NBDPN Webinar
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DYSMORPHOLOGY &
SYNDROME DELINEATION

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Subjective and Objective
Art and Science
Gestalt and Details
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Looking at faces: A natural instinct

We all look at faces.

Dysmorphology refines a natural instinct to a skill used in clinical genetics.
Aims of Talk

1) Practice the art-science of looking at bodies and faces. Appreciate speech, movement and behavior patterns.

2) Learn specific terms, expand your vocabulary.

3) Enhance your skills in abstracting a physical exam. Understand what might be relevant to a syndrome’s diagnosis (but coding is not discussed).

3) Learning specific syndromes is not the main goal. The ones mentioned can be reviewed later in familiar texts, etc.

What is abnormal?

Study of features: “Dys-” vs. "eumorphology"

Morphology = μορφή (form, shape) + λόγος (study)

“Eumorphology“ = (neologism) study of normal

Dysmorphology = study of abnormal features

With thanks to Dr. Eirini Nestoridi
What is abnormal?

Overlap:
Normal, physical anthropology, aesthetics, dysmorphology

Instead of “abnormal” vs. normal
Think variation, spectrum of physical differences
Instead of “patients”, think persons.
Is there still a role for dysmorphology?

Traditional: From phenotype to genotype
- Look at the face, body (voice, movements)
- Postulate syndrome
- Order tests (e.g., microarray)

New era: Genotype to phenotype
- Chromosome microarray detects imbalances
- Microdeletion/duplications “syndromes” defined

Identify new phenotypes, confirm genotype

Rich tradition: Dysmorphology “family trees”

- David W. Smith
  - Ken Jones
  - Jon Aase
  - John Carey
  - Cynthia Curry
  - Jaime Frias
  - John Graham
  - Bryan Hall
  - Judy Hall
  - Gene Hoyme
  - Jim Hanson
  - Anne Marie Sommers
  - Roger Stevenson
  - Margot Van Allen
  - David Weaver
  - Michael Cohen
- Lewis B. Holmes
- Murray Feingold
- Victor McKusick
- Robin Winter, Dian Donnai
- Alasdair Hunter
- Judith Allanson
- Elaine Zackai
- Robert Gorlin

A partial list!
What to call these features?

Birth defects

Malformations
  Major
  Minor

Anomalies

Congenital birth problems

Congenital physical differences

Approach to anomalies

Types of Problems in Morphogenesis

- Poor formation of tissue
- Unusual forces on normal tissue
- Breakdown of normal tissue
- Abnormal organization of cells in tissue

Malformation or Malformation sequence

Deformation or Deformation sequence

Disruption or Disruption sequence

Dysplasia or Dysplasia sequence
**Specific Anomalies**

**Malformation**

Morphologic defect of an organ or body part  
Intrinsically abnormal early developmental process  
Etiologically heterogeneous, different causes

**Examples**  
Duplex kidney  
Congenital heart defect  
Hemivertebrae

**Specific Anomalies**

**Deformation**

Abnormal form or shape caused by extrinsic forces

**Examples**

1. Plagiocephaly (asymmetric skull), e.g. from “back to sleep” positioning.
2. Compressed ear in a premature baby
Specific Anomalies

Dysplasia
Abnormal organization of cells into tissues

Examples
(1) Polycystic kidney
(2) Inherited connective tissue - Marfan syndrome

Specific Anomalies

Disruption
Defect of organ or region of body
Extrinsic breakdown or interference with normal process

Examples
(1) Amniotic band disruption sequence/spectrum
Specific Anomalies

Disruption (cont.)

(2) Congenital rubella infection

*Terms not mutually exclusive: A disruption (amniotic bands) results in malformations (facial clefts)

Patterns of Defects

Syndrome
Multiple anomalies thought to be pathogenetically related

Examples
Down syndrome (chromosome abnormality)
Achondroplasia (single gene)
Fetal alcohol syndrome (environmental agent)
Patterns of Defects

Association

Nonrandom, *pathogeneticaly unrelated*, multiple anomalies

2 or more individuals, *statistically related*

Not known to be field defect, sequence, or syndrome (may occur within syndrome)

With more knowledge, may become a syndrome
CHARGE “Association” became a syndrome when the *CHD7* gene was discovered

Patterns of Defects

Association (cont.)

Example

VACTERL Association
Vertebral defects
Anus, imperforate Anus
Cardiac
TEF
Renal
Limb

Butterfly vertebrae, hemivertebrae
Result in structural scoliosis
Patterns of Defects

Sequence
Cascade from single known anomaly or mechanical factor

Examples
Pierre Robin sequence
(jaw constraint → micrognathia, glossoptosis, U-shaped cleft palate)

Oligohydramnios sequence
(Potter’s facies)

Patterns of Defects

Field Defect
Derived from the disturbance of a single developmental field

Examples
(1) DiGeorge complex:
3rd and 4th arch derivatives
Mostly deletion 22q11.2

One of Dr. DiGeorge’s patients

22q Support Group 2008 Calendar
Patterns of Defects

Field Defect (cont.)

(2) Holoprosencephaly spectrum

*Terms not mutually exclusive.
DiGeorge complex due to deletion 22q11.2
Truncus arteriosus, thymic/parathyroid aplasia.
Chromosome syndrome AND 4th pharyngeal arch field defect

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Frequency of Anomalies

<table>
<thead>
<tr>
<th></th>
<th>Newborn: 15 - 40%</th>
<th>2 - 4%</th>
<th>10 yrs: 6-8%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 minor</td>
<td>1 major</td>
<td>1 major</td>
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</table>

Risk of major malformation in baby with 3 minor ones

- 20% Lew Holmes
- 90% David Smith

"Judge an anomaly by the company it keeps"

Significance of anomalies: Indicators of altered morphogenesis, i.e. first 8 weeks gestation
Syndrome Delineation

1. Individual: Provisionally unique syndrome.
3. Several patients: Case series.
4. Define phenotype: Core features, severity spectrum “The syndrome” and syndrome-like
5. Determine etiology: Chromosome, gene defect, environmental agent, multifactorial
6. Correlate phenotype/genotype, karyotype

Signs & Syndromes: Discourage Old Terms

- Food: Peau d’orange (skin)
  Salt and pepper (hair)
  Tea colored (urine), Milky (plasma)
  Café au lait (hyperpigmented macule)
  Pea/grape/egg/grapefruit (size of lump)
- Animals: Cat-eye syndrome (tetrasomy 22q, trisomy 22q)
  Cri-du-chat syndrome (deletion 5p)
  LEOPARD syndrome (Noonan with multiple lentigines)
- Misc: 
  Michelin tire baby (familial constriction rings)
  Mongoloid, -ism (Down syndrome)
  Coeur en sabot (tetralogy of Fallot)
  Crepe paper, cigarette rolling paper (skin)
  Ash leaf (macule)
  Shagreen ( verrucous papule)
  Coast of Maine, of California (CLS)

Archaic, discouraged
Dysmorphology: Definitions

Elements of Morphology: Introduction

Judith E. Allanson, Leslie G. Biesecker, John C. Carey, and Raoul C.M. Hennekam

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Received 4 September 2008; Accepted 19 September 2008

An international group of clinicians working in the field of dysmorphology has initiated the standardization of terms used to describe human morphology. The goals are to standardize these terms and reach consensus regarding their definitions. In this way, we will increase the utility of descriptions of the human phenotype and facilitate reliable comparisons of findings among patients. Discussions with other workers in dysmorphology and related fields, such as developmental biology and molecular


http://elementsofmorphology.nih.gov/
**Dysmorphology Exam: Overall**

- Stooped posture
- Mild contractures
- Multiple flexion contractures
- Webbing of neck
- Positional deformities of lower extremities

**How would you describe this 9 month old?**

- Healthy appearing
  - (very cute!)
- Down syndrome
- Facial features:
  - Flat face
  - Small eyes
  - Small nose
  - Protruding tongue
- Short forearms?
- Hypotonic:
  - Open mouth
  - Neck tilt
  - Not sitting
The Face Changes with Time

Down syndrome  Turner syndrome  VCFS syndrome
Deletion 22q11

Lin et al., Genetics in Medicine, 2008

The Face Changes with Time

Williams syndrome  Noonan syndrome

Lin et al., Genetics in Medicine, 2008
The “Gestalt” is Influenced by Presentation

Sotos syndrome. Jones’ “Smith’s Recognizable Patterns of Malformations, 2006

The Face Changes with Treatment

Severe FTT, coarse face (thick lips), hypotonia, rectal prolapse

Congenital hypothyroidism, treated.

Courtesy of Susan Nagele, MD
Specific features: Head

- **Macrocephaly**
  - High forehead
  - Elongated face
  - Small chin
  - (Sotos syndrome)

- **Microcephaly**
  - Apparently large ears
  - Face not dysmorphic
  - (no syndrome)

- **Microcephaly**
  - Dysmorphic
  - (Seckel syndrome)

Head

- **Brachycephaly**
  - Coronal craniosynostosis
  - High forehead
  - Exorbitism
  - Maternal inheritance
  - (Crouzon syndrome)

- **Plagiocephaly**
  - Non-synostotic

- **Elongated face**
  - Non-synostotic
  - (Marfan syndrome)
Face: Asymmetry

Asymmetric crying face

CHARGE Syndrome
www.chargesyndrome.org

Cranial nerve 7 palsy
CHARGE syndrome

Face: Asymmetry

Asymmetric lower face

Branchio-oculo-facial Syndrome:
Acquired: Hemiatrophy: Romberg-Parry syndrome
(atrophic left side in both)
Neck

- Short Webbing
- Loose skin (Turner syndrome)
- Short Webbing
- Prominent trapezius muscle (Noonan syndrome)


Skin

- Diffuse erythematous papules (Congenital rubella)
- Keloid (Noonan syndrome)
- Capillary malformation, “stork bite”
- Hemangioma
**Skin**

Lentigines
Noonan syndrome with
Multiple lentigines, “LEOPARD”

Neurofibromatosis, Type I:
Café au lait macule (CALM)

GeneReviews.org

**Ears**

Pinna landmarks

Overfolded helices

Down syndrome
Small ears

Lobule creases
Ears

- Low-set, posteriorly rotated
- Anotia
- Severe microtia
- Microtia
- Mycophenolate mofetil (Cellcept)
- Microtia, dysplastic ear

Eyes

- Asian epicanthal fold
- Asian upslanting palpebral fissure
- Epicanthal folds, upslanted eyes
  (Down syndrome)
- Blue sclera
  (Osteogenesis imperfecta)
Eyes

- Iris coloboma
- Epibulbar dermoid
- Heterochromia irides
- Anophthalmia
- Synophrys (Brachmann-de Lange syndrome, Non syndromic)

Eyes

- Ptosis
- Hypertelorism (increased interpupillary distance)
- Subjective, hypotelorism
Nose

Short, upturned nares (Above: Deletion 4q) (Below: Opitz G)
Bulbous, pear-shaped Tricho-rhino-phalangeal (TRPS) syndrome
Prominent glabella (Deletion 4p, "Greek warrior helmet")

Mouth: Elements of Morphology, AJMG 2009
Sample of how one facial region is presented

Anatomy of the Lips, Mouth, and Oral Region
The appearance of the lips varies with facial movement. Smiling and crying can alter dramatically the shape of the upper lip, as do pursing or pouting. Therefore, the lips must be assessed when the subject has a relaxed (neutral) face: the eyes are open, the lips make gentle contact, and the teeth are slightly separated. The neck, jaw, and facial muscles should not be stretched nor contracted, and the face should be positioned using the Frankfurt horizontal (a line joining the orbitale and the porion) [Farkas, [1981]].

Uvula: A conical projection of soft tissue extending inferiorly from the posterior edge of the middle of the soft palate.
Mouth

“Carp-shaped” mouth
(Deletion 4p)

Inverted triangle, hypotonic
(ATR-X syndrome)

Open mouth, hypotonic
(no diagnosis)

Mouth

Smooth philtrum
Thin upper lip
(Fetal alcohol syndrome)
Lower face

- Cleft lip
- Chin dimple
- Micrognathia

Different types of malocclusion

Chest

- Pectus excavatum (Nonsyndromic)

Pectus:
- Superior carinatum
- Inferior excavatum
  (Noonan syndrome)

NEJM, 2008;359
Chest

Bell-shaped
Small thorax,
Skeletal dysplasias
(Osteogenesis imperfecta)

Apparently wide-spaced nipples
(Turner syndrome)

Back

Kyphosis
www.spineuniverse.com

Scoliosis
**Arms**

- **Cubitus valgus** (Turner syndrome)

- **Joint laxity, wrist**
  (Ehlers-Danlos syndrome, Other connective tissue disorders)

- **Absent radii, absent thumbs**
  (Holt-Oram syndrome)

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**Hands: Extra digits**

“I thought of Miss Slocum: She possessed an arresting defect: vestigial thumbs that were attached to the outside of her normal thumbs. Why, in God’s name, asked my father, hadn’t she had she had them removed?”

*A Tidewater Morning*  
William Styron

- **Polydactyly, postaxial**
  (Ellis-van Creveld syndrome, Trisomy 13)
Fingers

- Tapered (22q11 deletion, mother, son)
- Absent fingers (4q32 deletion)
- Arachnodactyly (Marfan syndrome)

Hands: Palmar creases

- Short 5th fingers "Hockey stick" transverse crease (Brachydactyly type A3?)
- Brachydactyly Single transverse crease (11q deletion, Jacobsen syndrome)
- 5th finger clinodactyly (trisomy 21, Down syndrome)
### Nails

Hypoplastic nails

- Fryns syndrome
- Trisomy 18
- Adams-Oliver syndrome

### Legs

- Clubfeet

- Lordosis
- Bowing
  (Schmid metaphyseal dysplasia)

[source](newborns.stanford.edu/PhotoGallery/ClubFeet1.html)
**Feet, Toes**

- Arachnodactyly
- Pes planus (Marfan syndrome)
- Macrodactyly
- Pedal edema (Turner syndrome)
- Postaxial polydactyly, type A
- Trisomy 13
- Ellis-van Creveld syndrome

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**Genitalia, male**

Hypospadias
### PHENOTYPES: Beyond face and body

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior</td>
<td>Williams syndrome</td>
</tr>
<tr>
<td></td>
<td>Prader-Willi syndrome</td>
</tr>
<tr>
<td>Voice, speech</td>
<td>Williams syndrome</td>
</tr>
<tr>
<td></td>
<td>Down syndrome</td>
</tr>
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<td></td>
<td>Fragile X syndrome</td>
</tr>
<tr>
<td>Psychologic</td>
<td>Fragile X syndrome</td>
</tr>
<tr>
<td>Movement</td>
<td>Rett syndrome</td>
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</table>

### TEST YOUR DYSMORPHOLOGY SKILLS

<table>
<thead>
<tr>
<th>Feature</th>
<th>Opitz G syndrome characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face shape</td>
<td>Squarish</td>
</tr>
<tr>
<td>Forehead</td>
<td>Metopic fontanelle</td>
</tr>
<tr>
<td></td>
<td>High forehead</td>
</tr>
<tr>
<td>Brows</td>
<td>Sparse eyebrows</td>
</tr>
<tr>
<td>Eyes</td>
<td>Hypertelorism</td>
</tr>
<tr>
<td></td>
<td>Telecanthus</td>
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<tr>
<td></td>
<td>Epicanthal folds</td>
</tr>
<tr>
<td>Nose</td>
<td>Short nose</td>
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<td></td>
<td>Anteverted nares</td>
</tr>
<tr>
<td>Mouth</td>
<td>Flat philtrum</td>
</tr>
<tr>
<td></td>
<td>Thin lips</td>
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