January 20, 2010
Congenital Heart Disease Lecture: HHSC 401; 11:00 – 11:30 AM
Laboratory will be in PH17-Gross Labs 11:45 AM – 12:50 PM

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Congenital Heart Disease: An Overview

I. Prevalence

A. Bicuspid aortic valve in 1-2% of live births.
B. Other CHD: 1.5 – 2.5/1000 live births
C. Estimated >20,000 open heart procedures yearly for CHD and >500,000 adults in the U.S. have CHD.
D. Post-op pulmonary stenosis, patent ductus and secundum-type ASD (except when part of a syndrome prone to arrhythmias – see II.C.7. below) have normal life expectancy.

II. Etiologies

A. 70 – 80% are “multifactorial”
   1. R/O Mendelian inheritance; R/O environmental; apparently distinct malformations may be pathogenetically organized (e.g. bicuspid AV associated with hypoplastic left heart syndrome)
   2. Risk of recurrence in a family with 1 affected sib or father with CHD = 2-4%
   3. Risk of recurrence in a family with 2 affected sibs or mother with CHD = 6-12%
   4. In half these families, the same defect recurs

B. 6 – 12% Chromosomal syndromes (aneuploidy)
   1. Trisomy 18 (100% affected): VSD, pulmonary or aortic stenosis
   2. Trisomy 21 (40% affected): endocardial cushion defect (21q22.3 – q22.1)
   3. Trisomies 13 or 15: VSD, ASD, transposition of great vessels
   4. Trisomy 9: (?Retinoid X Receptor gene) VSD, DORV, AV canal, PA, PDA, truncus
   5. XO (Turner): aortic coarctation, aortic stenosis, VSD
   6. XXY (Klinefelter): Tetralogy of Fallot, Ebstein’s anomaly

C. 10 - 15% Defects in a single gene or in 2 or more contiguous genes
   1. Connexin 43 (6q21-q23.2): pulmonary stenosis (PS), heterotaxy
   2. Elastin gene (7q): Supravalvular aortic stenosis (SVAS) (autosomal dominant)
   3. William’s syndrome (del 7q11.23): SVAS, peripheral PS, abnormal facies, retardation
   4. Smith-Magenis (del 17p11.2): various defects
6. Holt-Oram (HOS-1; TBX5; 12q24.1): ASD + limb defects + VSD
(mutations in different regions of the protein are involved in different phenotypes)
7. NKX2.5 (5q35; tinman in Drosophila): ASD + heart block + looping defects + Tetralogy of Fallot + Tricuspid valve anomalies.
8. Wolf syndrome (del 4p16): ASD, VSD
9. Cat-eye syndrome (dup 22q11): Tetralogy, anomalous pulmonary veins
10. Alagille syndrome (20p12; Jagged-1): biliary atresia + pulmonary stenosis/Tetralogy
   CATCH22 – Cardiac anomalies (interrupted aortic arch, truncus, Tetralogy, transposition); Anormal facies; Thymic hypoplasia; Cleft palate; Hypocalcemia; 22nd chromosome (22q11.2 – probably TBX1 gene).
   This region associated with full-blown DiGeorge syndrome is also deleted in 10-30% of individuals with conotruncal anomalies (interrupted aortic arch, truncus, Tetralogy, TGV, VSD, aortic coarc, DORV) including individuals who do not have other features of DiGeorge syndrome. These microdeletions may be inherited from a parent with minimal syndromic features and no history of congenital heart disease.

D. 1% Maternal disease
1. Type I Diabetes Mellitus (2% affected)
2. Phenylketonuria, if not controlled
3. Systemic lupus erythematosus: heart block, structural anomalies

E. 1% Teratogen exposure
1. Fetal alcohol syndrome (30% have CHD)
2. Anticonvulsants (2-3X increased risk of CHD)
3. Lithium
4. Retinoic acid (first trimester): VSD, DORV, truncus, Tetralogy, TGV
5. Viral: Rubella

III. Embryology/Cardiac Development: There are more than 5,000 genes involved in cardiac development. CHD in humans is most often due to haploinsufficiency with subtle phenotypes, variable penetrance, and appearance at birth or later in life. Genetic studies of CHD in animal models usually involve homozygous loss of function mutations, resulting in severe phenotypes often lethal in early embryogenesis.

1. Early heart muscle cells: originate in anterior-lateral plate mesoderm; Mesp1,2 (bHLH transcription factor family) may be one of the early markers; Wnt genes block cardiogenesis + promote blood formation; Nkx2.5 (tinman in flies) in lateral plate; chamber-specific myosin heavy chains; myofibrillar proteins.
2. Are there inducers of cardiac tissue? - maybe the anterior endoderm or BMP2,4 (bone morphogenic proteins); little is known about this now.

3. Laterality (looping is normally to the right)
   - Right: snail family of zinc finger proteins (cSnR)
     - DHAND/HAND2 (basic helix-loop-helix)
     - Myosin light chain 2v
     - Desmin (cis)
     - Versican
   - Left: TGFbeta family genes (Nodal)
     - eHAND/HAND1 <- Nkx2.5
     - Myosin light chain 3F
     - Ptx2

4. Neural Crest: (Postulated as cause of 30% of CHD)
   - Post-ganglionic parasympathetic innervation is present in the heart.
   - Contributes to the septum of outflow tract (neural crest removal results in truncus arteriosus). Genes include *endothelin-1, dHAND, neuropilin-1* and:
     - Pax-3 deletion – associated with conotruncal abnormalities
     - Hox 1.5 mutations – abnormal aortic arch, thymus, parathyroid like
     - DiGeorge syndrome
     - Neurofibromin (NF1) mutations - associated with truncus and VSD, like DiGeorge syndrome
     - Retinoic acid receptors – single and double mutations associated with truncus, aortic arch

5. Endocardial cushions and valves: TGFbeta, fibulin, neuregulin, Nf1 (via downregulation of ras) in endothelial cells, and calcineurin are important for development. Factors from myocytes (?PDGFalphaR) are also required.

6. Atrial v. ventricular muscle differentiation: Chicken iroquois-related homeobox gene *IrX-4* promotes Ventricular MHC-1 and suppresses Atrial MHC-1.
   - Ventricle - ?Nkx2.5 also?

7. Proliferation of ventricular myocytes: Neuregulin growth factors from endocardium + their myocardial receptors ErbB2, ErbB4; VEGF; angiopoietin from endocardium.

8. Conduction system: arterial endothelin-1 signaling.

### IV. Some genetic associations for specific congenital heart defects:

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<tr>
<th>Morphologic Defect</th>
<th>Genetic associations</th>
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<tbody>
<tr>
<td>1. Supravalvular AS:</td>
<td>Elastin gene (7q11)</td>
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<td>Williams Syndrome (7q11.23): multiple adjacent genes are deleted</td>
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<td>2. ASD:</td>
<td>Holt-Oram (12q24.1 with highly penetrant autosomal dominant inheritance) 5q34 (nKx2.5)</td>
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<td>Ellis van Creveld (recessive) – dwarfism + ASD (4p16?multiple genes)</td>
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<td>3. Conotruncal:</td>
<td>DiGeorge</td>
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<td>Neural crest deletions (see above)</td>
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<td>4. AV Canal:</td>
<td>Trisomy 21 (22q22.1 – 22.3 critical region)</td>
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?modifier genes (only 40% of Down’s have CHD)
Neural crest cells?
5. **Laterality:** Connexin 43 (6q21 – q23.2 group)
6. **Total anomalous pulmonary venous return:** 1/10,000; ?VEGFR
   Partial anomalous venous return – some are autosomal dominant
7. **Hypoplastic Left Heart Syndrome:** 11q23 (?autosomal dominant – 12% recurrence rate); XO, Trisomy 13, Trisomy 18
   Coarctation of aorta:  XO
   Bicuspid aortic valve: some familial (autosomal dominant)
   Aortic stenosis: some familial (autosomal dominant)
   Subaortic stenosis: rare familial
   Aberrant coronary arteries: one family
   HLH + retardation + dysmorphic facies: Jacobsen Syndrome (11q terminal deletion; 11q23.3-q24.1)
8. **Right sided lesions:**
   Tricuspid atresia (some autosomal recessive)
   Ebstein anomaly (some autosomal dominant)
   Pulmonary atresia with intact septum (some autosomal recessive; some dominant)
   Pulmonary valve dysplasia (Noonan syndrome – short stature, abnormal facies, skeletal anomalies, 70% CHD): 12q.
   Pulmonary stenosis; Tetralogy of Fallot (20p12; *Jagged-1*)
9. **Aortic aneurysm:** Marfan’s (15q21.1; *fibrillin-1*)
10. **Patent ductus arteriosus:** (Iran-autosomal recessive-12q24; 6p12; *TFAP-2B*)
11. **X-linked myxomatous valvular dystrophy:** (Xq28; involves AV and MV)
12. **Non-compaction of left ventricular myocardium with congenital heart defects:**
    (18q12.1 – q12.2; *alpha-dystrobrevin*)