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
Etiologic heterogeneity of cleft lip/palate

- Teratogens
- 22q deletion
- Primary mandibular hypoplasia
- Trisomy 13
- Amniotic band syndrome
- Kniest dysplasia
- Van der Woude syndrome
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
Empiric Recurrence Risks (%) for Selected Birth Defects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Affected Relatives(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Cleft lip/palate</td>
<td>0.1</td>
</tr>
<tr>
<td>Neural Tube Defect</td>
<td>0.1</td>
</tr>
<tr>
<td>Heart Defect</td>
<td>0.3</td>
</tr>
</tbody>
</table>

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.
Causes of recognized development 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 in an organ or structure due to an intrinsically abnormal problem with 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
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 accident

Disruption of lip formation due to amniotic bands
Amniotic Bands

Banding can cause amputation while in the womb

AMNIOTIC BANDS SYNDROME

IN THIS DETAIL, AMNIOBIC BANDS CONSTRIC THE BLOOD SUPPLY TO THE FINGERS

AMNION IS SEPERATED FROM THE UTERUS

WALL OF THE UTERUS

AMHION (INNER MEMBRANE)

FETUS AT 16 MONTHS

AMNIOTIC CONSTRIC BANDS ARE CAUSED BY DAMAGE TO THE PLACENTA CALLED THE AMNION. DAMAGE TO AMNION PRODUCES FIBER-LIKE BANDS THAT CAN TRAP PARTS OF THE DEVELOPING BABY.

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

- Syndromes
- Associations
- Sequences
- Dysplasias
Sequence

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

Symptoms
- Cleft soft palate
- High-arched palate
- Small opening in roof of the mouth (might cause choking)
- Jaw that is abnormally small (Micrognathia)
- Jaw placed abnormally far back in the throat
- Downward displacement of the tongue (Glossoptosis)
- Large tongue
- Natal teeth
- Ear infections
Preoperative frontal and lateral views of an infant with Pierre Robin sequence.
Bilateral renal agenesis or bilateral multicystic dysplastic kidneys

Reduced fetal urine excretion

Oligohydramnios causing fetal compression

Potter facies:
- Low-set ears
- Beaked nose
- Prominent epicanthic folds and downward slant to eyes
- Pulmonary hypoplasia causing respiratory failure
- Limb deformities

Potter’s sequence
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
**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
Difficulties in diagnosing syndromes

- Some are very rare disorders - not well described
- Variable expression
- Incomplete penetrance
- Sex-influenced or limited expression
- Pleiotropy
- Etiologic heterogeneity
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 (Craniosynostosis [FGFR3 gene], CF [CFTR gene])
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.
Facial Angiofibromas

Tuberous Sclerosis

Periungual Fibromas

Shagreen Patches

Facial Angiofibromas

Tuberoius Sclerosis
Penetrance

- proportion of individuals carrying a particular variant (or allele) of a gene (the genotype) that also express an associated trait (the 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
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 their families. Whenever any physician is confronted by a patient with a birth defect, he or she becomes, for the moment at least, a dysmorphologist."

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 insignificant familial traits (e.g. finger syndactyly)
- Not only external variety, but also that 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://symptomscausетreatmentprevention.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
Mongoidalne/antymongoidalne ustawienie 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
Tools in dysmorphology

- 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)
Facial Gestalt (eLife; 3: e02020)
American Journal of Medical Genetics Part A
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Special Issue: Elements of Morphology: Standard Terminology

January 2009
Volume 149A, Issue 1
Pages 1–127
Standardization of dysmorphology terminology

Elements of Morphology: Standard Terminology for the Head and Face

Judith E. Allanson, Christopher Cunniff, H. Eugene Hoyme, Julie McGaughran, Max Muenke, and Giovanni Neri

Elements of Morphology: Standard Terminology for the Lips, Mouth, and Oral Region

John C. Carey, M. Michael Cohen Jr., Cynthia J.R. Curry, Koenraad Devriendt, Lewis B. Holmes, and Alain Verloes
Anatomic reference points

Abnormal skull shape

- Brachycephaly – anterio-posterior shortening of the skull
- Dolichocephaly – increased AP dimension
Abnormal skull shape

- Plagiocephaly – skull asymmetry
- Trigonocephaly
Facial dysmorphism

- Flat facial profile
- Coarse facial features
Coarse features in mucopolysaccharidoses

Choroby Hurlera (MPS IH)
Choroba Morquio (MPS IV)
Choroba Sanfilippo (MPS III)
Choroba Sly (MPS VII)
Choroba Hunter (MPS II)
Choroba Maroteaux-Lamy (MPS VI)

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

- Frontal bossing
- Prominent glabella
Facial dysmorphism

- Micrognathia
- Retrognathia
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
**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.

**Redundant nuchal skin**

**Webbed neck**
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

Blepharophimosis

Cryptophthalmos
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.

Synophrys
Dysmorphism of the oral region
Thin upper lip

Cupid bow mouth

Tented upper lip

Wide mouth

„Cupid bow” mouth

Lip pits
Dysmorphology of ears
Crumpled ears

Cupped ear

Attached earlobe

Upturned lobes

Microtia

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

Cupped ear
Finger anomalies
Finger syndactyly

Clenched fist

Brachydactyly

Tapering 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 eudactylyous 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.
- Enter one or more search terms.
- Use Limits to restrict your search by search field, chromosome, and other criteria.
- Use Index to browse terms found in OMIM records.
- Use History to retrieve records from previous searches, or to combine searches.

OMIM™ - Online Mendelian Inheritance in Man™
1. **602642. TUMOR NECROSIS FACTOR LIGAND SUPERFAMILY, MEMBER 11; TNFSF11**
   - Matched terms: rank

2. **603499. TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY, MEMBER 11A; TNFRSF11A**
   - Cytogenetic location: 18q21.33, Genomic coordinates (GRCh37): 18:89,992,519 - 18:90,054,942
   - Matched terms: rank

3. **114480. BREAST CANCER**
   - BREAST CANCER, FAMILIAL, MALE, INCLUDED
   - Cytogenetic location: 1p34.1, 2q35.1, 2q35, 3q26.32, 6q28, 6q28.2, 8q11.23, 11p13.4, 11p13.1, 11q22.3, 12p12.1, 13q13.1, 14q32.33, 14q32.33, 16q12.1, 16q12.1, 17q13.1, 17q21.33, 17q23.2, 17q23.2, 22q12.1

4. **602643. TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY, MEMBER 11B; TNFRSF11B**
   - Cytogenetic location: 8p24.12, Genomic coordinates (GRCh37): 8:119,935,795 - 8:119,944,582
   - Matched terms: rank

5. **600489. NUCLEAR FACTOR OF ACTIVATED T CELLS, CYTOPLASMIC, CALCINEURIN-DEPENDENT 1; NFATC1**
   - Matched terms: rank

6. **602355. TNF RECEPTOR-ASSOCIATED FACTOR 6; TRAF6**
   - Cytogenetic location: 11p12, Genomic coordinates (GRCh37): 11:36,805,316 - 11:36,831,862
   - Matched terms: rank
Spinal Muscular Atrophy

Includes: Amyoplasia Multiplex Congenita, Spinal Muscular Atrophy (SMA-CAN), Congenital Axonal Neuropathy, SMA-1, Spinal Muscular Atrophy 2 (SMA2), Spinal Muscular Atrophy 3 (SMA3), Spinal Muscular Atrophy 4 (SMA4)

Thomas W Price, PhD, FACPAM and Barry E Rosenman, MD.

Summary

Disease characteristics. Spinal muscular atrophy (SMA) is characterized by progressive muscle weakness resulting from degeneration and loss of the anterior horn cells in the spinal cord and the cranial nerve nuclei. Onset ranges from before birth to adolescence or young adulthood. Poor weight gain, feeding 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: SMA0 (proposed), with prenatal onset and severe joint contractures, facial diplegia, and respiratory failure; SMA1, with onset before age six months; SMA2, with onset between age six and 12 months; SMA3, with onset in childhood after age 12 months; and SMA4, with adult onset.

Diagnosing SMA. 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%-96% 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 SMN2 intronic deletion. SMN2 deletion is...
The portal on rare diseases and orphan drugs

"Rare diseases are rare, but rare disease patients are numerous."

Access our Services

- Inventory, classification and encyclopedias of rare diseases, with genes involved
- Inventory of orphan drugs
- Directory of patient organisations
- Directory of professionals and institutions
- Directory of expert centres
- Directory of medical laboratories providing diagnostic tests
- Directory of ongoing research projects, clinical trials, registries and databases
- Collection of thematic reports: Orphanet Reports Series
Genetic syndromes with dysmorphic features

- Groupwork: report on frequency, clinical synopsis including dysmorphic features, diagnosis, surveillance
  - Gr. A: Noonan syndrome
  - Gr. B: Cornelia de Lange syndrome
  - Gr. C: Achondroplasia
  - Gr. D: Mowat-Wilson syndrome
  - Gr. E: Rubinstein-Taybi syndrome
  - Gr. F: Kabuki syndrome
Noonan syndrome

Inverted triangle–shaped head
Coarse facial features
Curly/wooly hair
Wide forehead
Neck skin webbing
Small chin

Pectus sternal deformity (prominent superior sternum and depressed inferior sternum)
Cubitus valgus deformity of upper extremity (increased carrying angle at elbow joint)
Widely spaced nipples

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

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

CdLS

- 1:10 000 – 1: 200 000
- Gene mutations: NIPBL (50%), SMC1A (5%), SMC3 (1%), unknown etiology (40%)
- Facial dysmorphism: synophrys, long philtrum, wide-spaced teeth
- Developmental delay, hyperactivity
- Hand/foot anomalies
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 dysmorphism (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
- 16p13.3 microdeletion, mutations in CREBBP or EP300 genes
- Broad, angulated thumbs and toes, short stature, facial dysmorphism (downslanted palpebral fissures, beaked nose), ID of varying degrees
- Congenital heart defects, urinary tract abnormalities, eye defects
Rubinstein Taybi syndrome
https://www.youtube.com/watch?v=rdVlzLogHY0
Kabuki syndrome

- Facial dysmorphism: everted lower eyelid, arcuate eyebrows, ear malformations
- Skeletal abnormalities
- Mild/moderate ID
- Congenital heart defect
Kabuki syndrome

- *KMT2D* (formerly *MLL2*) gene, *KDM6A*
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