Chromosome Syndromes associated with Congenital Heart Defects

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THE HEART AS DYSMORPHIC FEATURE

Fetus or child with multiple congenital anomalies

Face: Eyes, shape, nose, mouth → Facies?

Body parts: Proportion, number and size → Habitus?

CHD (common or distinctive) → Cardiac phenotype?

Distinctive face, body, heart, other malformations, voice, behavior, growth → Syndrome
CHDs: INDIVIDUALS vs. FAMILIES

ASD  VSD  PDA  HLHS  AVC  DORV  COA  TGA  TA  TA  MA  PA  AA  IAA

vs.

“EARLY” Development
1. Laterality defects, situs, heterotaxy
   Looping, complex single ventricle
2. Conotruncal, aortic arch
3. Atrioventricular canal
4. Some VSDs (conoventricular), ASDs (primum type)

“LATER”
5. Right and left heart obstruction, Ebstein
6. Most VSDs, ASDs
7. Anomalous pulmonary venous return
OBJECTIVES FOR TALK

• Trade-off: Scope over detail
  (a little about many, rather than a lot about a few)

• Learn common syndromes, or distinctive ones

• Learn associated CHDs, when possible, patterns and CHD “families”

• Focus on phenotype (appearance) rather than performance, growth, development, associated diseases

• Focus on one or two “take home” message for each
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASD</td>
<td>atrial septal defect</td>
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<tr>
<td>AVC</td>
<td>atrioventricular canal</td>
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<tr>
<td>AVSD</td>
<td>atrioventricular septal defect</td>
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<tr>
<td>BAV</td>
<td>bicuspid aortic valve</td>
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<tr>
<td>CHD</td>
<td>congenital heart defect</td>
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<tr>
<td>COA</td>
<td>coarctation</td>
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<tr>
<td>DORV</td>
<td>double outlet right ventricle</td>
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<td>HLHS</td>
<td>hypoplastic left heart syndrome</td>
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<tr>
<td>IAA,B</td>
<td>interrupted aortic arch, type B</td>
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<tr>
<td>LVOTO</td>
<td>left ventricular outflow tract obstruction</td>
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<tr>
<td>PA</td>
<td>pulmonary atresia</td>
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<tr>
<td>PDA</td>
<td>patent ductus arteriosus</td>
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<tr>
<td>PS</td>
<td>pulmonary stenosis</td>
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<tr>
<td>RVOTO</td>
<td>right ventricular outflow tract obstruction</td>
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<tr>
<td>SI</td>
<td>situs inversus</td>
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<tr>
<td>SV</td>
<td>single ventricle</td>
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<tr>
<td>TA</td>
<td>truncus arteriosus</td>
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<tr>
<td>TOF</td>
<td>tetralogy of Fallot</td>
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<tr>
<td>TGA</td>
<td>transposition of great arteries</td>
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<tr>
<td>VSD</td>
<td>ventricular septal defect</td>
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CHROMOSOME ANALYSIS
DOWN SYNDROME: Review

Trisomy 21
Translocation 21
Mosaicism

Microbrachycephaly
Sparse hair
Facial:
  Small eyes
  Upslanted eyes
  Small nose
  Small mouth
  Large tongue
Excess nuchal skin/edema
GI anomalies
Hematologic anomalies
Skeletal:
  5\textsuperscript{th} finger clinodactyly
  Joint laxity
  C1-C2 instability
DOWN SYNDROME: Cardiac

All types: 40%

AV Canal “family”
  40%
  Complete AVC
  Primum-type ASD

VSD, all types
ASD, secundum type
Patent ductus arteriosus
Tetralogy of Fallot

ECG Superior axis,
counterclockwise loop
WHAT’S NEW: DOWN SYNDROME

CHD surgery outcomes

BACKGROUND:
Many prior studies with conflicting results about DS as a risk factor for poor outcome.

LB prevalence has increased by 1/3 in 2 decades
(Shin M, CDC et al., Pediatrics, 2009)

Methods:
National STS CHD Database
4350 DS patients (~41,000 non-DS).

Results:
No difference in mortality.
More complications
Length of stay increased ASD, VSD, TOF (not AV canal)

Limitations:
Society for Thoracic Surgery is a voluntary DB (includes CHB).
(Fudge JC, et al., Pediatrics, 2011)
TRISOMY 18: Overall

Trisomy 18
Rarely translocation

SGA, IUGR
Craniofacial
  Microcephaly
  Prominent occiput
  Small features
  “Normal”

Overlapping fingers
Short sternum
CNS (posterior fossa)
Renal anomalies
GU anomalies
Rocker bottom feet
TRISOMY 18: Cardiac

All types: 95%

Conotruncal
  VSD, conoventricular
  TOF
  DORV

Complete AV canal

95% Polyvalvar dysplasia
  Nodular, thick valves
  Bicuspid aortic valve
TRISOMY 13: Overall

Craniofacial
  Cleft lip/palate
  Microphthalmia/anophthalmia
  Scalp cutis aplasia

Postaxial polydactyly

Renal/GU anomalies

CNS anomalies:
  Holoprosencephaly
TRISOMY 13: Cardiac

All types: 50-80%

Conotruncal
  DORV
  TOF
Common AV canal
ASD
VSD
PDA

Polyvalvar dysplasia: 60%
Less common compared to Trisomy 18
## WHAT’S NEW: TRISOMY 13 TRISOMY 18

<table>
<thead>
<tr>
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<th>Intensive treatment</th>
<th>Increased survival to 1 year: 25% vs 5%. Only 2/24 survived to age 2 years.</th>
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<td><em>(Kosho T et al., 2006, 2008 AJMG)</em></td>
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<td>Impact of cardiac surgery</td>
<td>23 pts, 6 (23%) operations, survival increases (smaller #, milder defects).</td>
<td>34 pts, 9 (34%) operations <em>(Muneuchi et al., 2010, Cardiol Young)</em></td>
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<td><em>(Maeda et al., 2011 AJMG)</em></td>
<td>134 pts, 32 (25%) operations: Cardiac surgery increases survival Mosaicism contributes 25% alive at age 1</td>
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<td><em>(Maeda et al., 2011, AJMG)</em></td>
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<td>Trend in prevalence</td>
<td>Texas, population-based surveillance, 1999-2003. Trisomy 18: Prevalence ~1/10,000 LBs, 1 year survival 3%</td>
<td>Trisomy 13: Prevalence ~0.8/10,000, 1 year survival 3%</td>
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<td>No ethnic difference.</td>
<td><em>(Vendola et al., 2010, AJMG)</em></td>
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TURNER SYNDROME: Overall

No single phenotype
Varies with age:
  Hydropic fetus (sab)
  Infant with CHD
  Girl with short stature
  Girl with coarctation
  Teen with delayed puberty
  Woman with infertility
  Someone you know with short stature
Malformed pinnae
100% short stature
Most infertile
Renal: horseshoe kidney
Neck webbing, edema
Skin: nevi, keloids

Courtesy of the Turner Syndrome Support Association web site

Courtesy of family
TURNER SYNDROME: Cardiac

All types: 25%

Left-sided obstruction
“LVOTO”
  Bicuspid aortic valve
  Coarctation
  Aortic stenosis
  MV anomalies
  HLHS

Partial APVR
ASD2, VSD

Aortic dilation, dissection

Hypertension
ECG abnormalities
### WHAT’S NEW: TURNER SYNDROME

**Reproduction:**
Assisted reproductive technology (ART)

1) Risk factors for aortic dissection: BAV, COA, HTN
   5-10% have no risk factor (pregnancy itself?)
2) Spontaneous puberty ~10%; pregnancies 2-5%

*(Hadnott and Bondy, Exp Rev Obstet Gynecol, 2011)*

145 pregnancies in 76 women
Overall risk for major pregnancy complications ~10%
Risk for maternal death ~3.5%
Method of conception: ~17% ART (after 1989)
More risk with ART (9/24, ~38%, vs. 6/102, ~6% spontaneous)
Karyotype: 45,X more common
Underlying CV abn: 100% (7/7), BAV, PIH, COA, aortic dilation.

**Counseling**

1) Speak of “being a mother” rather than “having a baby”.
   Begin early, include adoption as an option.
2) Ineligible: BAV, COA, aortic stenosis, with/without surgery
   Pre-existing aortic dilation, hypertension
   Serious medical condition,
3) More conservative: View TS as having vasculopathy
DELETION 1p36 SYNDROME: Overall

Straight eyebrows
Small, open mouth

All cardiac: 80%

CHDs 70%
Including Ebstein
Noncompaction LV 20%
Dilated cardiomyopathy 4%

(abnormality of trabecularion)

Gajecka et al., AJMG PartC 2007
DELETION 4p SYNDROME: Overall

Wolf-Hirschhorn syndrome

Craniofacial
“Greek war helmet”
Prominent glabella
Hypertelorism
Downcurved mouth
Abnormal ears
Cleft lip/palate

GU anomalies

www.emedicine.com
medgen.genetics.utah.edu
DELETION 4p SYNDROME: Cardiac

- All types: 40%
- Most common: Pulmonic stenosis
- ASD
- VSD
DEL 7p/ WILLIAMS SYNDROME: Overall

Craniofacial
- Stellate irides
- Eyebrow flare
- Periorbital fullness
- Wide mouth, full lips

Laxity, then contractures

Distinctive personality
- Irritable infancy
- Personable
- Talkative
- Anxious

Hyperacusis
- Hoarse voice
- Abnormal calcium levels

medgen.genetics.utah.edu

www.williams-syndrome.ro
DEL 7p / WILLIAMS SYNDROME: Cardiac

All types: 75%

Left and right heart Obstruction:

Supravalvar Ao stenosis
+/- Ao Valve stenosis
Coarctation
Aorta hypoplasia

PV stenosis
Peripheral pulmonic stenosis

ASD, VSD
Renal artery stenosis
Coronary artery stenosis

Courtesy of Drs. Leslie Smoot and Ron Lacro, CH, Boston
DELETION 22q11 SPECTRUM: Overall

DiGeorge syndrome
Velo-cardio-facial (VCFS)
CATCH-22

Craniofacial
Narrow palpebral fissures
Cleft palate
Straight nose
Wide nasal root
Small mouth
Thin lips
Absent thymus
Hypocalcemia
Speech problems
Psychiatric disorders

www.cardiogenetics.org
DELETION 22q11 SPECTRUM: Cardiac

All types: 75-85%

Striking
Conotruncal
   IAA, type B
   Truncus arteriosus
   TOF
   TOF with pulmonary atresia
   VSD, malalignment
   DORV

Aortic arch anomaly
   Aberrant subclavian

VSD, membranous
VSD, muscular
TETRASOMY 22p/ CAT-EYE SYNDROME

- Iris coloboma
- Pre-auricular pit/tag
- Rectal anomalies
- GU anomalies

- CHD, all types: 50%
  - TAPVR
  - PAPVR
- Assorted VSD
ACKNOWLEDGEMENTS FOR DIAGRAMS

Google the hospital, search for pediatric cardiology site:
Children’s Hospital of Boston, MA
Children’s Hospital of Philadelphia, PA
Cincinnati Children’s Hospital, OH
Melbourne Children’s Hospital, Australia
Nemours / A.I. Du Pont Children’s Hospital, DE
Mayo Clinic, MN
Yale Medical School, CT

http://www.rch.org.au/cardiology/
http://embryology.med.unsw.edu.au/Medicine/ILPheart.htm
http://www.mayoclinic.org/patientinfo/
http://www.heart-vessels.com/cardiovascular-diseases/
http://www.childrenshospital.org/cfapps/mml/