An approach to dysmorphology for the fellowship paediatric examination (Australia)

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Why bother – don’t we all just do an exome now?
Detailed phenotyping improves the diagnostic yield of genomic testing

• Why does exome sequencing not get an answer

Technological limitations
(noncoding or expansion mutations, incomplete coverage, uniparental disomy, large indels, chromosomal rearrangements, and copy-number variants)

Unknown gene-disease associations

More complex genetics (polygenic, epigenetic, multi-factorial,... Non-genetic – yes it happens!!!!)

Reanalysis of exome data win collaboration with referring physician can boost diagnosis by ~12%
(Salmon et al. 2018)
And it might just help you describe new genetic conditions for your patients!
De Novo Variants Disrupting the HX Repeat Motif of ATN1 Cause a Recognizable Non-Progressive Neurocognitive Syndrome

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• **RLIM** is a candidate dosage sensitive gene for individuals with varying duplications of Xq13, intellectual disability and recognizable facial features

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Dys (disordered) morph (shape, form)

• Try and study and attempt to interpret patterns of human growth and structural defects

• **Malformation** (an intrinsic developmental anomaly, e.g., spina bifida),

• **Disruption** (an event disrupting intrinsically normal development, e.g., amniotic bands),

• **Deformation** (an external force altering the shape of development, e.g., face shape due to severe oligohydramnios) and

• **Dysplasia** (abnormal growth and maturation of cells, e.g., achondroplasia).

• **Syndrome** ”a recognizable pattern of dysmorphic signs that have a common cause”
Dysmorphology is just part of the puzzle

- 3 generation pedigree

- Look at the parents and sibs – ideally parent baby/child photos

- What is the pattern of functional/ congenital anomalies

- First line tests ... [ now will be CMA and exome ]
Terminology is important

• We are all dysmorphic to some extent
• Be gentle
• ‘distinctive’ ...
• ‘features that are unique to them/not similar to the rest of the family’
Some good resources

Elements of Morphology: Standard Terminology for the .... (ACMG series: Allanson et al....2009)
An approach ... with thanks to Noe

A) General inspection

A1) Growth

• HC
• Length/ Height
• Weight
• BMI

• Centiles
• Mid parental height
Short and tall stature

• Q? Proportionate or not proportionate. Compare to siblings. Pre or post natal onset
• Short stature: non proportionate
  • Consider skeletal dysplasia

**MANY** chromosomal and single gene neurodevelopmental genetic disorders affect growth
**Tall:** Marfan, Homocystinuria, Klinefelters, Sotos

- [https://info.marfan.org/](https://info.marfan.org/)
- Diagnostic criteria
  - An *FBN1* pathogenic variant known to be associated with Marfan syndrome AND one of the following:
    - Aortic root enlargement (Z-score ≥2.0)
    - Ectopia lentis
  - Demonstration of aortic root enlargement (Z-score ≥2.0) and ectopia lentis OR a defined combination of features throughout the body yielding a systemic score ≥7

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### CALCULATION OF SYSTEMIC SCORE

<table>
<thead>
<tr>
<th>SYSTEMIC CALCULATOR</th>
<th>Value</th>
<th>Click to Include</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Z-Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARMD AND Thumb sign</td>
<td>+ 3</td>
<td>☐</td>
</tr>
<tr>
<td>West OR thumb sign</td>
<td>+ 1</td>
<td>☐</td>
</tr>
<tr>
<td><strong>TESTING INFO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pectus Carinatum Deformity</td>
<td>+ 2</td>
<td>☐</td>
</tr>
<tr>
<td>Pectus Excavatum or Chest Asymmetry</td>
<td>+ 1</td>
<td>☐</td>
</tr>
<tr>
<td><strong>SOMATIC DIAGNOSIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hindfoot Deformity</td>
<td>+ 2</td>
<td>☐</td>
</tr>
<tr>
<td>Main Flat Foot</td>
<td>+ 1</td>
<td>☐</td>
</tr>
<tr>
<td><strong>RELATED DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous Pneumothorax</td>
<td>+ 2</td>
<td>☐</td>
</tr>
<tr>
<td>Dental Ectasia</td>
<td>+ 2</td>
<td>☐</td>
</tr>
<tr>
<td>Protusos Acluelum</td>
<td>+ 2</td>
<td>☐</td>
</tr>
<tr>
<td>Scoliosis or Thoracolumbar Kyphosis</td>
<td>+ 1</td>
<td>☐</td>
</tr>
<tr>
<td>Reduced Elbow Extension</td>
<td>+ 1</td>
<td>☐</td>
</tr>
<tr>
<td>3 of 5 Facial Features</td>
<td>+ 1</td>
<td>☐</td>
</tr>
<tr>
<td>Skin Striae</td>
<td>+ 1</td>
<td>☐</td>
</tr>
<tr>
<td>Severe Myopia</td>
<td>+ 1</td>
<td>☐</td>
</tr>
<tr>
<td>Mitral Valve Prolapse</td>
<td>+ 1</td>
<td>☐</td>
</tr>
<tr>
<td>Reduced Upper Segment / Lower Segment &amp; Increased Arm span / Height</td>
<td>+ 0</td>
<td>☐</td>
</tr>
</tbody>
</table>

*A score of ≥ 7 is considered a positive systemic score.*
Obesity: Prader-Willi, Bardet-Biedl

- Hypotonia
- Hypogonadism
- Hyperphagia
- Cognitive impairment; difficult behaviours

Typical facial features; these are often subtle and are not always present. Features include deeply set eyes, widely spaced eyes, downslanted palpebral fissures, a depressed nasal bridge, small mouth, malar flattening, e. Brachydactyly and scars from excision of accessory digits f. Dental crowding g. High palate

h. Fundoscopy demonstrating rod-cone dystrophy
Development, characteristic behaviours/autistic features

• Rett syndrome – Clinical findings
  • Most distinguishing finding: A period of regression (range: ages 1-4 years) followed by recovery or stabilization (range: ages 2-10 years; mean: age 5 years)
  • Main findings
    • Partial or complete loss of acquired purposeful hand skills
    • Partial or complete loss of acquired spoken language or language skill (e.g., babble)
    • Gait abnormalities: impaired (dyspraxic) or absence of ability
    • Stereotypic hand movements including hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms
  • Supportive findings
    • Breathing disturbances when awake
    • Bruxism when awake
    • Impaired sleep pattern
    • Abnormal muscle tone
    • Peripheral vasomotor disturbances
    • Scoliosis/kyphosis
    • Growth retardation
    • Small, cold hands and feet
    • Inappropriate laughing/screaming spells
    • Diminished response to pain
    • Intense eye communication - “eye pointing”

Fragile X syndrome: autistic features
  • Gaze avoidance very common, flapping hands, hyperactivity,
Head

- Head circumference
- Shape
- Craniosynostosis - 0.5-3.4%
  - Sagittal 50% (dolicocephaly)
  - Coronal 22% (brachycephaly)
  - Metopic 6% (trigonencephaly)
  - Look at hands
- Fontanelles –
  - Size and time of closure
- Radiology-
  - sutures
  - Thick/thin/hyperostosis

<table>
<thead>
<tr>
<th>Head: size, shape, fontanelles, sutures, hair (quality, quantity), position of hairline</th>
<th>Craniosynostosis syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face: shape, symmetry, forehead</td>
<td>Alagille’s</td>
</tr>
</tbody>
</table>

Craniosynostosis syndromes are conditions where one or more of the cranial sutures fuse prematurely, leading to abnormal skull shape and growth. Common craniosynostosis syndromes include Apert syndrome, Crouzon syndrome, Pfeiffer syndrome, and Saethre-Chotzen syndrome. Each syndrome is characterized by specific craniofacial features and may also be associated with other medical conditions.
Ears

- Microtia/Anotia
- Macrota
- Shape
- Position
- Configuration
- Auricular tag
- Pits
- Creases
- Hearing!

Low set ears

**Definition**: Upper insertion of the ear to the scalp below an imaginary horizontal passing through the inner canthi and extend that line posteriorly to the ear.

Deafness: Goldenhar, CHARGE, Waardenburg, Treacher Collins, Alport, NF-2, BOR, GJB2 (connexin 26), Jervell and Lange Nielsen, Alport
Nose

- size,
- shape,
- nasal bridge,
- tip,
- nostrils,
- philtrum

Fetal exposure to alcohol during the first trimester affects development of facial features. A range of facial anomalies can occur as result of prenatal alcohol exposure. There are three features which commonly occur across age, gender and ethnic groups:

- Small palpebral fissures: short horizontal length of the eye opening, defined as the distance from the endocanthion to the exocanthion (points A and B on photo below)
- Smooth philtrum: diminished or absent ridges between the upper lip and nose
- Thin upper lip: with small volume

Eyes

Telecanthus – increased distance between inner canthus - varies with ethnicity

Critically – is the intrapupillary distance increased or not

Hypertelorism - widely spaced eyes - increased intrapupillary distance
Mouth

- mouth,
- jaw,
- lips,
- teeth,
- palate,
- tongue,
- uvula,
- midline defects

Cleft lip/palate: 22q11 deletion, Stickler

Approx 50% of cleft lip/palate will have other anomalies
- isolated CP (30%)
- isolated CL (11%)
- CLP (9%)

Recurrence risk depends on family history and type:

Non syndromal cleft palate (CP)
- One affected child RR 2%
- One affected parent RR 6%
- One affected parent and one affected child RR 15%

Non syndromal Cleft lip and palate
- One affected child RR 4%
- One affected parent RR 4%
- One affected parent and one affected child RR 10%
Mandible

- Agnathia
- +/- holoprosencephaly
- Micrognathia –
- associated with > 130 syndromes
- >47 chromosomal abnormalities
- Contribution to sequence, e.g. Pierre Robin
- Retrognathia
- Normal size and shape - posteriorly positioned jaw
**Limbs**

**Hands:** shape, size, symmetry, nails, finger length and shape, palmar creases

**Length:** –brachdactyly/arachnodactyly

**Digits:**
- oligodactyly
- polydactyly
- clinodactyly
- syndactyly

**Arms:** segment proportions, asymmetry, joint hypermobility

Marfan, Ehler Danlos, Beckwith-Wiedemann
Joint hypermobility scale (Beighton)

https://www.ehlers-danlos.com/assessing-joint-hypermobility/

- (A) With the palm of the hand and forearm resting on a flat surface with the elbow flexed at 90°, if the metacarpal-phalangeal joint of the fifth finger can be hyperextended more than 90° with respect to the dorsum of the hand, it is considered positive, scoring 1 point.

- (B) With arms outstretched forward but hand pronated, if the thumb can be passively moved to touch the ipsilateral forearm it is considered positive scoring 1 point.

- (C) With the arms outstretched to the side and hand supine, if the elbow extends more than 10°, it is considered positive scoring 1 point.

- (D) While standing, with knees locked in genu recurvatum, if the knee extends more than 10°, it is considered positive scoring 1 point.

- (E) With knees locked straight and feet together, if the patient can bend forward to place the total palm of both hands flat on the floor just in front of the feet, it is considered positive scoring 1 point.

Hypermobility EDS requires three criteria to be met
- Generalized joint hypermobility (Criterion 1)
- Evidence of syndromic features, musculoskeletal complications, and/or family history (Criterion 2)*
- Exclusion of alternative diagnoses (Criterion 3)#

Must do an echo to look at aortic root size
Repeat 3-5 years if N to late teens

- Management: low impact exercise, physical therapy, splints/supports/pen/pencil accommodations (OT)/GI/yoga/meditation/family therapy/pain therapy

≥6 for prepubertal children
≥5 for pubertal children and adults up to age 50
≥4 for those age >50 years

*musculoskeletal pain, joint dislocations/instability
# e.g. skin fragility, atrophic scaring, vascular findings,Stickler, Williams, aortic enlargement
Skin

Skin: scars, neurocutaneous stigmata, pigmentation

Café-au-lait macules: NF-1, Fanconi Anemia, McCune-Albright Hypopigmentation: Tuberous sclerosis

Tuberous sclerosis diagnostic criteria

Major features
- Angiofibromas (≥3) or fibrous cephalic plaque
- Cardiac rhabdomyoma
- Cortical dysplasias, including tubers and cerebral white matter migration lines
- Hypomelanotic macules (3 to >5 mm in diameter)
- Lymphangioleiomyomatosis (LAM) Multiple retinal nodular hamartomas
- Renal angiomyolipoma (Shagreen patch)
- Subependymal giant cell astrocytoma (SEGA)
- Subependymal nodules (SENGs)
- Ungual fibromas (≥2)

Minor features
- “Confetti” skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs)
- Dental enamel pits (>3)
- Intraoral fibromas (≥2)
- Multiple renal cysts
- Nonrenal hamartomas
- Retinal achromic patch

Neurofibromatosis 1 (NF1) should be suspected in individuals who have any of the following findings:

Six or more café au lait macules (Figure 1) >5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals
Two or more neurofibromas (Figure 2) of any type or one plexiform neurofibroma (Figure 3)
Freckling in the axillary or inguinal regions
Optic glioma
Two or more Lisch nodules (iris hamartomas)
A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis
A first-degree relative (parent, sib, or offspring) with NF1 as defined by the above criteria
<table>
<thead>
<tr>
<th>Torso</th>
<th>Noonan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck: webbing, skin folds</td>
<td>Noonan</td>
</tr>
<tr>
<td>Back/chest: spine (scoliosis, surgery, stature), sternum, chest, nipples, heart sounds</td>
<td>Klippel Feil                  Congenital cardiac malformations in various syndromes (partly also covered in cardiology)</td>
</tr>
<tr>
<td>Abdomen: organomegaly, scars, hernia</td>
<td></td>
</tr>
<tr>
<td>Lower limbs and feet</td>
<td></td>
</tr>
<tr>
<td>Legs: segment proportions, asymmetry, hypermobility</td>
<td>Beckwith-Wiedemann</td>
</tr>
<tr>
<td>Feet: nails, toes, webbing, foot size and shape (flat, curved, symmetry)</td>
<td>Syndactyly</td>
</tr>
<tr>
<td>Genitalia</td>
<td></td>
</tr>
<tr>
<td>Phallus, scrotum, testes (size and development), labia, puberty</td>
<td>Pubertal delay: Turner, Klinefelter</td>
</tr>
<tr>
<td>Anus: position/perforate</td>
<td>VACTERL</td>
</tr>
</tbody>
</table>
SELECTED GENETIC DISEASES WITH DYSMORPHIC FEATURES

- For the conditions listed below: features on examination/dysmorphic features; where applicable - diagnosis, treatment, prognosis for the condition.
  - Alagille syndrome
  - Disorders of chromosomal duplication or deletion, such as cri-du-chat syndrome
  - Duchenne and Becker muscular dystrophy (DMD) – also covered in neurology
  - Fragile X syndrome (FXS)
  - Genetic imprinting disorders:
    - Angelman syndrome
    - Beckwith–Wiedemann syndrome
    - Prader–Willi syndrome
  - Genetic disorders with neurological features (also covered in neurology)
    - Ataxia telangiectasia
    - Charcot–Marie–Tooth disease
    - Huntington disease
    - Rett syndrome
    - tuberous sclerosis
  - Genetic disorders of growth and musculoskeletal development
    - achondroplasia
    - Treacher Collins syndrome
    - Klinefelter syndrome
    - Marfan syndrome
  - Microarray abnormalities:
    - 15q11.2 deletion
    - 16p11.2 deletion or duplication
    - 22q11.2 deletion or duplication
  - Myotonic dystrophy (also covered in neurology)
  - Neurofibromatosis type 1 (NF1) and type 2 (NF2)
  - Noonan syndrome (NS)
  - Osteogenesis imperfecta (OI)
  - Trisomy 13, 18, 21
  - Turner syndrome
  - Williams syndrome
• Moving into the frontier technology age
.... Facial recognition software