NBDPN Webinar
March 31, 2011

DYSMORPHOLOGY & SYNDROME DELINEATION

Angela E. Lin, MD, FAAP, FACMG
Associate Clinical Professor in Pediatrics, Harvard Medical School
Genetics Unit, MassGeneral Hospital for Children, Boston, MA
Consultant, MA Birth Defects Monitoring Program, MA for Center Birth Defect Research and Prevention

☯☯ ☯☯

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

What is abnormal?

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
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

<table>
<thead>
<tr>
<th>Arachnodactyly</th>
<th>Lens dislocation</th>
<th>Narrow, high palate</th>
</tr>
</thead>
</table>

**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, *pathogenetically 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
CHASE “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

Patterns of Defects

Frequency of Anomalies

<table>
<thead>
<tr>
<th></th>
<th>Newborn: 15 - 40%</th>
<th>1 minor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 - 4%</td>
<td>1 major</td>
</tr>
<tr>
<td>10 yrs:</td>
<td>6-8%</td>
<td>1 major</td>
</tr>
</tbody>
</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.
2. **Single family**: Private 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,1 Leslie G. Blieseker,2 John C. Carey,3 and Raoul C.M. Hennekam4,5,*

1Department of Genetics, Children’s Hospital of Eastern Ontario, Ottawa, Canada
2National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland
3Division of Medical Genetics, Department of Pediatrics, University of Utah, Salt Lake City, Utah
4Clinical and Molecular Genetics Unit, Institute of Child Health, Great Ormond Street Hospital for Children, UCL, London, UK
5Department of Paediatrics, Academic Medical Center, UVA, Amsterdam, The Netherlands

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

How to Cite this Article:
Allanson JE, Blieseker Lg, Carey JC, Hennekam RCM. 2009. Elements of

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
- Dyshomorphic
  (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

**Asymmetric lower face**

Cranial nerve 7 palsy

**CHARGE Syndrome**

www.chargesyndrome.org

**Hemiatrophy: Romberg-Parry syndrome**
(atrophic left side in both)

**Face: Asymmetry**

Branchio-ocular-facial Syndrome: Asymmetric lower face

ACQUIRED:

Hemiatrophy: Romberg-Parry syndrome
**Neck**

- Short Webbing
- Loose skin
  (Turner syndrome)

- Short Webbing
- Prominent trapezius muscle
  (Noonan syndrome)


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**Skin**

- Diffuse erythematous papules
  (Congenital rubella)

- Capillary malformation, “stork bite”

- Keloid (Noonan syndrome)

- Hemangioma
Skin

Lentigines
Noonan syndrome with Multiple lentigines, “LEOPARD”

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

GeneReviews.org

Ears

Pinna landmarks

Overfolded helices

Lobule creases

Down syndrome
Small ears
### 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  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.

- Uvula, Absent
- Uvula, Bifid: See Uvula, Cleft
- Uvula, Broad
- Uvula, Cleft
- Uvula, Hypoplastic: See Uvula, Short
- Uvula, Long
- Uvula, Narrow
- Uvula, Short
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)

**Hands: Extra digits**

“I though 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 fingers (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)

newborns.stanford.edu/PhotoGallery/ClubFeet1.html
Feet, Toes

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

Genitalia, male

- Hypospadias

Source: Adv Neonatal Care © 2004 W.B. Saunders
## PHENOTYPES: Beyond face and body

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Williams syndrome</th>
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<tbody>
<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>
<tr>
<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>
</tr>
</tbody>
</table>

## TEST YOUR DYSMORPHOLOGY SKILLS

![Opitz G syndrome]

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