Dysmorphology

- The study of abnormal form
- Focuses on structural abnormalities of development
- Encompasses embryology, clinical genetics, pediatrics

Embryology

Pediatrics

Genetics
Normal and Abnormal Embryogenesis

- **Prenatal**
  - Implantation – fertilization to end of week 3
  - Embryonic – week 4 to end of week 7
  - Fetal – week 8 to birth
Implantation

- Fertilization to end of week 3
- Rapid cell proliferation and early cell differentiation
- All or nothing effect
  - Abnormal development results in fetal loss. Accounts for about 15% of conceptions
Embryonic

- Week 4 to end of week 7
- Primary tissue differentiation
- Formation of organs

- Abnormal
  - Structural anomalies
Fetal

- Week 8 to birth
- Human form achieved
- Complete organ differentiation
- Growth in size
- Last 8 weeks increase in body fat and maturation of lungs
Birth Defects

- About 3% of children born have a significant congenital abnormality
  - More than cosmetic concern
  - Uncorrected leads to interference with normal functioning

- Children with birth defects account for 30% of pediatric hospital admissions
Distribution of Congenital Abnormalities in Populations

Incidence in all populations

Single system vs. MCA

 Syndromes by etiology
Pathogenetic Mechanisms

- Deformation
- Disruption
- Dysplasia
- Malformation
Deformation

- Aberrant mechanical forces disrupt otherwise normal structures
  - Examples
    - Tibial bowing
    - Club feet
- May correct spontaneously or need treatment through mechanical force
Disruption

- Destruction of previously normal tissue
- Affects several tissue types in a demarcated anatomic region
Dysplasia

- Abnormal cellular organization or function within a specific tissue type
- Results in apparent structural changes
- Caused by major mutant genes
Malformation

- Failure of completion of one or more embryonic processes leading to arrested development of a particular tissue or organ system
- Error occurs early
Malformations

- Single-System
  - Cleft lip
  - Club foot
  - Congenital Hip Dislocation
  - CHD

- Most are multifactorial

- Most common
Malformations

Associations

- Association of non-random physical features not strong enough to define a syndrome
  - VACTERL
    - (Vertebral, anal, cardiac, TE fistula, renal, limb)
  - CHARGE
    - (Coloboma, heart, choanal atresia, retardation, genital ear)
Malformations

**Sequences**

- Result of a cascade of unrelated consequences beginning with a single system malformation

  - Potter (renal agenesis)
  - Pierre Robin (mandibular hypoplasia)
Malformations

- Complexes
  - Abnormalities in adjacent structures within the embryo
  - Often due to vascular disruption
    - Hemifacial microsomia
    - Poland anomaly
Malformations

- Syndromes
  - Repeated consistent pattern of malformation

- Examples
  - Mucopolysaccharidoses
  - Noonan
  - Down
Dysmorphology Evaluation

1. Suspicion
   - Congenital abnormalities
   - Growth problems
   - Mental Deficit
Dysmorphology Evaluation

- Evaluation
  - History
    - Pedigree
    - Pregnancy
    - Birth
    - Health
    - Growth
    - Development
  - Prior Labs and Xrays
Dysmorphology Evaluation

- Physical Exam
  - Anatomic regions
  - Organ systems
  - Measurements
  - Photos
- Labs, xray
Assessment of Ear Position

Low set and posteriorly angulated

Normal
Low Set
Angulation of the Auricle

- Vertical Plane of head
- Horizontal plane
- Longest Diameter
- Protrusion
Large Protruding Ears

What syndrome can be associated with this finding?
Fragile X Syndrome

- Mental retardation
  - Moderate/severe (IQ 20-60)
- Long narrow face
  - Narrow inner canthi
  - Prominent forehead
  - Prominent jaw
- Macroorchidism after puberty
Normal Spacing of the Orbits
Hypertelorism
Zellweger Syndrome – Peroxisomal Biogenesis Disorder

- Characteristic facies
  - Frontal bossing
  - High forehead
  - Hypertelorism
  - Dolichocephaly
- Hypotonia
- Enlarged Liver

Abnormal VLCFA, Plasmalogens
Hypotelorism
Unbalanced Chromosome – distal duplication 14p
Palpebral Fissures

- Uplslanted
- Downslanted
Downslanted Palpebral Fissures
Cornelia de Lange

- Synophrys
- Thin downslanting upper lip
- Micromelia
  - Microbrachycephaly
  - Depressed nasal bridge
  - Anteverted nares
  - Long philtrum
  - Mental retardation

Clinical Diagnosis
Upslanted Palpebral Fissures
Trisomy 21
Variations of the Nose

- Short columella
- Bulbous Tip
- Hypoplastic alae
- Broad high bridge
Lip Variations

- Carp Mouth
- Long smooth philtrum
- Mandibular asymmetry
Mouth - Macroglossia
Beckwith-Wiedemann
Beckwith-Wiedemann

- Macrosomia
- Macroglossia
- Omphalocele
- Visceromegaly
- Embryonal tumors

- Clinical Diagnosis
- Testing
  - <1% abnormal 11p15
  - 50% loss of methylation
    KCNQ1OT1
  - 10-20% paternal UPD 11p15
  - CDKN1C mutations in 5-10% of simplex cases and 40% of familial
Facial Dysmorphism
Facial Dysmorphism: Aarskog Syndrome
(Faciogenital dysplasia)

- Widow’s Peak
- Small nose
- Chin crease
- Hypertelorism
- Long philtrum carp mouth
Aarskog Child

- Hypertelorism
- Brachydactyly
- Shawl Scrotum
- X-Linked
- Mutation in FDG 1 gene
Palmar Crease Variations

A  B  C  D

Single  Fused  Sydney  Hockey-
(Simian)     stick
Hands and Feet
Trisomy 8 Mosaicism
Feet: Turner S. Newborn
Webbed Neck: Turner Syndrome
Syndrome 1

- IUGR
- Small narrow head
- Open metopic sutures
- Prominent occiput
- Low rotated ears
- Small mouth/micrognathia
- Short sternum
- CHD
- Overlapping fingers
- Rockerbottom feet
Trisomy 18

- IUGR
- Small narrow head
- Open metopic sutures
- Prominent occiput
- Low rotated ears
- Small mouth/micrognathia
- Short sternum
- CHD
- Overlapping fingers
- Rockerbottom feet
Syndrome 2

- Hypertelorism
- Low set ears
- Webbed Neck
- CHD – pulmonic stenosis
- Short Stature
Noonan Syndrome

- Hypertelorism
- Low set ears
- Webbed Neck
- CHD – pulmonic stenosis
- Short Stature

Clinical Diagnosis

Mutation in PTPN11 in about 40% of cases
Syndrome 3
Fetal Alcohol Syndrome

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

Clinical Diagnosis
Syndrome 4

- Postnatal growth retardation
- Lax skin
- Curly hair
- Short Stature
- Coarse Facies
Costello Syndrome

- Postnatal growth retardation
- Lax skin
- Curly hair
- Short Stature
- Coarse Facies

Clinical Diagnosis
Syndrome 5

- Pre/Post natal growth retardation
- Microcephaly
- Cleft palate
- Cardiac
- Genital
- Poly/syndactyly
Smith-Lemli-Opitz Syndrome

Defect in cholesterol biosynthesis
FISH

**PROBE PREPARATION**
- Labeled Probe
- Denature
- Prehybridize

**HYBRIDIZATION**
- Probe Added, Coverslipped, and Sealed
- Incubate
- Wash
- View

**SLIDE PREPARATION**
- Metaphase or Interphase Chromosomes
- Denature
- Dehydrate and Air Dry
22q11 Deletion – DiGeorge, etc.

Cardiac
Immune
Palate
Williams Syndrome

- Elfin facies
- Supravalvular aortic stenosis
- Hypercalcemia
- F.I.S.H. test

Contiguous gene defect on chromosome 7q11.23
FISH with ELN Probe
Williams Syndrome

Control

Affected
Detection of William Syndrome Variant with Chromosome Microarray

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Evaluation of the Dysmorphic Child

- Historical Clues
- Physical Exam Clues
- Pivotal Features
- Special Testing
- Pattern Recognition
- Cross Reference
- Definitive Diagnosis
- Time