Random Pearls in Dysmorphology and Genetics

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Random Pearls in Dysmorphology in Genetics
Evolution of Diagnostic Criteria

- Berlin nosology 1986
  - Beighton et al.

- FBN1 identified 1991

- Ghent criteria 1996

Original Ghent Criteria

major criteria in 2 systems + involvement of 3rd

<table>
<thead>
<tr>
<th>System</th>
<th>Major</th>
<th>Minor</th>
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<tbody>
<tr>
<td>Skeletal system</td>
<td>Reduced cone or bowl-shaped anterior chamber</td>
<td>Enlarged sella turcica</td>
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<td></td>
<td>Hypoplastic or aplastic ribs</td>
<td>Hypoplastic ribs</td>
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<td></td>
<td>Sacroiliac joint fusion</td>
<td>Coccygeal vertebrae</td>
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<td></td>
<td>Midsagittal suture or lambdoid suture</td>
<td>Hypoplastic clavicle</td>
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<td></td>
<td>Metatarsus adductus</td>
<td>Hypoplastic renal collecting system</td>
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<td></td>
<td>Tricuspid valve dysplasia</td>
<td>Hypoplastic or aplastic ductus arteriosus</td>
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<td>Pulmonary artery stenosis</td>
<td>Hypoplastic interatrial septum</td>
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<tr>
<td></td>
<td>Persistent truncus arteriosus</td>
<td>Persistent truncus arteriosus</td>
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<tr>
<td></td>
<td>Upper lip notched or single</td>
<td>Patent ductus arteriosus</td>
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<tr>
<td></td>
<td>Palatine cleft</td>
<td>Patent ductus arteriosus</td>
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<td></td>
<td>Cardiac septal defects</td>
<td>Patent ductus arteriosus</td>
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<td></td>
<td>Mitral valve prolapse</td>
<td>Patent ductus arteriosus</td>
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<tr>
<td></td>
<td>Aortic dissection or rupture</td>
<td>Patent ductus arteriosus</td>
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<tr>
<td></td>
<td>Pneumothorax or spontaneous pneumothorax</td>
<td>Patent ductus arteriosus</td>
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<tr>
<td></td>
<td>Pulmonary hypertension</td>
<td>Patent ductus arteriosus</td>
</tr>
<tr>
<td></td>
<td>Bronchial stenosis</td>
<td>Patent ductus arteriosus</td>
</tr>
<tr>
<td></td>
<td>Persistent tricuspid stenosis</td>
<td>Patent ductus arteriosus</td>
</tr>
<tr>
<td></td>
<td>Tricuspid valve regurgitation</td>
<td>Patent ductus arteriosus</td>
</tr>
<tr>
<td></td>
<td>Pulmonary valve regurgitation</td>
<td>Patent ductus arteriosus</td>
</tr>
</tbody>
</table>

For the cardiovascular system to be involved, a major criterion or any one of the minor criteria must be present.
Revised Ghent Criteria
Loeys BL, et al.

• Criteria in absence of family history
  – Ao (Z ≥ 2) + ectopia lentis
  – Ao (Z ≥ 2) + FBN1 mutation
  – Ao (Z ≥ 2) + systemic features (≥ 7 points)
  – Ectopia lentis + FBN1 mutation with known aortic involvement

Ao = aortic diameter above indicated Z score or aortic dissection

https://www.marfan.org/dx/score

Positive wrist and thumb  3
Positive wrist or thumb  1
Pectus carinatum          2
Pectus excavatum/asymmetry 1
Hindfoot deformity        2
Flat feet                  1
Spontaneous pneumothorax  2
Dural ectasia             2
Protrusio acetabulae     2
Scoliosis/kyphosis        1
Reduced elbow extension   1
3 of 5 facial features    1
Skin striae               1
Severe myopia             1
Mitral valve prolapse     1
Reduced U/L segment ratio & Increased span to height 1
Upper/lower segment ratio

- Measure height
- Measure lower segment
  - Top of symphysis to heel
- Derive upper segment
- Measure span
- Divide

- www.marfan.org/dx/score

Special case for young children

- Systemic features are age related
- Hypotonia
- Contractures
- Joint laxity
- Motor delays
Management of Marfan syndrome

- Ophthalmologic follow up
  - Avoid LASIK
- Cardiac follow up
  - No competitive sports
  - Beta blockers
  - Losartan
  - Elective replacement aortic root
  - Avoid decongestants and caffeine
- Orthotics

Other diagnoses

- Loeys-Dietz syndrome
- Vascular Ehlers-Danlos
- Shprintzen-Goldberg
- Familial thoracic aortic aneurysms
- Homocystinuria
- Stickler syndrome
- Fragile X
Content of the Human Genome

- 46 chromosomes (23 pairs)
  - 1956
- 20-25,000 protein coding genes
  - disease causing mutation in ~5000
- 3+ billion base pairs (A,G,T,C)
  - 16569 mitochondrial
  - double helix 1953
  - draft of sequence June 2000
  - completed sequence Spring 2003
- First Genome Sequenced 2007

Packaging Problems

- Aneuploidy
- Translocation
- Deletion
- Duplication
- Inversions
- Markers
Random Pearls in Dysmorphology in Genetics

Chromosomes

Fluorescence in-situ hybridization

Fluorescence In-Situ Hybridization (FISH)
Comparative Genomic Hybridization Array

- Coding/non-coding regions
- 1:1000 to 1:100-300 base pairs
- SNP close to gene is marker for gene
- SNP in coding region may alter protein structure

Single Nucleotide Polymorphism
CGH-SNP Array

- Copy number abnormalities
- Identity by descent
- Consanguinity
- Incest
- Uniparental disomy

Sanger sequencing
**Issues with Genome Sequencing**

- Patient autonomy
  - Right to know or not
  - Adult vs. Children
- Laboratory: NOT
  - Structural variants
  - Repeat expansion
  - Copy number variants
  - Imprinting abnormalities

Issues with Genome Sequencing

- Pathogenic findings
- Incidental findings
- Laboratory
  - Point mutations
  - Small insertions/deletions
- VUS

Variants of Uncertain Significance (VUS)

- Evaluate in context of family history
- Test other family members
- Review literature relative to gene function

Direct to Consumer Testing

- Traits
- Carrier screening
- Wellness
- Ancestry
  - Validated
  - FDA approved
  - Exploring pharmacogenomics

- Interpretome
- GeneticGenie
- Promethease

MTHFR

Two common polymorphisms

- c.665C>T (C677T)
  >25% Hispanics
  10-15% Caucasians
- c.1286A>C
MTHFR

- Do not order genotyping
- If known homozygote, fasting homocysteine
- If homocysteine is normal, reassure
- If elevated, suggest a multivitamin


Question

Chromosomal microarrays have obviated the need to do chromosome testing

- True
- False
Question

Whole exome sequencing can detect triplet repeat and methylation abnormalities

– True
– False

Thank You!

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