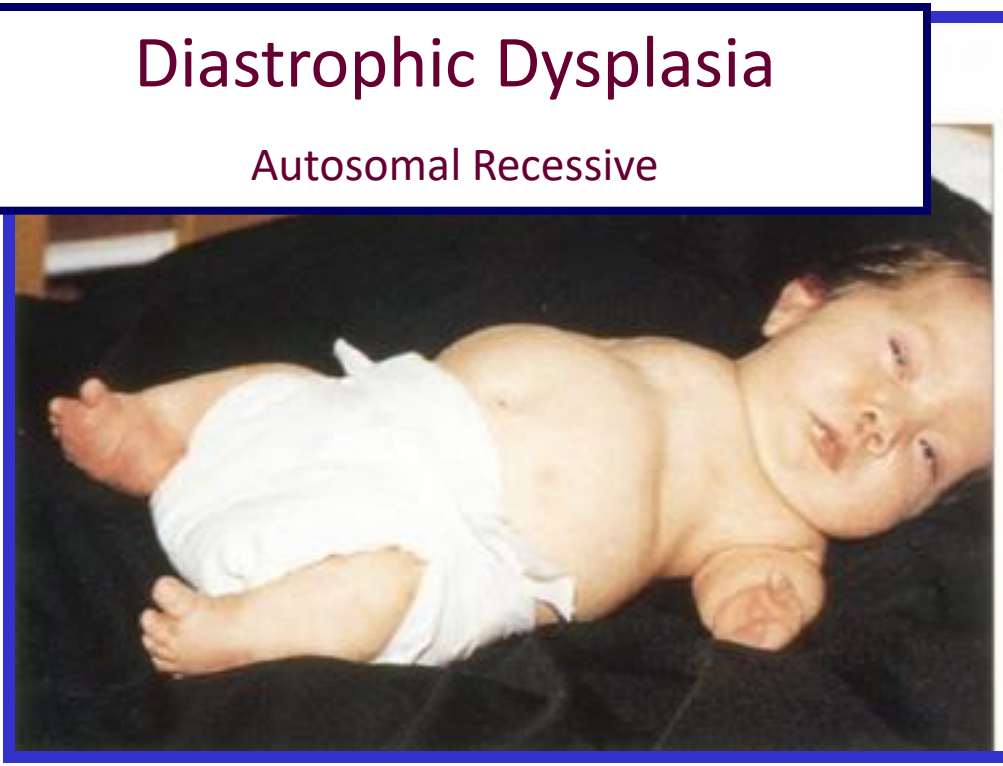
https://www.nfed.org/learn/types/clouston-syndrome/

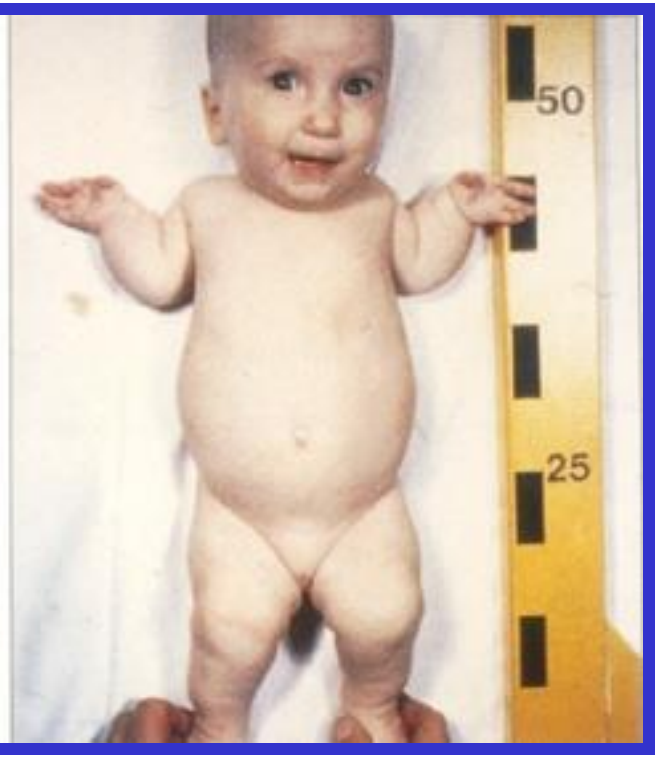


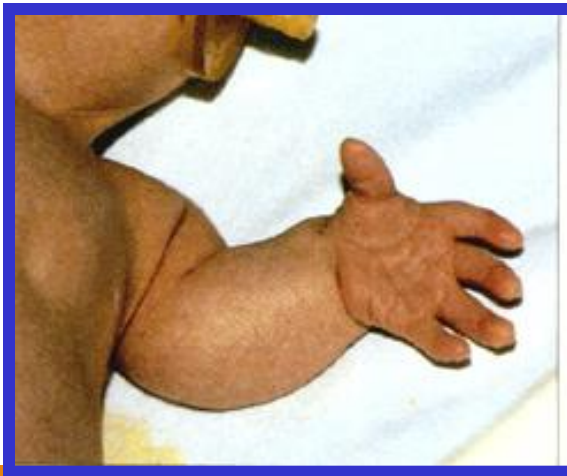
https://pl.wikipedia.org/wiki/Zesp%C3%B3%C5%82_Cloustona

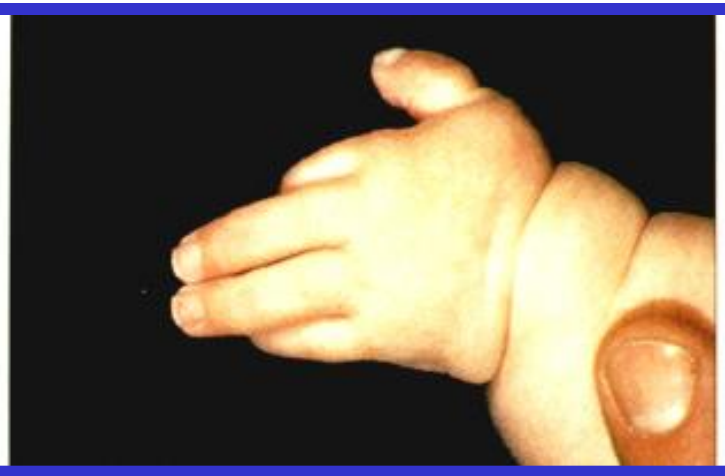
Diastrophic Dysplasia

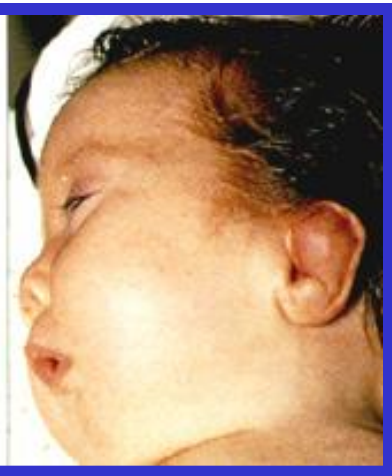
Autosomal Recessive











Recognizable Patterns of Anomalies

- Sequences
- Associations
- Syndromes
- Dysplasias

Sequence

- a particular set of developmental anomalies occurring together in a recognizable and consistent pattern AND a consequence of a primary anatomical defect (e.g. Pierre Robin sequence = mandibular hypoplasia → tongue displacement → cleft palate and upper airway obstruction)

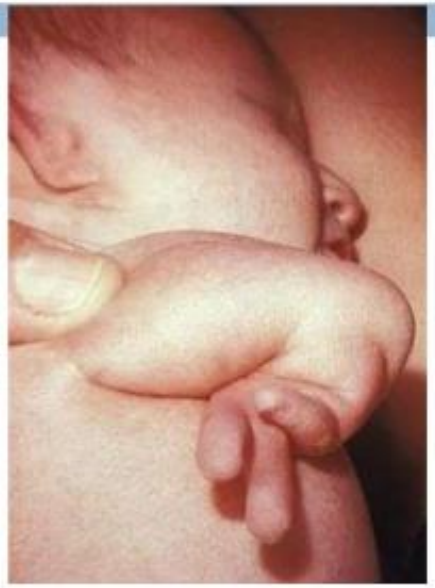
Association

Non-random occurrence of a combination of several anomalies not yet identified as a specific sequence or syndrome that occur more often together than by chance alone.

- VACTERL association

VACTERL Association

- **Features**
- V - Vertebral anomalies
- A - Anal atresia/ Imperforate Anus
- C - Cardiovascular anomalies
- T - Tracheoesophageal fistula
- E - Esophageal atresia
- R - Renal (Kidney) and/or radial anomalies
- L - Limb defects



Newborn with radial atresia of the right arm, is displaying a limb anomaly included in VACTERL Association

http://www.slideshare.net/nijhum57/genetic-principles-in-paediatric-surgery

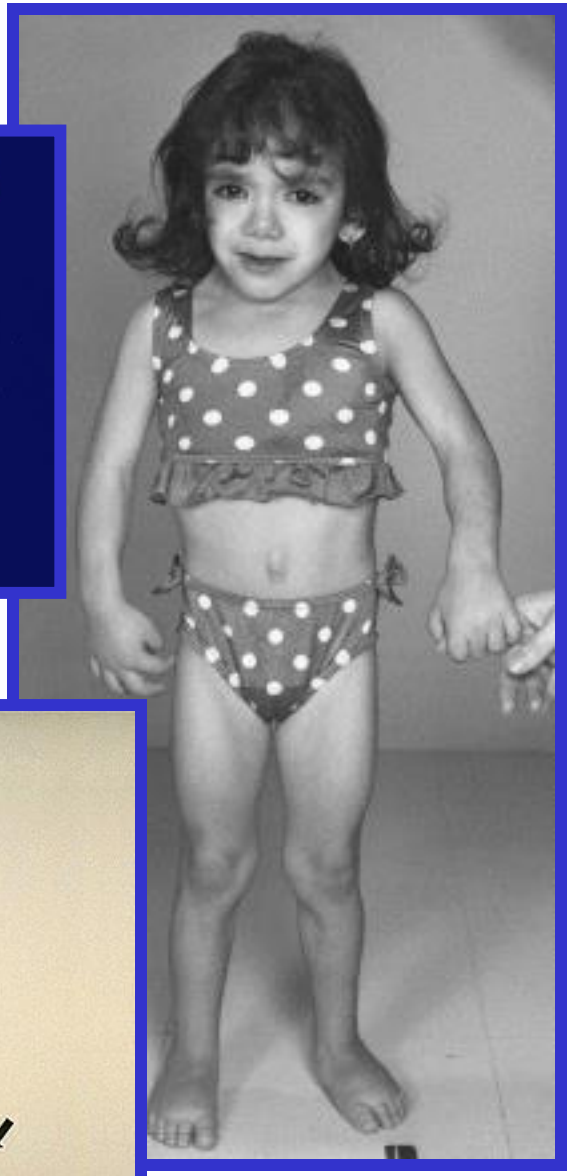
Syndrome

From Greek meaning “running together”

Multiple anomalies in one or more tissues or structures thought to be pathologically related due to a specific etiologic mechanism (chromosome disorder, single gene defect, environmental agent, or unknown factor)

- Down syndrome, Williams syndrome, FAS, Turner syndrome

Turner syndrome



Challenges in diagnosing genetic syndromes

- Mostly rare disorders
- Variable expression
- Incomplete penetrance
- Sex-influenced or limited expression
- Pleiotropy
- Etiologic heterogeneity

Variable Expression

Morphological features expressed at different degrees of severity in individuals having the “same” abnormality

Each individual with a particular syndrome, sequence, or association will not have every known feature of that disorder, even within the same family.

The degree of variable expression may correlate with the degree of pleiotropy in single gene disorders

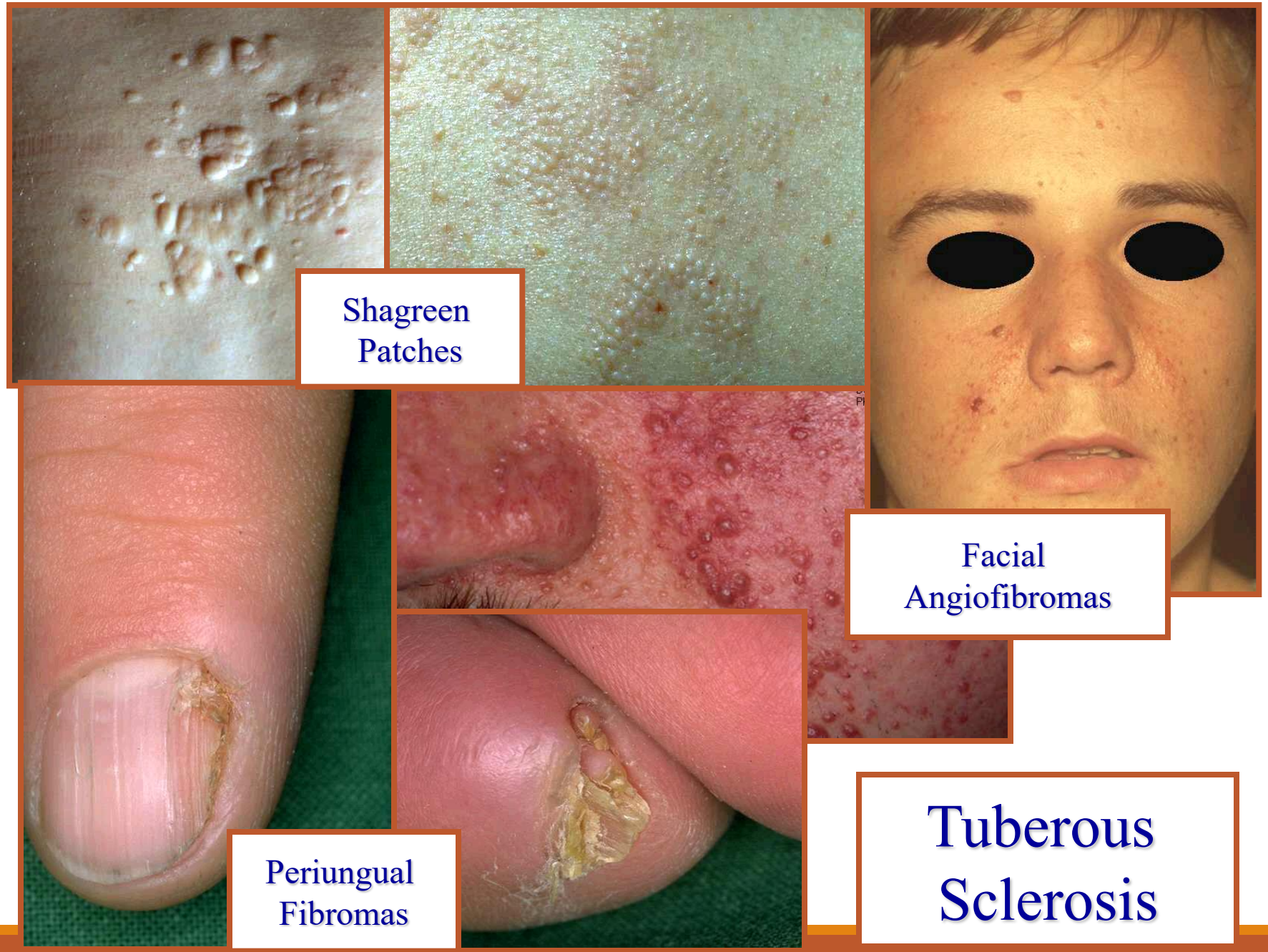
Penetrance

- proportion of individuals carrying a particular variant (or allele) of a gene (genotype) and who express an associated trait (phenotype).
- Complete penetrance – neurofibromatosis type 1
- Incomplete penetrance – familial breast cancer due to *BRCA1* gene mutations

Sex-Influenced or Limited Expression

Some congenital anomalies and/or genetic syndromes due to autosomal defects are more easily recognized, or only recognized, in individuals of a particular gender

- Sex-influenced: Genital hypoplasia, hypospadias, virilization with hypertrophy of the clitoris
- Sex-limited: Hereditary prostate cancer


Shagreen Patches
Facial Angiofibromas
Periungual Fibromas
Tuberous Sclerosis

Etiologic heterogeneity

Locus heterogeneity: a similar phenotype is produced by mutations at different loci (Tuberous Sclerosis, PKD)

Allelic heterogeneity: a similar phenotype is produced by different alleles within the same gene (CF [*CFTR* gene])

Elements of dysmorphology

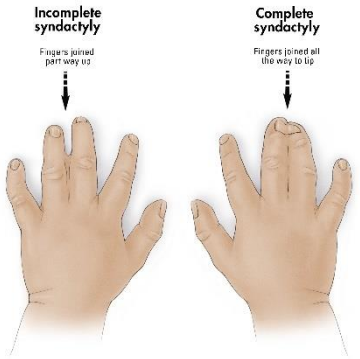
Dysmorphology

- recognition and study of birth defects (congenital malformations) and syndromes [David Smith, 1960]
- Gr. „dys” – abnormal, defective; „morph” – form

"As a medical subspecialty, dysmorphology deals with people who have congenital abnormalities and with th eir families. Whenever any physician is confronted by a patient with a birth defect, he or she becomes, for the moment at least, a dysmorphologist.„
(JM Aase: Diagnostic Dysmorphology, 1990, Plenum, New York).

What does ‘dysmorphic’ mean?

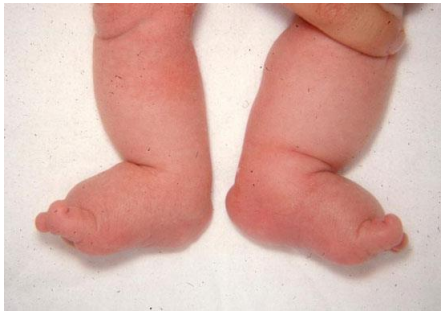
- Children whose physical features are not usually found in a child of the same age or ethnic background (Be aware of parental looks!)
- Some features are obvious dysmorphisms (e.g. premature cranial suture fusions) whereas others could be insignificant familial traits (e.g. finger syndactyly)
- Not only external features, but also those of internal organs



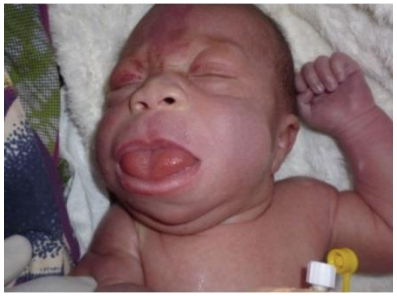
http://www.childrenshospital.org/conditions-and-treatments/conditions/syndactyly/symptoms-and-causes

Dysmorphology in neonatology and pediatrics

http://www.medicalnewstoday.com/articles/145554.php



http://symptomscausestreatmentprevention.blogspot.com/2014/01/what-is-turner-syndrome.html



http://www.forgottendiseases.org/assets/Beckwith_Wiedemann_syndrome.html

https://www.hindawi.com/journals/crig/2012/247683/fig1/

Mild congenital anomalies

Hypertelorism/hypotelorism

Epicanthus

Simian crease

Slanted palpebral fissures

Ear tag, ear pit

Iris coloboma

Fifth finger clinodactyly

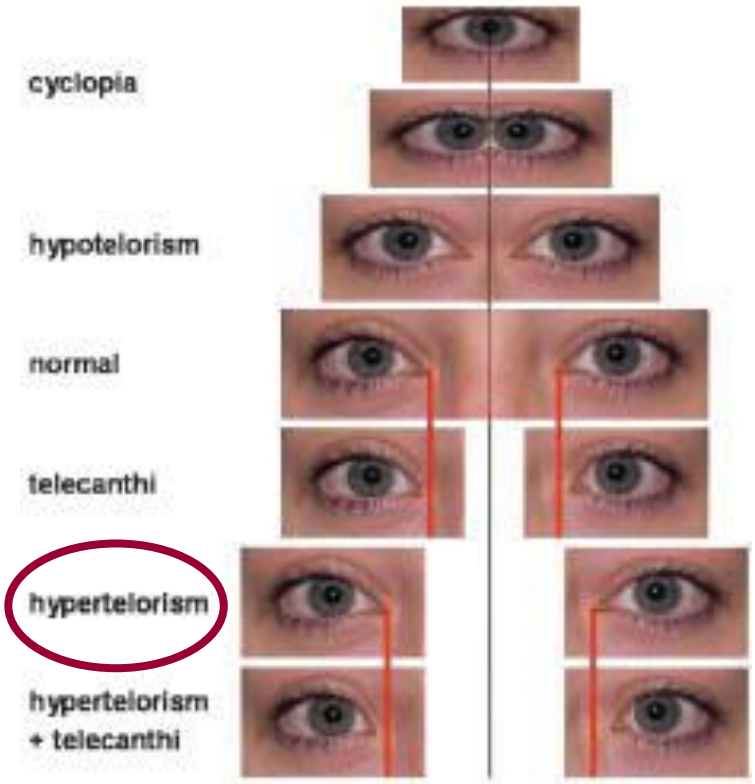
Finger syndactyly

Umbilical hernia

Supernumerary nipple

Hypospadia

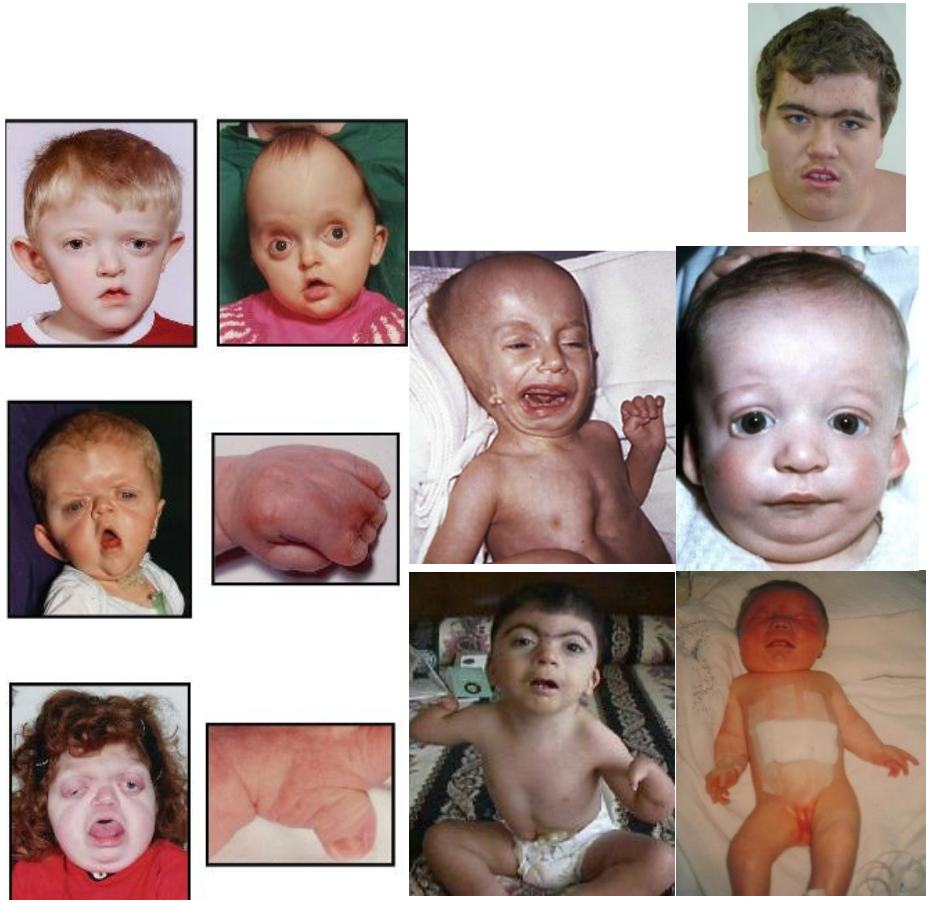
Bifid uvula



Conglomeration of mild anomalies = greater risk of coexistent major anomaly

Phenotypic diagnosis on the basis of „facial gestalt”

Cornelia de Lange s.
Cri-du-chat s.
Down s.
Wolf – Hirschhorn s.
Goldenhar s.
Apert s.
Crouzon s.
CHARGE
Treacher-Collins s.
Smith-Lemli Opitz s.
Rubinstein-Taybi s.
Mucopolysacharridosis

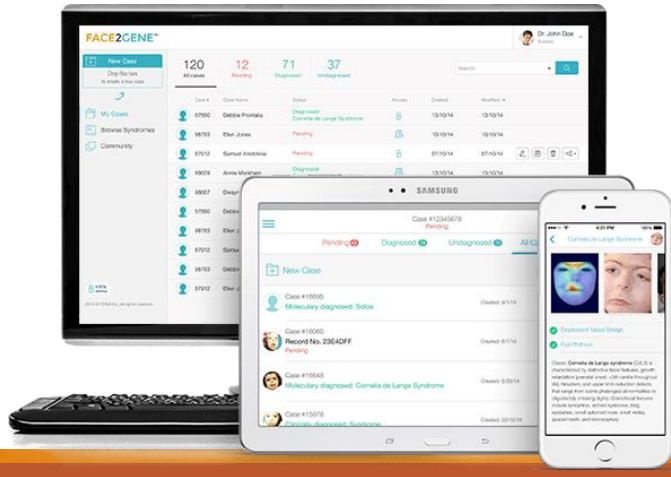


Dysmorphology tools

Anthropometric measurements

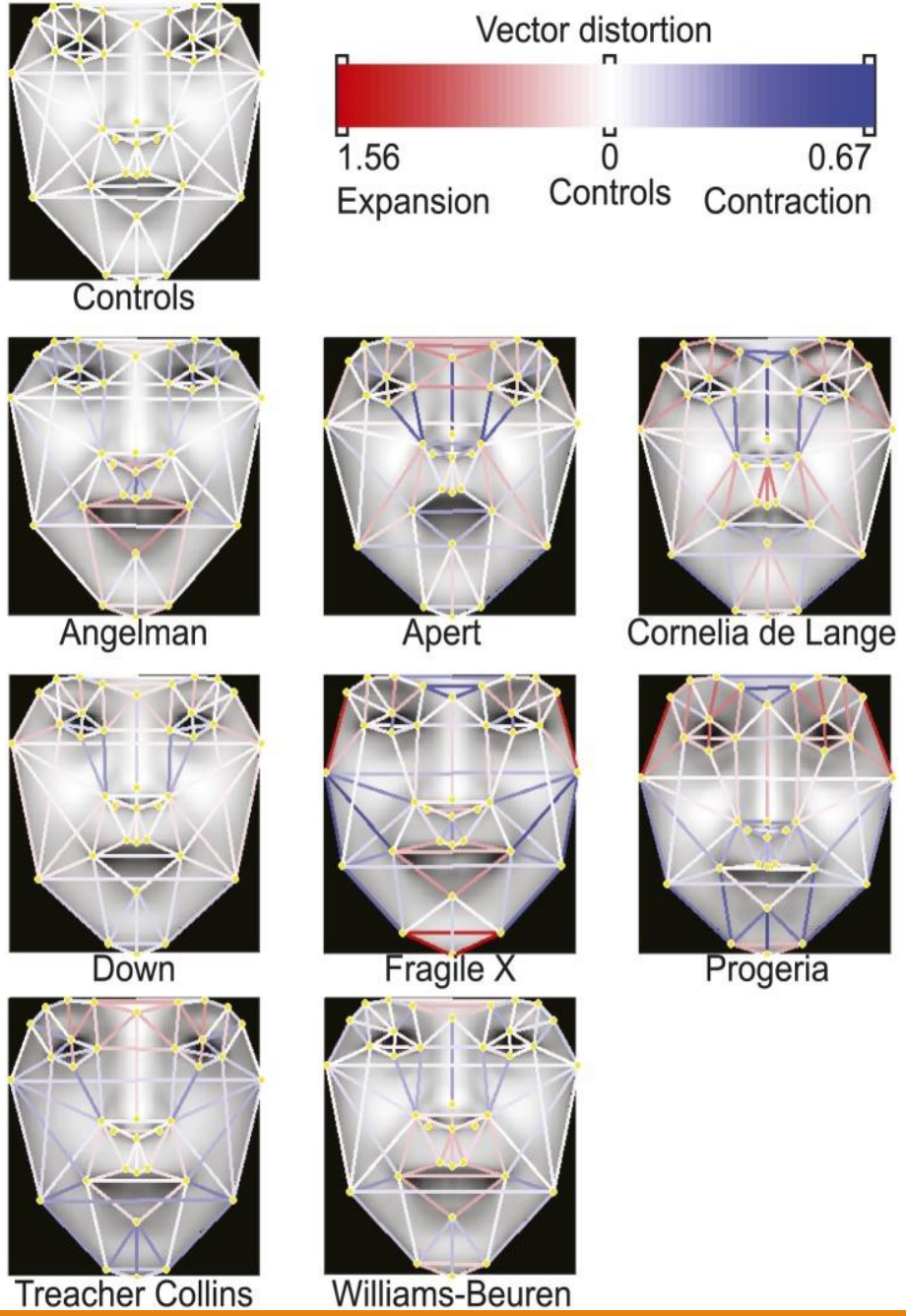
Dysmorphology databases

- Phenomizer
- POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations)
- London Dysmorphology Database (LDDB)
- Face2gene



http://www.fdna.com/hipaa-compliance-declaration/

Facial *Gestalt* modelling (eLife; 3: e02020)

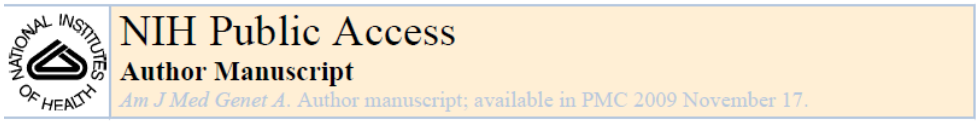


American Journal of Medical Genetics Part A

Special Issue: Elements of Morphology: Standard Terminology

January 2009
Volume 149A, Issue 1
Pages 1–127

Standard dysmorphology terminology

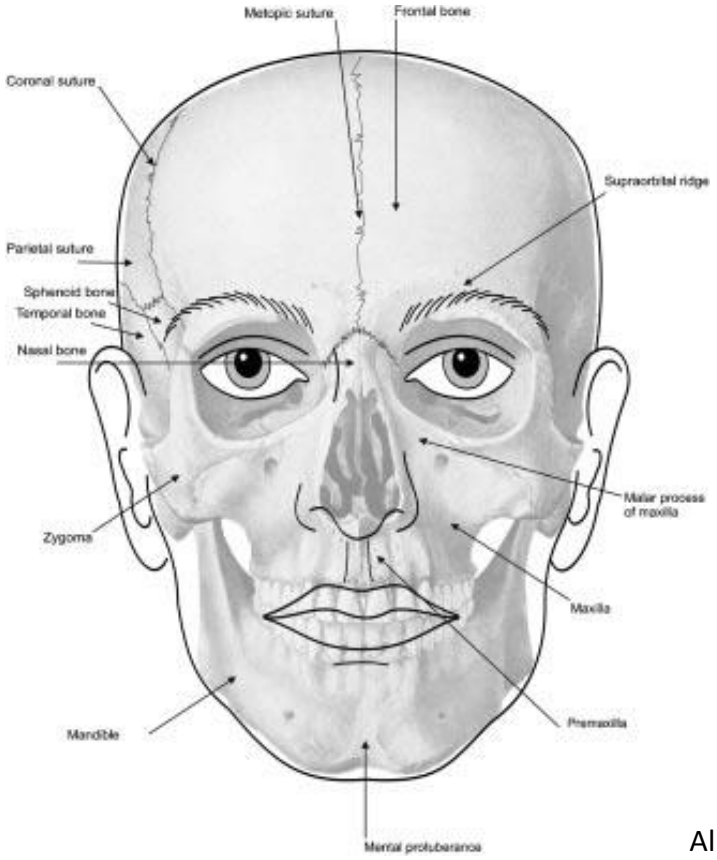


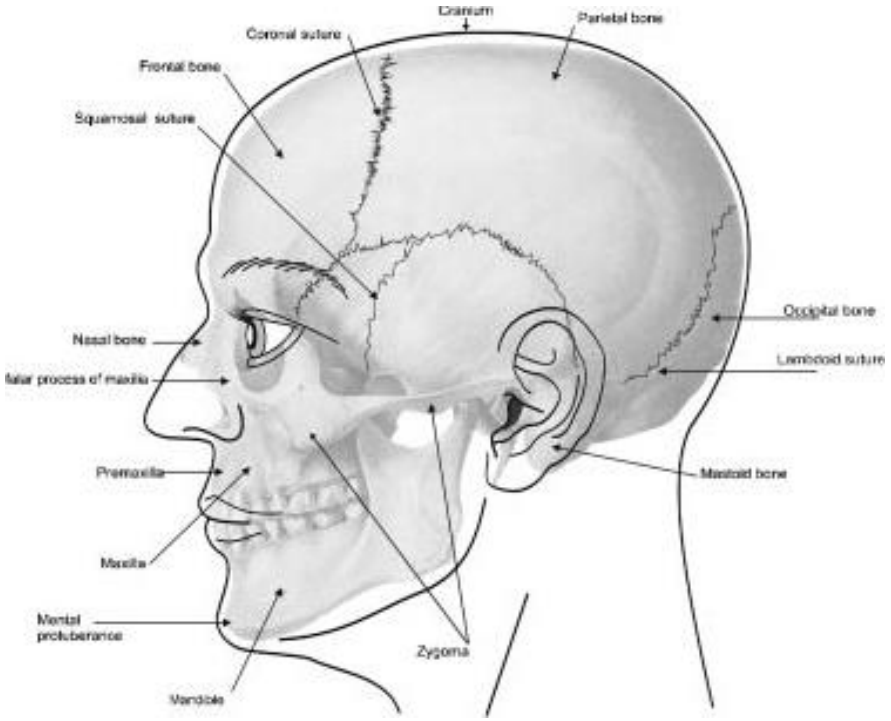
Published in final edited form as:
Am J Med Genet A. 2009 January ; 149A(1): 6–28. doi:10.1002/ajmg.a.32612.

Elements of Morphology: Standard Terminology for the Head and Face

Judith E. Allanson[1,*], Christopher Cunniff[2], H. Eugene Hoyme[3], Julie McGaughran[4], Max Muenke[5], and Giovanni Neri[6]

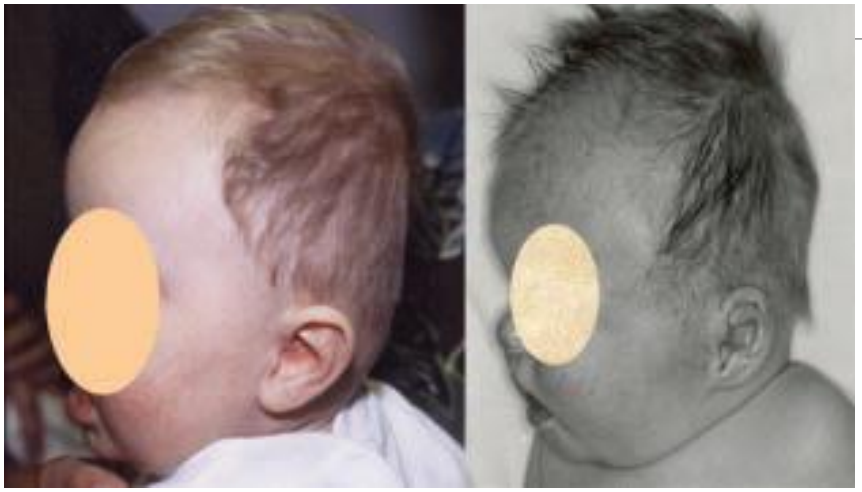
Anatomic reference points





Allanson JE, Cunniff C, Hoyme HE, McGaughran J, Muenke M, Neri G. 2009. Elements morphology: Standard of terminology for the head and face. Am J Med Genet Part A 149A:6–28.

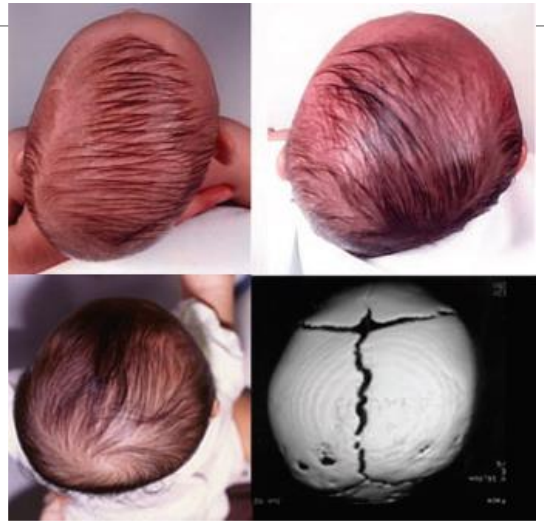
Abnormal skull shape



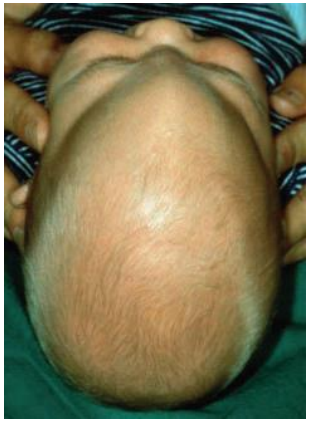
Brachycephaly –anterio-posterior shortening of the skull

Dolichocephaly – increased AP dimension

Abnormal skull shape

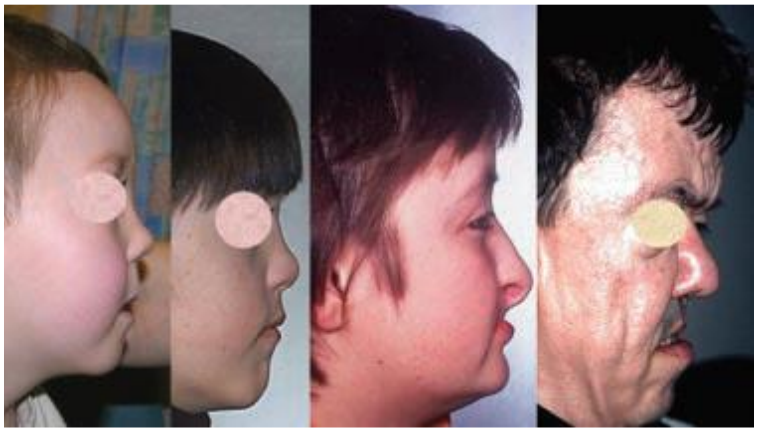


Plagiocephaly – skull assymetry

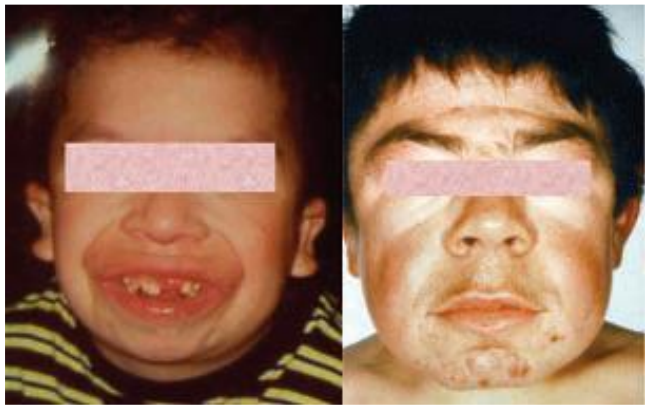


Trigonocephaly

Facial dysmorphy



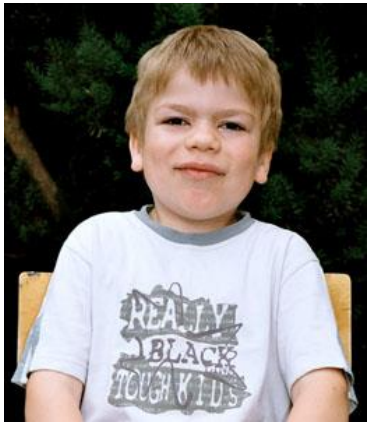
Flat facial profile



Coarse facial features

Coarse features in mucopolysaccharydoses

Hurler syndrome (MPS IH)



Hunter syndrome (MPS II)

Morquio syndrome (MPS IV)

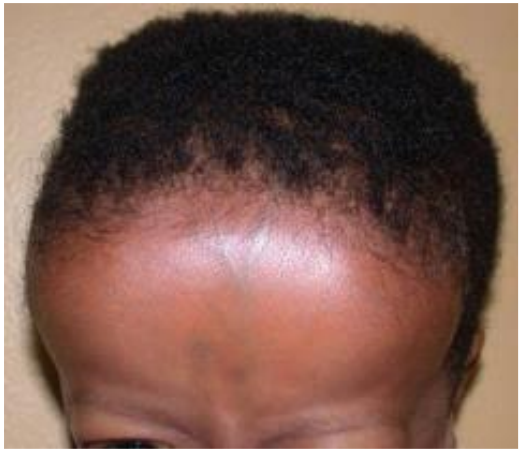
Sanfilippo syndrome (MPS III)

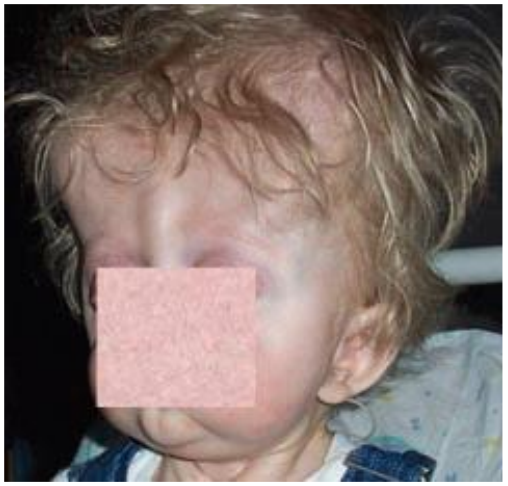
Maroteaux-Lamy syndrome (MPS VI)

Sly syndrome (MPS VII)

Stowarzyszenie Chorych na MPS
http://chorobyrzadkie.pl/?s=5

Facial dysmorphy

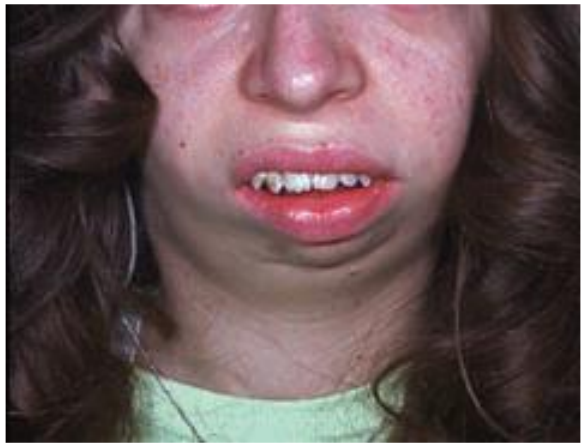




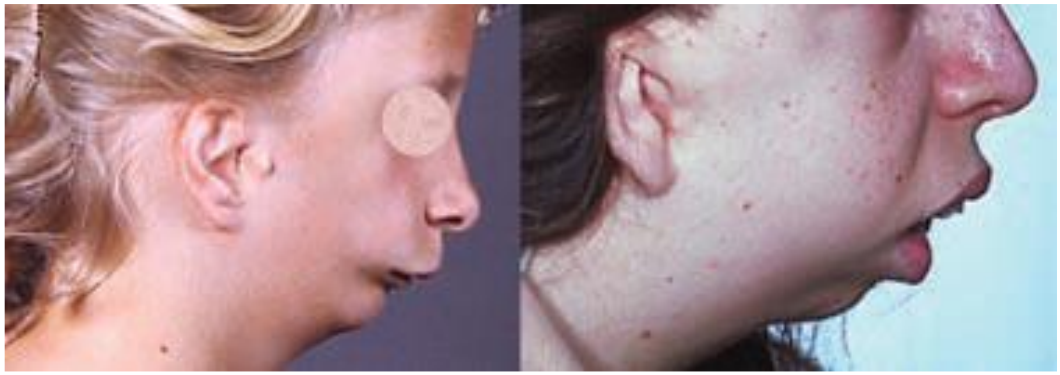
Frontal bossing

Prominent glabella

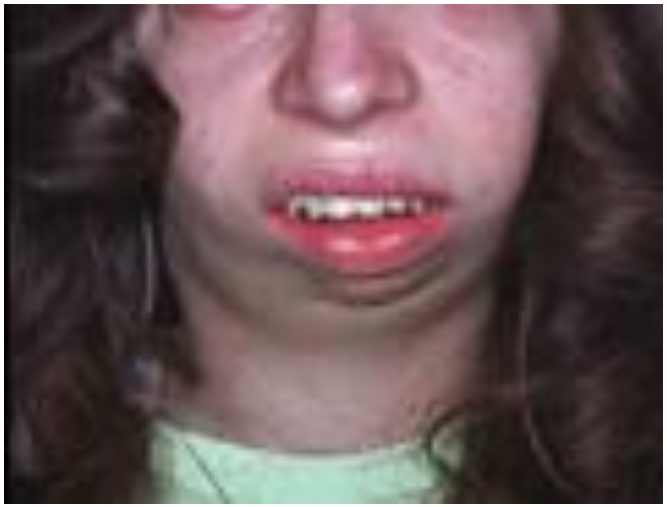
Facial dysmorphy



Micrognathia



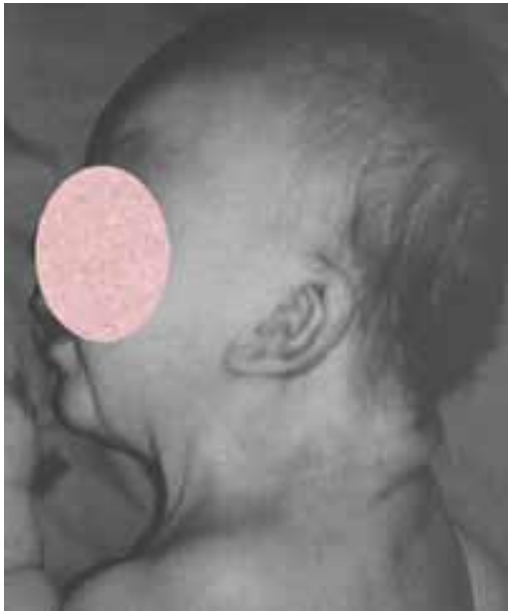
Retrognathia



Micrognathia

Definition: Apparently reduced length and width of the mandible when viewed from the front but not from the side

Comments: This is a bundled term comprising shortening and narrowing of the mandible and chin. It is defined here as it is a term in common usage.
Synonyms: Micrognathism; Jaw, small

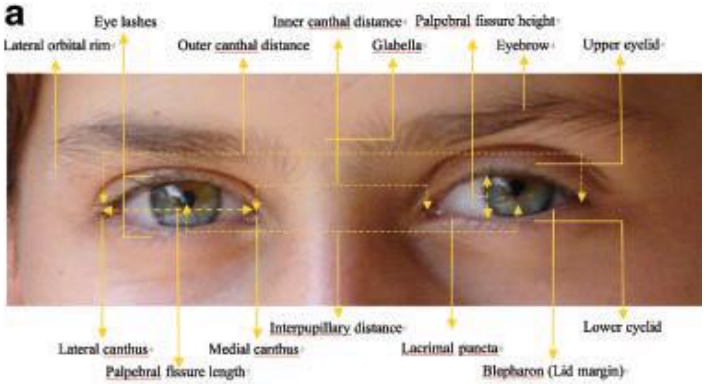


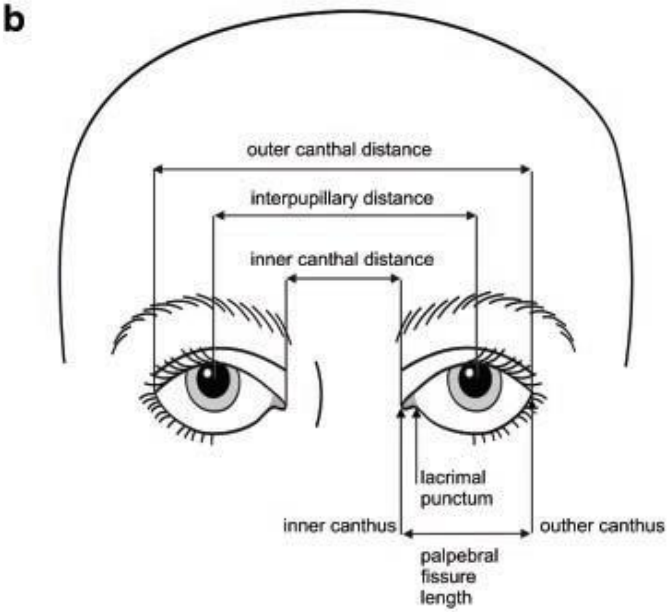
Redundant nuchal skin

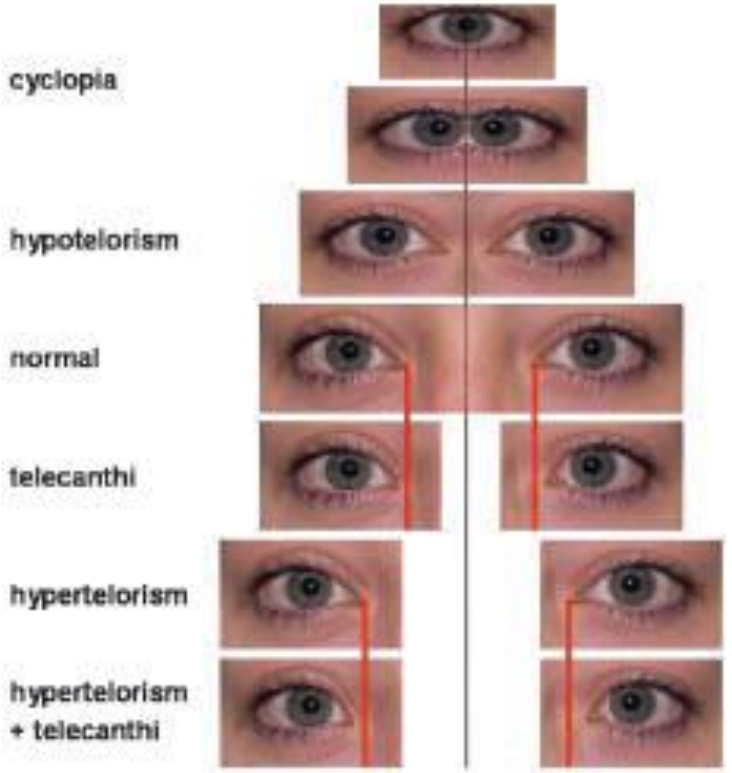
Definition: Excess skin around the neck, often lying in horizontal folds.

Comments: With age and increased vertical growth of the neck, excess nuchal skin may disappear and the neck may become broad or webbed. If the skin folds are vertical or paravertical, the term ***Neck webbing*** should be used.

Webbed neck


a
Eye lashes
Lateral orbital rim
Outer canthal distance
Inner canthal distance
Palpebral fissure height
Glabella
Eyebrow
Upper eyelid
Interpupillary distance
Lower eyelid
Lateral canthus
Medial canthus
Lacrimal puncta
Palpebral fissure length
Blepharon (Lid margin)

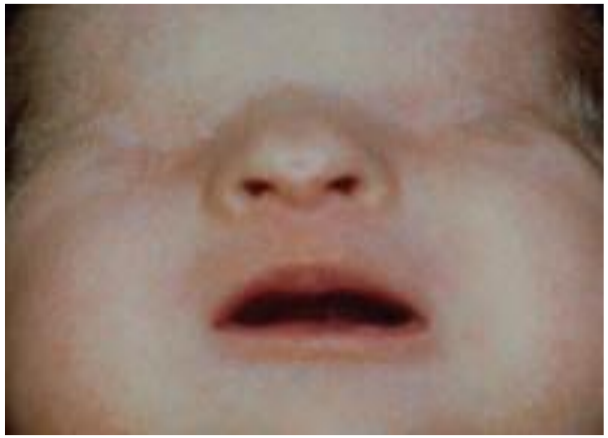

b
outer canthal distance
interpupillary distance
inner canthal distance
lacrimal punctum
inner canthus
outher canthus
palpebral fissure length


cyclopia
hypotelorism
normal
telecanthi
hypertelorism
hypertelorism + telecanthi

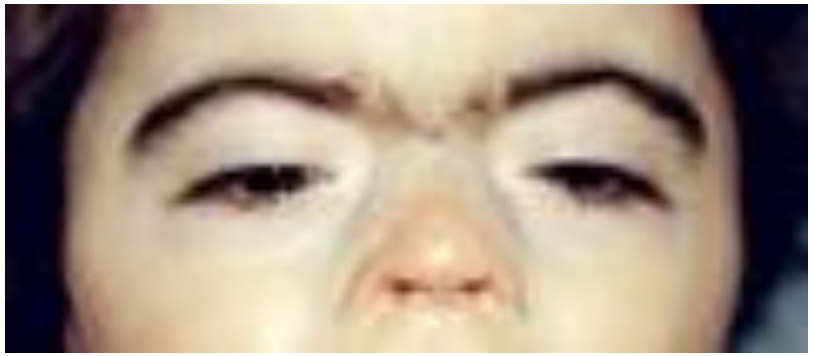
Blepharophimosis

Definition: A fixed reduction in the vertical distance between the upper and lower eyelids with short palpebral fissures.

Comments: This term is based on Saal et al. 1992. This is an acknowledged bundled term, though the separate coding of the components (palpebral fissure absence; presence of eyelashes) was deemed impractical. This is typically associated with a rudimentary or small globe. Frequently, a tuft of hair accompanies the aberrant skin



Cryptophthalmos

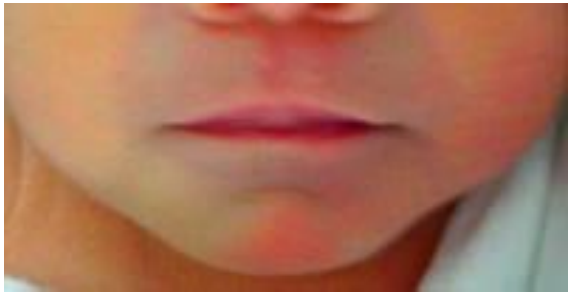


Synophrys

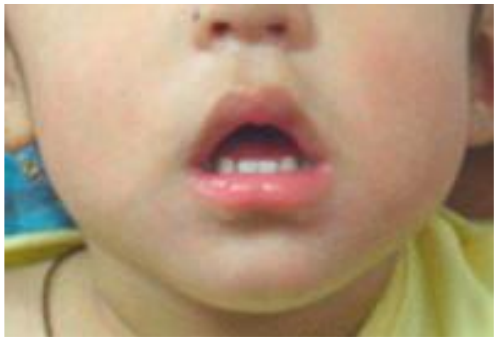
Meeting of the medial eyebrows in the midline.

Cosmetic hair removal or shaving may obscure this feature. It is controversial whether the medial eyebrows must meet in the midline to warrant this descriptor, as opposed to eyebrows that extend markedly toward the midline but do not meet.

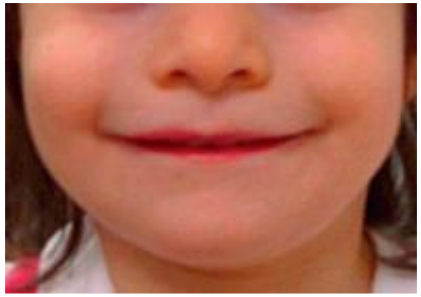
Dysmorphy of the oral region



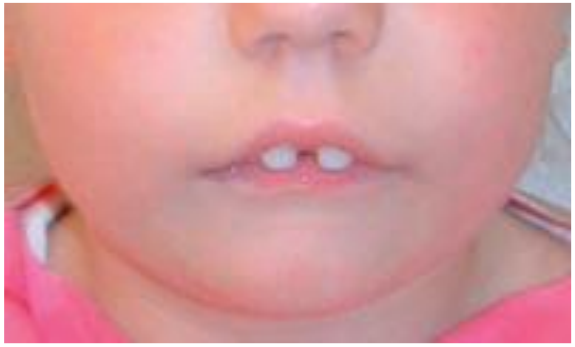
Thin upper lip



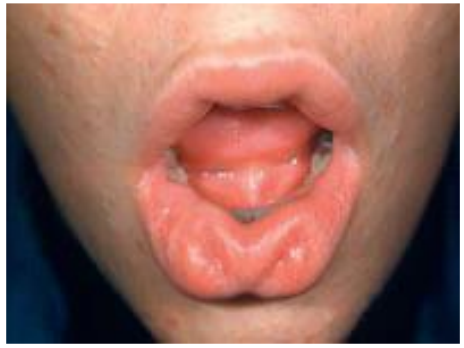
Tented upper lip



Wide mouth

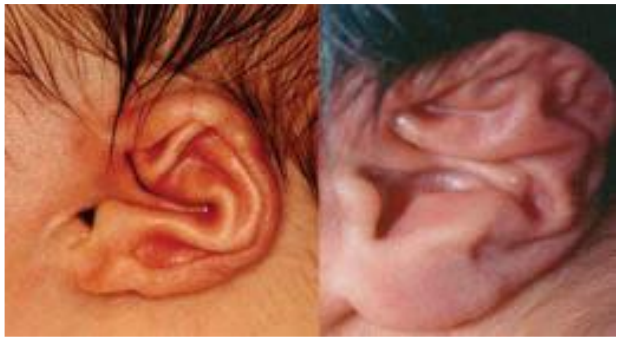


„Cupid bow” mouth

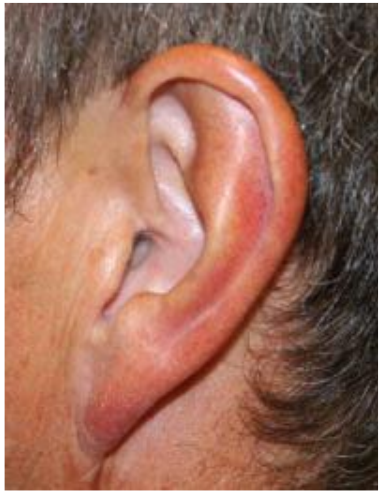


Lip pits

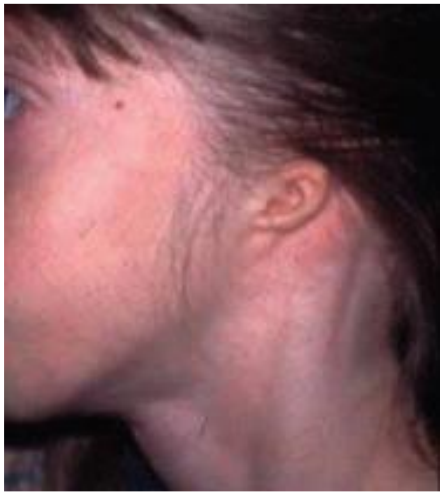
Dysmorphy of ears



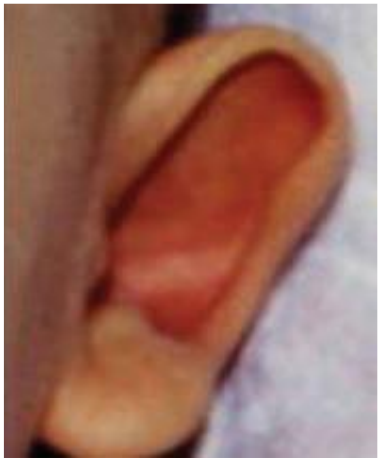
Crumpled ears



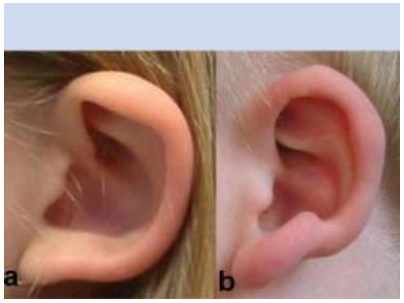
Attached earlobe



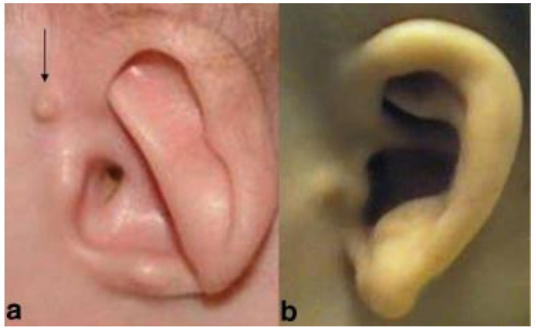
Microtia



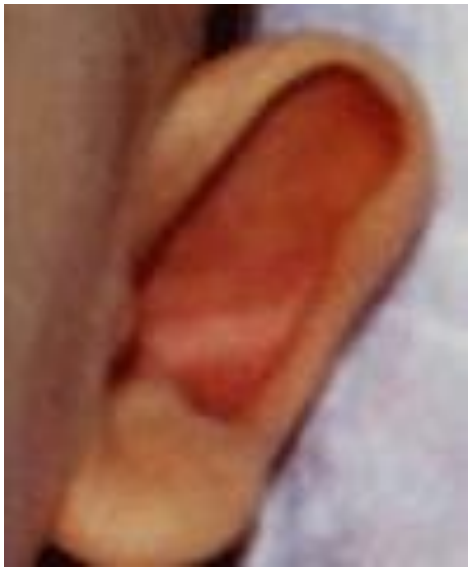
Cupped ear



Upturned lobes



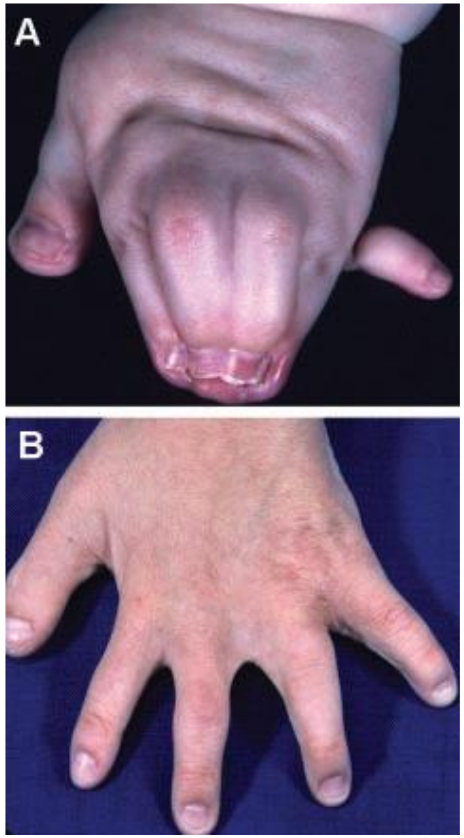
Preauricular tag



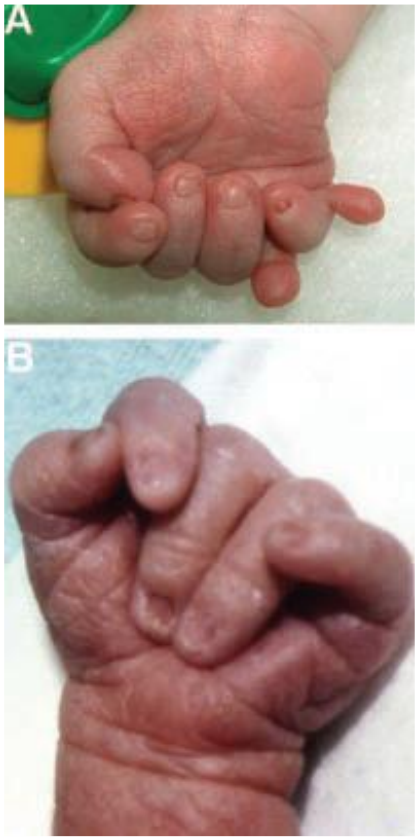
Cupped ear

Definition: Laterally protruding ear that lacks antihelical folding (including absence of inferior and superior crura)

Finger anomalies

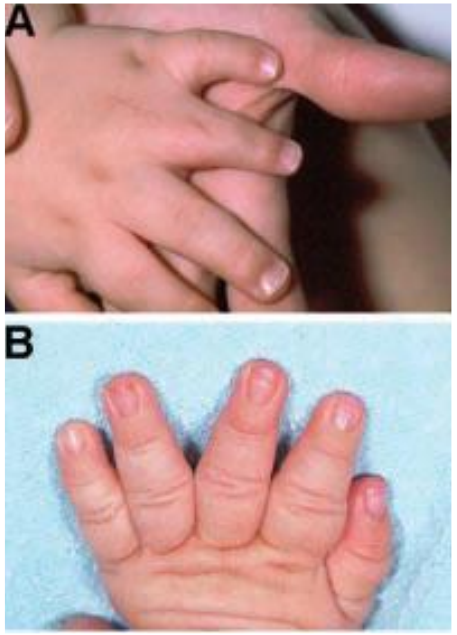


Finger syndactyly



Clenched fist

Brachydactyly

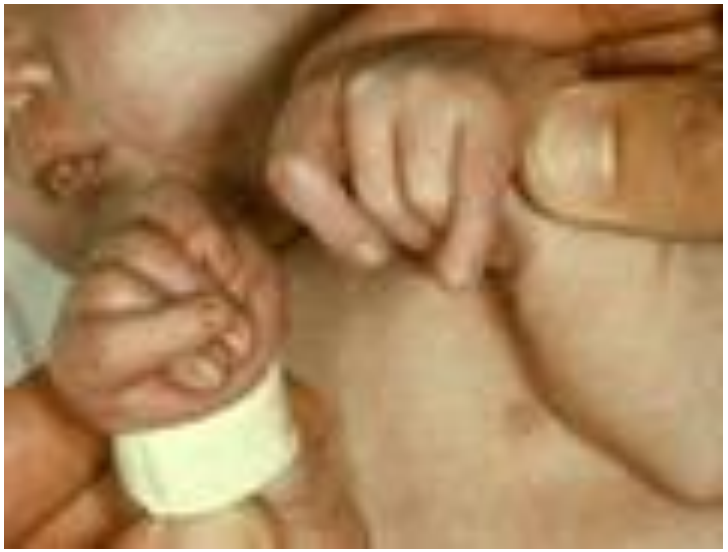


Tapering fingers

Short fingers

The middle finger is more than 2 SD below the mean for newborns 27–41 weeks EGA or below the 3rd centile for children from birth to 16 years of age AND the five digits retain their normal length proportions relative to each (i.e., it is not the case that the middle finger is the only shortened digit)

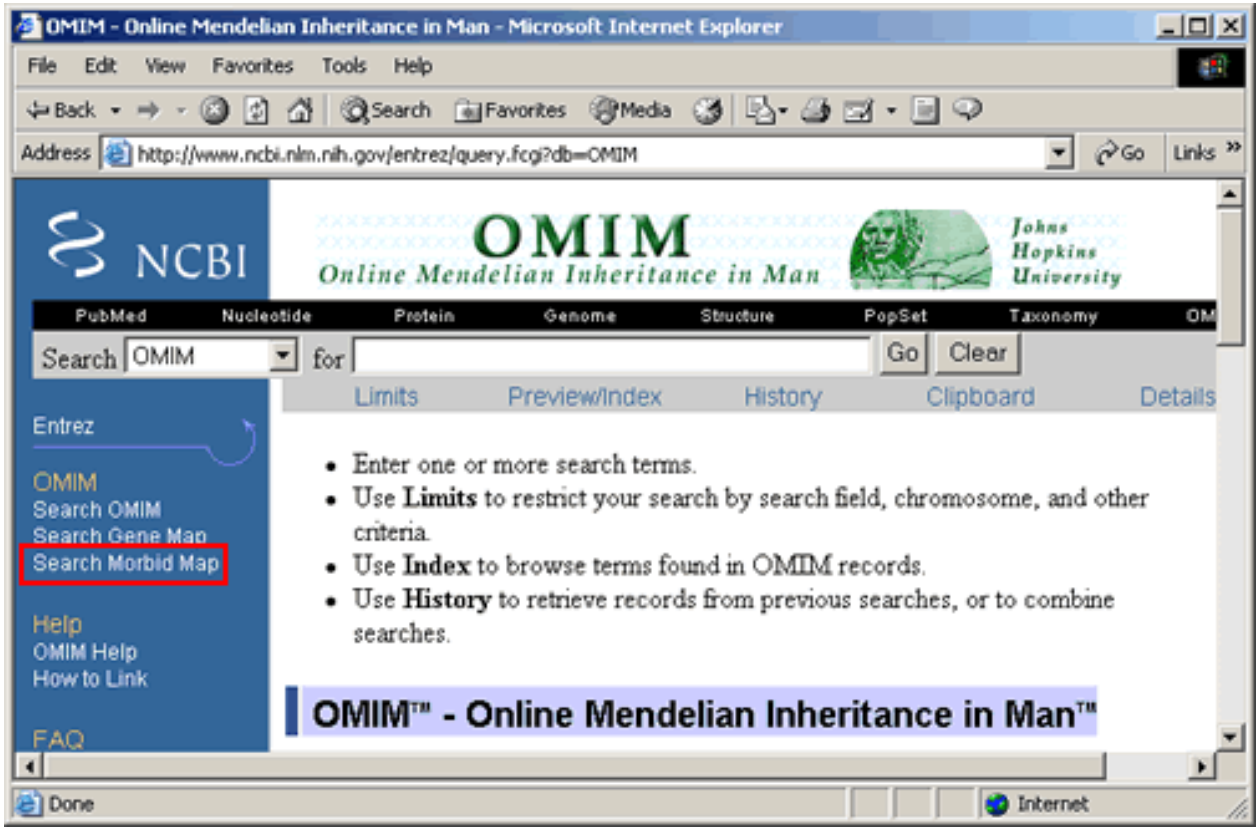
This is an acknowledged bundled term as the definition in most anthropometric sources assumes that the other fingers are all as relatively short as is the middle finger. As the determination of the proportionality of the other four digits is clearly subjective, the term must be regarded as subjective.



Clenched hand

Definition: All digits held completely flexed at the metacarpophalangeal and interphalangeal joints

Comment: Is distinguished from ***Camptodactyly,*** as that term may describe fewer than five digits of a eudactylous hand and does not involve the MCPJ. The digits may overlap when they lie flexed in the palm. It is not necessary to specify the overlapping fingers finding separately.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1: * 602642. TUMOR NECROSIS FACTOR LIGAND SUPERFAMILY, MEMBER 11; TNFSF11 Links
Cytogenetic location: 13q14.11, Genomic coordinates (GRCh37): 13:43,136,871 - 43,182,148
Matching terms: rankl

2: * 603499. TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY, MEMBER 11A; TNFRSF11A Links
Cytogenetic location: 18q21.33, Genomic coordinates (GRCh37): 18:59,992,519 - 60,054,942
Matching terms: rankl

3: # 114480. BREAST CANCER ICD+, Links
BREAST CANCER, FAMILIAL MALE, INCLUDED
Cytogenetic locations: 1p34.1, 2q33.1, 2q35, 3q26.32, 5q34, 6p25.2, 8q11.23, 11p15.4, 11p15.1, 11q22.3, 12p12.1, 13q13.1, 14q32.33, 14q32.33, 15q15.1, 16p12.2, 16q22.1, 17p13.1, 17q21.33, 17q23.2, 17q23.2, 22q12.1
Matching terms: rankl

4: * 602643. TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY, MEMBER 11B; TNFRSF11B Links
Cytogenetic location: 8q24.12, Genomic coordinates (GRCh37): 8:119,935,795 - 119,964,352
Matching terms: rankl

5: * 600489. NUCLEAR FACTOR OF ACTIVATED T CELLS, CYTOPLASMIC, CALCINEURIN-DEPENDENT 1; NFATC1 Links
Cytogenetic location: 18q23, Genomic coordinates (GRCh37): 18:77,155,771 - 77,289,322
Matching terms: rankl

6: * 602355. TNF RECEPTOR-ASSOCIATED FACTOR 6; TRAF6 Links
Cytogenetic location: 11p12, Genomic coordinates (GRCh37): 11:36,505,316 - 36,531,862
Matching terms: rankl


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Spinal Muscular Atrophy

Includes: Arthrogryposis Multiplex Congenita-Spinal Muscular Atrophy (AMC-SMA), Congenital Axonal Neuropathy (CAN), Spinal Muscular Atrophy 0 (SMA0), Spinal Muscular Atrophy I (Werdnig-Hoffmann Disease, SMA I), Spinal Muscular Atrophy II (SMA II), Spinal Muscular Atrophy III (Kugelberg-Welander Disease, SMA III), Spinal Muscular Atrophy IV (SMA IV)

Thomas W Prior, PhD, FACMG and Barry G Rosenman, MD

Initial Posting: February 24, 2000; Last Update: January 27, 2011.

Summary

Disease characteristics. Spinal muscular atrophy (SMA) is characterized by progressive muscle weakness resulting from degeneration and loss of the anterior horn cells (i.e., lower motor neurons) in the spinal cord and the brain stem nuclei. Onset ranges from before birth to adolescence or young adulthood. Poor weight gain, sleep difficulties, pneumonia, scoliosis, and joint contractures are common complications. Before the genetic basis of SMA was understood, it was classified into clinical subtypes; however, it is now apparent that the phenotype of SMA associated with disease-causing mutations of the SMN1 gene spans a continuum without clear delineation of subtypes. Nonetheless, classification by age of onset and maximum function achieved is useful for prognosis and management; subtypes include: SMA 0 (proposed), with prenatal onset and severe joint contractures, facial diplegia, and respiratory failure; SMA I, with onset before age six months; SMA II, with onset between age six and 12 months; SMA III, with onset in childhood after age 12 months; and SMA IV, with adult onset.

Diagnosis/testing. The diagnosis of SMA is based on molecular genetic testing. The two genes associated with SMA are SMN1 and SMN2. SMN1 (survival motor neuron 1) is primarily involved: about 95%-98% of individuals with SMA are homozygous for a deletion or truncation of SMN1 and about 2%-5% are compound heterozygotes for an SMN1 deletion or truncation and an SMN1 intragenic mutation. SMN1 deletion or

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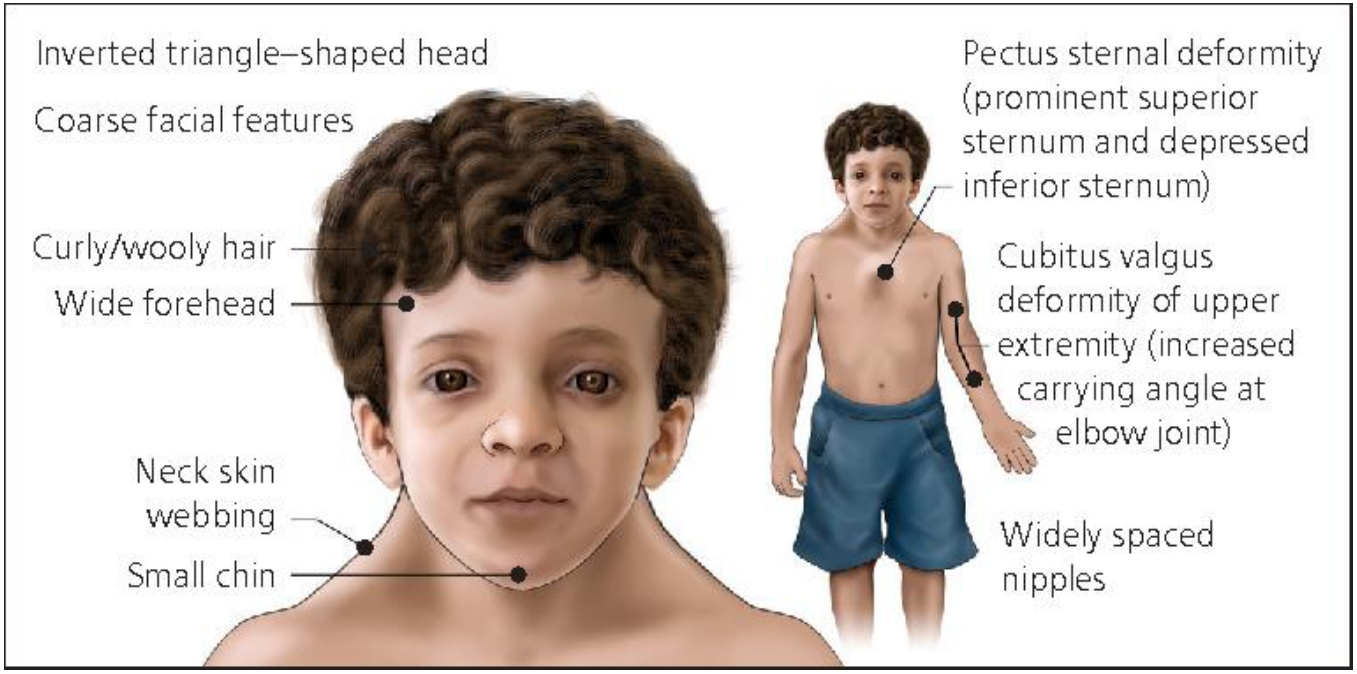
Genetic syndromes with dysmorphic features

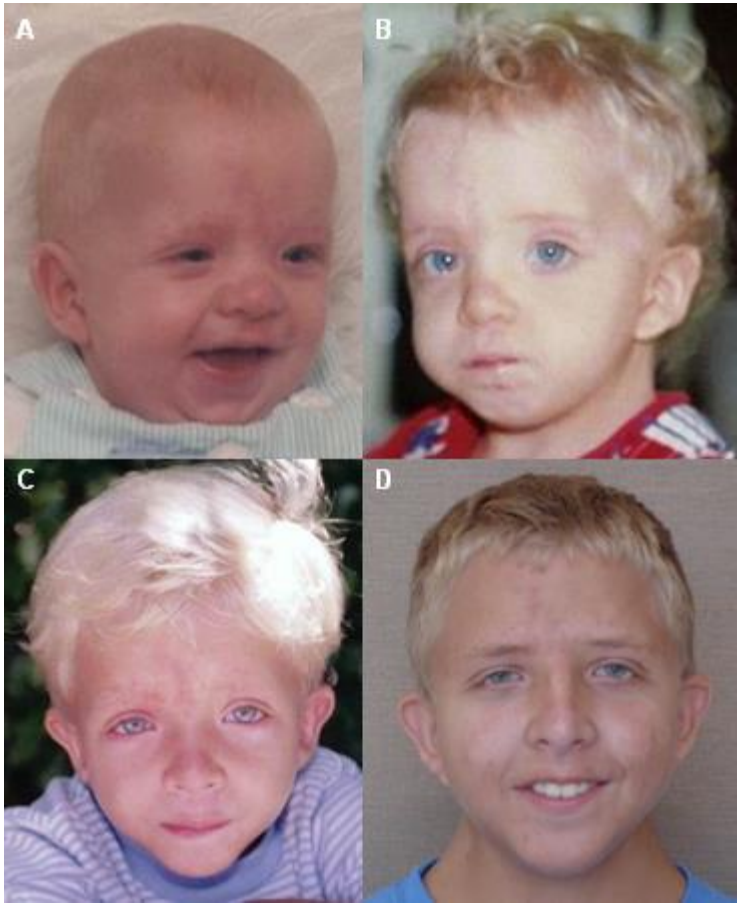
Groupwork: report on frequency, clinical synopsis including dysmorphic features, diagnosis, surveillance

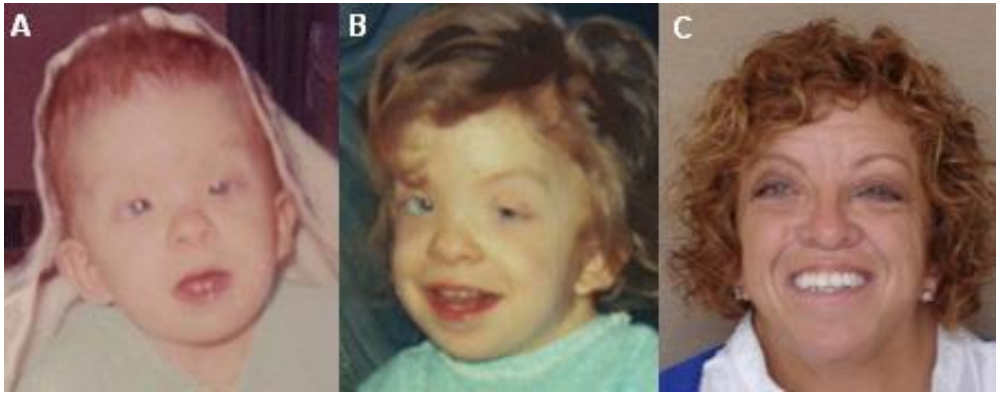
- Gr. A: Noonan syndrome
- Gr. B: Achondroplasia
- Gr. C: Mowat-Wilson syndrome
- Gr. D: Rubinstein-Taybi syndrome

Noonan syndrome



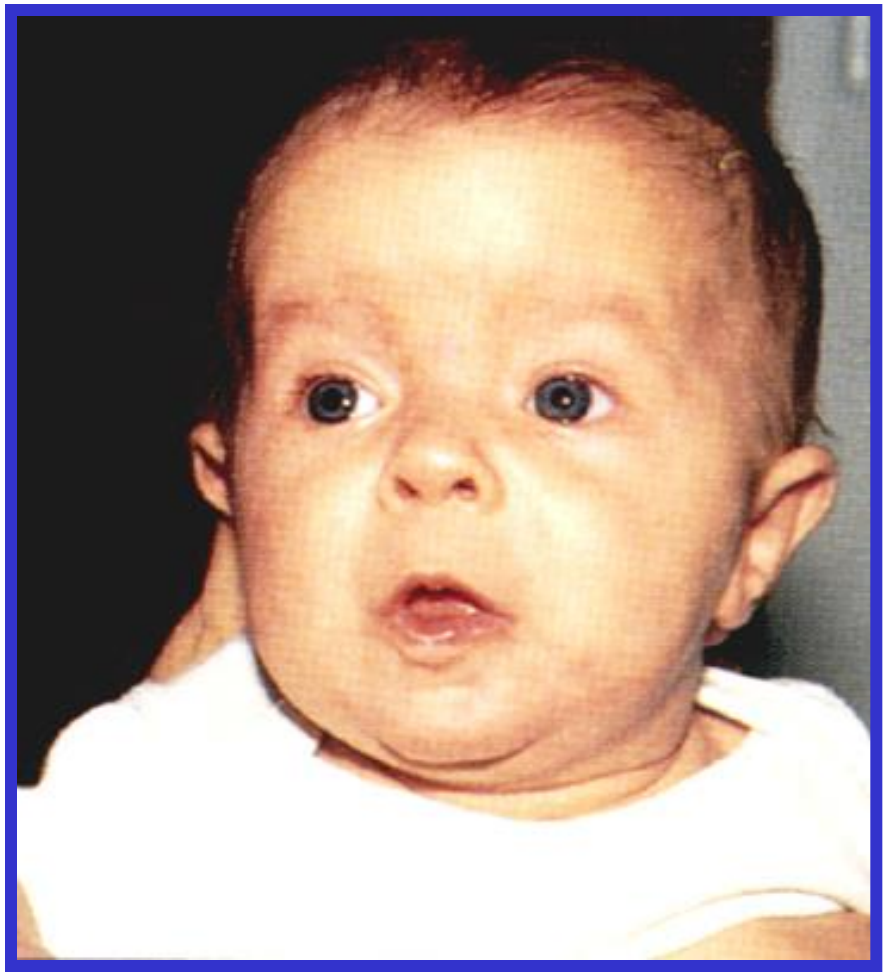
https://www.semanticscholar.org/paper/Noonan-syndrome.-Bhambhani-Muenke/e0bc62192573261a39ac392c3bc887883dfb3149/figure/4

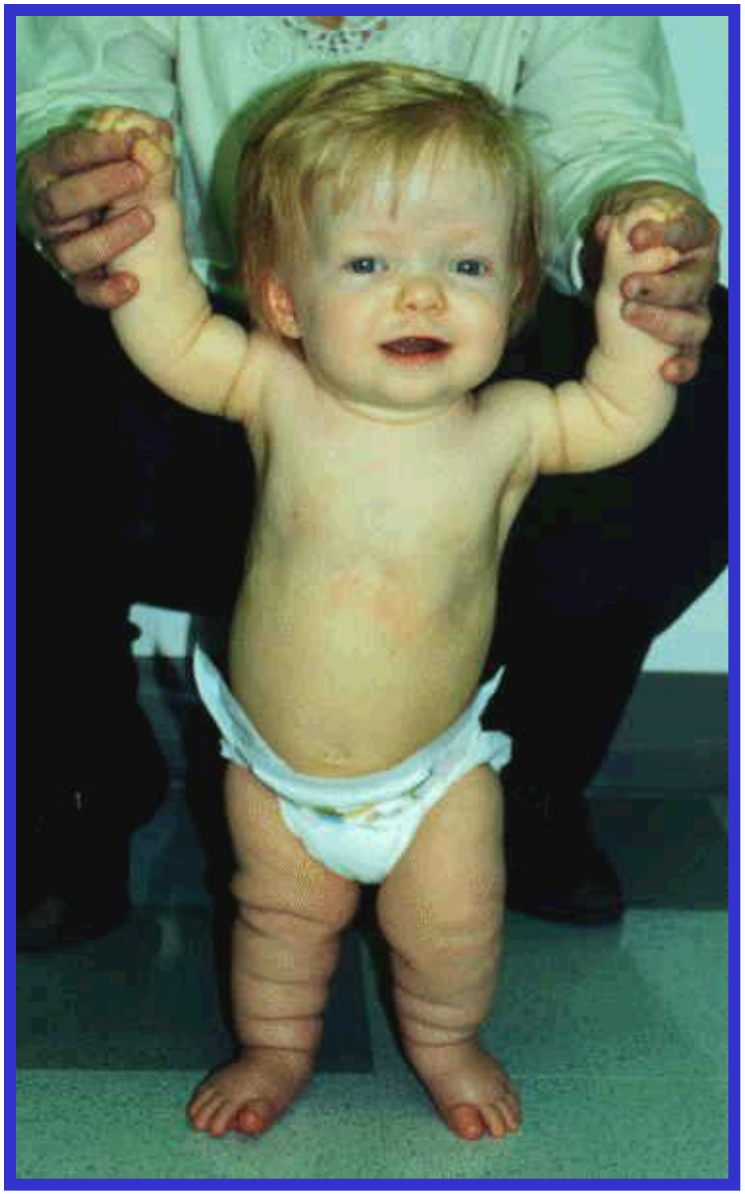

A
B
C
D


A
B
C

Noonan syndrome

- Frequency 1:1000 – 1:2500
- AD, RAS-MAPK genes: *PTPN11, RAF1, KRAS, SOS1, BRAF, NF1, NRAS*
- Short stature, facial dysmorphy (hypertelorism, downslanted palpebral fissures, ptosis, low-set ears), cardiac defect (most frequently pulmonary stenosis (PS)), webbed neck, *pectus carinatum / excavatum*
- Clotting disorders





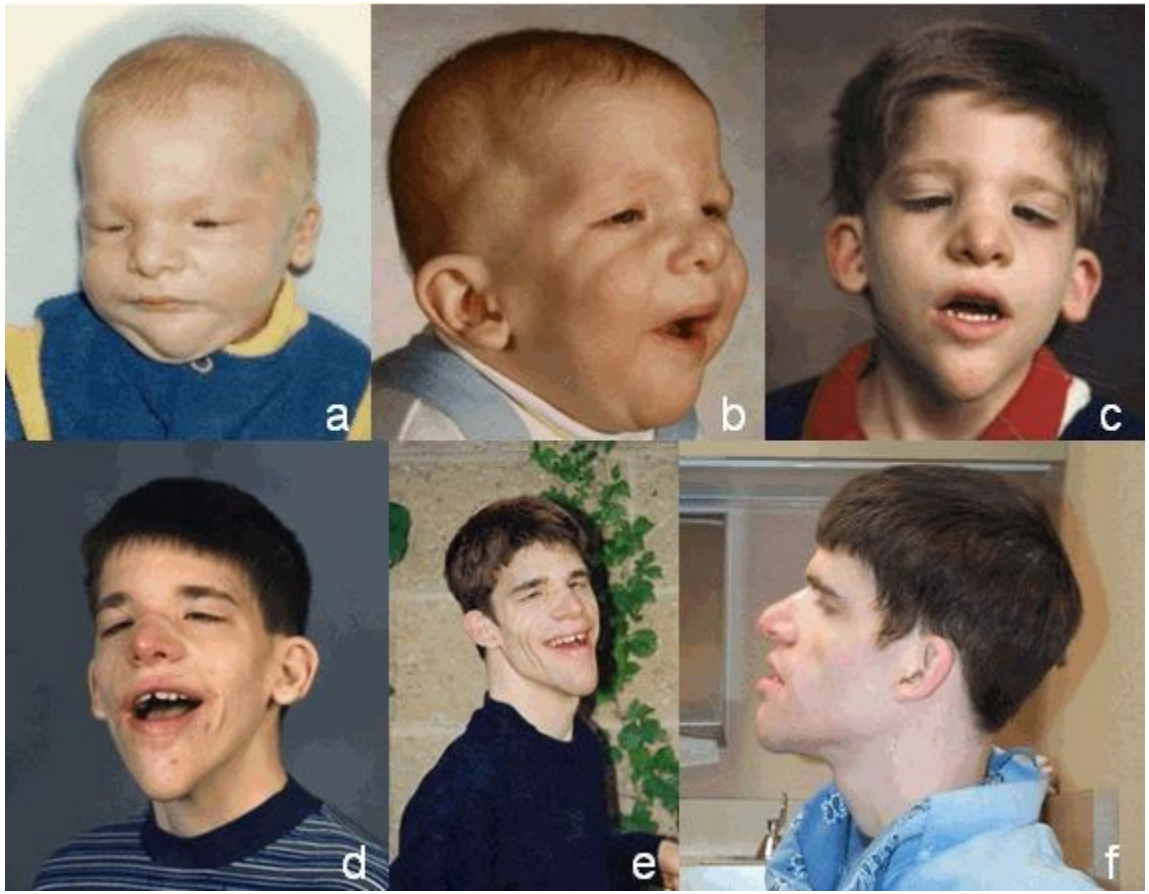
Achondroplasia

Autosomal Dominant

Achondroplasia

- *FGFR3* gene, AD
- Short stature, short limbs (particularly upper arms and thighs), hyperlordosis, valgus knee, prominent forehead, midface retrusion
- Normal intellectual development

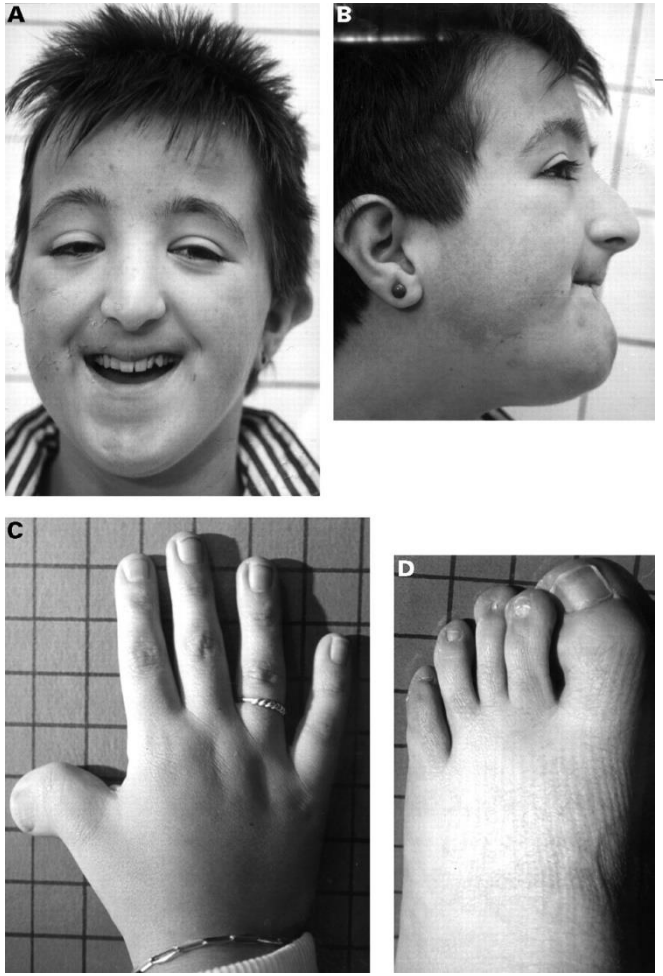
Mowat Wilson syndrome



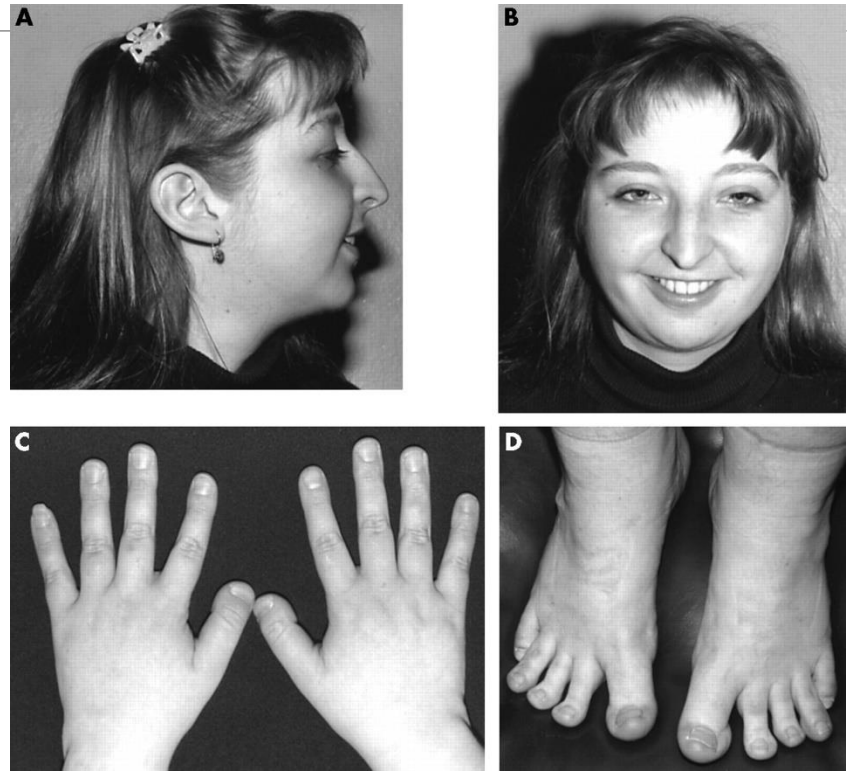
MWS

- *ZEB2* gene
- Facial dysmorphy (hypertelorism, broad medial eyebrows, uplifted earlobes, open-mouthed expression, prominent or pointed chin)
- Moderate to severe ID, seizures
- Congenital anomalies: microphthalmia, Hirschprung disease, hypospadias, agenesis of corpus callosum, heart defects

Rubinstein Taybi syndrome



https://bjo.bmj.com/content/84/10/1177



https://jmg.bmj.com/content/39/7/496

RTS

- 16p13.3 microdeletion, mutations in *CREBBP or EP300* genes
- Broad, angulated thumbs and toes, short stature, facial dysmorphy (downslanted palpebral fissures, beaked nose), ID of varying degrees
- Congenital heart defects, urinary tract abnormalties, eye defects

Rubinstein Taybi syndrome
https://www.youtube.com/watch?v=rdVIzLogHY0