Clinical Genetics

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August 9, 2013
Birth Defects: Mechanisms

Normal development

Deformation

Disruption

Dysplasia

Malformation
Abnormal fetal position  

Diminished fetal movement
Disruption

Amnion Disruption
Gastroschisis Disruption

- Usually a sporadic event
- Disruption of the omphalomesenteric artery
- Not associated with genetic syndromes
- 10-20% have associated anomalies
  - Intestinal atresia
Achondroplasia (FGFR3)
Malformation

- cleft lip and palate (single)
- Trisomy 13 (multiple)
Multiple Malformations can be Part of:

- **Syndrome**
  - Trisomy 13
- **Sequence**
  - Pierre Robin
- **Association**
  - VACTERL
Down (trisomy 21) Syndrome

- 1/800 newborns affected
- Advanced maternal age risk
- Precise mechanism is unknown
- Types
  - 94%: full trisomy, nondisjunction
  - 3%: mosaic trisomy
  - 4%: translocation (e.g. 14/21)

Brushfield spots
Sequence: a single event leads to a single anomaly having a cascading effect.

![Diagram showing genetic or environmental initial defect leading to secondary defects]

- **Initial defect**
  - Genetic or Environmental

- **Secondary defects**
  - A → B → D
  - A → C → E
  - A → D → F
  - A → E → G
Small jaw → upward positioning of tongue → interference with palate closure
Pierre Robin Sequence

- Glossoptosis
- Micrognathia
- Cleft palate
- Feeding problems
- Airway obstruction
- 1/3: due to syndromes
  - e.g., chromosome disorders and single gene defects
- 2/3: non-syndromic
Oligohydramnios Sequence

Decreased amniotic fluid

↓

Fetal constraint

Arthrogryposis, loose skin, facial changes: Potter’s facies

↓

Decreased lung fluid

Pulmonary hypoplasia

↓

Respiratory failure
Jugular Lymphatic Obstruction Sequence

Jugular lymph duct obstruction

Nuchal swelling (cystic hygroma)

Webbed neck
Urethral Obstruction Sequence
(Prune Belly Syndrome)

Urethral obstruction

→ Bladder distension

→ Hydroureter, renal dysplasia

→ Abdominal muscle deficiency

→ Excess abdominal skin
Holoprosencephaly Sequence
Holoprosencephaly Sequence

Embryonic midface/neural tissues are abnormal

Single upper incisor

Cleft lip and palate

Midface Malformations
Holoprosencephaly Types

- Normal
- Alobar
- Semilobar
- Lobar

Alobar, complete type

Lobar type, fused thalamus
Holoprosencephaly

- 1/16,000 incidence
- Alobar, semi-lobar, lobar types
- Etiologic heterogeneity
  - Many genes: SHH, ZIC2, SIX3, TGIF, PTCH, TMEM1, others
  - Trisomy 13 and other chromosomes
  - Teratogens (e.g., maternal diabetes)
  - Infections
Associations

Unknown cause(s) and pathogenesis

Multiple malformations that significantly associate with each other
VACTERL Association  
(VATER, VATERR)

- Vertebral: 70%
- Anal atresia: 50%
- Cardiac: VSD most common
- Tracheo-Esophageal fistula: 70%
- Renal: 50%
- Limb: 50%
  - Radial dysplasia, preaxial polydactyly, syndactyly
- Sporadic occurrence
VACTERL Association Hypothesis

Unknown cause

Blastocyst Stage

Multiple Malformations

L M N O
Referrals to Clinical Genetics

Facial dysmorphism

2-3 toe syndactyly
Facial Traits

- Hyper and hypotelorism
- Wide and short palpebral fissures
- Down-slanting palpebral fissures
- Smooth or flat philtrum
Wide palpebral fissures

Short palpebral fissures
Down-slanting palpebral fissures

Up-slanting palpebral fissures
Variations in philtrum development

Normal

Smooth philtrum with thin upper lip

Philtrum height
Philtral groove

Shallow groove
Thin upper lip

Images of variations in philtrum development.
Minor Congenital Anomaly

- One is present in about 13% of newborns
- 1% have two unrelated minor anomalies
- 1/2000 have three

Examples
- Sacral dimple/sinus
- Accessory nipples
- Postaxial polydactyly
- Umbilical hernia
- Single palmar crease
- 2-3 syndactyly/underriding toe
- Nevus flammeus
- Mongolian spot
- Ear sinuses and tags
- Cafe-au-lait, ash leaf spot
<table>
<thead>
<tr>
<th>Ear tag</th>
<th>Ear pit</th>
<th>Café-au-lait spot</th>
<th>Accessory nipple</th>
<th>2-3 toe syndactyly</th>
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</thead>
<tbody>
<tr>
<td>Polydactyly</td>
<td>Underlying toe</td>
<td>Single palm crease</td>
<td>Sacral dimple</td>
<td>Umbilical hernia</td>
</tr>
</tbody>
</table>
Examples of conditions with facial dysmorphism:

1. Treacher Collins syndrome
2. Fetal Alcohol Syndrome
Treacher Collins Syndrome

- Micrognathia
- Dysmorphic, small ears
- Atresia of middle-ear ossicles, conductive hearing loss
- Down-slanting palpebral fissures, lower eyelid coloboma
- Normal CNS
- Gene: TCOF1 (5q32)
Note on Language

• Not recommended:
  – Funny looking kid
  – Abnormal face
  – Mentally retarded

• Recommended:
  – Noteworthy facial appearance
  – Not a typical face
  – Intellectual deficiency

• “Dysmorphic-appearing” child, ±
Fetal Alcohol Syndrome

• Characteristic face
  – short palpebral fissures
  – flat philtrum, thin upper lip
  – mid-face hypoplasia

Sampson et al., Teratology, 1997
The End