Single Gene Disorders in Congenital Heart Disease

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Cincinnati Children’s Hospital
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University of Cincinnati

The Speaker has no disclosures
Single Gene Disorders in Congenital Heart Disease

- Significant effort devoted to identifying the genetic contributions to cardiovascular disease
  - Cardiomyopathy
  - Arrhythmias
  - Vasculopathy
  - Cardiovascular malformations
Single Gene Disorders in Congenital Heart Disease

- Congenital heart disease (CHD) remains the most common birth defect worldwide
- Accounts for 25-30% of all birth defects
- Birth prevalence 6-8/1000 live births
  - ~40,000 children born with CHD in the US each year
  - Additional 40,000 are born with subclinical disease
- Numbers increasing as improvements in diagnostic techniques allow for detection of milder forms of disease
Single Gene Disorders in Congenital Heart Disease

- With improvements in medical and surgical management, the majority of these patients survive into adulthood
  - Currently >1 million adults with CHD

- Significant impact on health care system
  - Reach reproductive age

- Understanding of genetics critical to these patients and their families
Genetic Basis of Congenital Heart Disease

- Chromosomal
  - Submicroscopic chromosomal aberrations
- Mendelian
  - Autosomal dominant (AD)
  - Autosomal recessive (AR)
  - X-linked
- Epigenetic-imprinting
- Multifactorial or Complex
Single Gene Disorders in Congenital Heart Disease

- Single gene disorders have been increasingly described in association with CHD

- Syndromic
  - Holt-Oram syndrome (TBX5)

- Nonsyndromic
  - NKX2.5
## Embryological Mechanisms

<table>
<thead>
<tr>
<th>Normal</th>
<th>Pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td>• establishment of cardiogenic field</td>
<td>• laterality and looping - heterotaxy</td>
</tr>
<tr>
<td>• formation of the heart tube</td>
<td>• mesenchymal cell (neural crest) migration - TOF, TGA</td>
</tr>
<tr>
<td>• chamber specification</td>
<td>• extracellular matrix - AV canal</td>
</tr>
<tr>
<td>• rightward looping</td>
<td>• targeted growth - TAPVR</td>
</tr>
<tr>
<td>• chamber formation and valve development</td>
<td>• apoptosis - muscular VSD</td>
</tr>
<tr>
<td>• neural crest contribution to outflow tract</td>
<td>• hemodynamic (flow) defects - LVOT, RVOT, PDA</td>
</tr>
</tbody>
</table>
Holt-Oram Syndrome

- ASD, VSD - 66%
- 17% with complex lesion e.g. HLHS
- Thumb anomaly, (absence in 19/44, hypoplasia in 17/44, triphalangeal thumbs in 8/44) absence of radius (10/44).
- AD 12q21.3-q22, mutations in the \textbf{TBX5} gene (601620) - transcription factor
Expression of Murine Tbx5 in the embryonic heart and limbs
TBX5

- Transcriptional activator of chamber-specific genes
  - cardiac specification
  - chamber morphogenesis
  - differentiation

Human atrial septal defects
Heart Defects Associated with Tbx5 mutations
Noonan, Cardio-Facio-Cutaneous, and Costello Syndromes

- Neuro-cardio-facio-cutaneous (NCFC) syndromes
  - Noonan syndrome
  - Costello syndrome
  - Cardio-facio-cutaneous (CFC) syndrome
  - LEOPARD syndrome
Noonan, Cardio-Facio-Cutaneous, and Costello Syndromes

- NCFC syndromes result from DNA mutations that result in alteration of complex protein signaling pathways
  - RAS/RAF/MEK
  - Controls cell growth

- There is a significant amount of clinical overlap between these disorders
- However, each is characterized by mutations in specific genes
Noonan, Cardio-Facio-Cutaneous, and Costello Syndromes

- Most Noonan syndrome patients have mutations in PTPN11 (~50%)
  - Mutations in SOS1, K-RAS, and RAF1 account for ~25%

- Most Costello syndrome patients have mutations in H-RAS

- Most patients with CFC syndrome have mutations in B-RAF
  - Also may involve MEK1 and MEK2
Noonan, Cardio-Facio-Cutaneous, and Costello Syndromes

- The RAS/RAF/MEK signaling pathway plays important roles in different cellular mechanisms
  - Metabolism, differentiation, cell death
- The malfunction of this pathway during embryologic development may result in multiple clinical abnormalities
  - Developmental delay
  - Mental retardation
  - Musculoskeletal disease
  - Cardiomyopathies (Heart muscle disease)
Noonan Syndrome

- Possible parent to child inheritance
  - But many cases are new mutations with no prior family history
- Occurs in every 1:1000 to 1:2500 live births
- Findings may include wide set eyes, low-set ears, breast bone abnormalities, neck webbing, bleeding abnormalities, short stature
- Mild intellectual deficits may also occur
Noonan Syndrome

- Cardiac disease is well described and occurs in ~50% to 80% of people
- Pulmonic stenosis is the most common finding (20% to 50% cases)
- Hypertrophic cardiomyopathy (HCM) may occur in 20% to 30%
- Vascular involvement may also occur
  - Pulmonary arteries
  - Aorta

Noonan Syndrome
Pulmonic Stenosis

Normal

Pulmonary stenosis

Pulmonary Valve
Aortic Valve
Pulmonary Artery
Noonan Syndrome
Aortic Dilation
Noonan Syndrome
Hypertrophic Cardiomyopathy
Cardio-Facio-Cutaneous Syndrome

- CFC is characterized by mental retardation, characteristic facies, ectodermal abnormalities, and cardiac disease.
- Recent review of 38 patients with proven mutations known to cause CFC.
  - 71% found to have cardiac disease.

## Cardio-Facio-Cutaneous Syndrome


### Table 1 Frequency of some cardinal features among the 38 individuals

<table>
<thead>
<tr>
<th>Feature</th>
<th>BRAF (32)</th>
<th>MEK1 (4)</th>
<th>MEK2 (2)</th>
<th>Respondents (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary valve stenosis</td>
<td>11/27</td>
<td>3/4</td>
<td>0/2</td>
<td>42</td>
</tr>
<tr>
<td>ASD</td>
<td>9/27</td>
<td>0/3</td>
<td>0/2</td>
<td>28</td>
</tr>
<tr>
<td>VSD</td>
<td>7/27</td>
<td>0/3</td>
<td>0/2</td>
<td>22</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>11/28</td>
<td>1/3</td>
<td>1/2</td>
<td>39</td>
</tr>
<tr>
<td>Hair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curly hair</td>
<td>29/32</td>
<td>3/4</td>
<td>2/2</td>
<td>92</td>
</tr>
<tr>
<td>Absent or sparse eyebrows</td>
<td>24/29</td>
<td>4/4</td>
<td>2/2</td>
<td>86</td>
</tr>
<tr>
<td>Sparse hair</td>
<td>27/32</td>
<td>3/4</td>
<td>2/2</td>
<td>84</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevi</td>
<td>23/31</td>
<td>3/4</td>
<td>2/2</td>
<td>76</td>
</tr>
<tr>
<td>Keratosis pilaris</td>
<td>16/22</td>
<td>1/2</td>
<td>2/2</td>
<td>73</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>13/23</td>
<td>2/3</td>
<td>2/2</td>
<td>61</td>
</tr>
<tr>
<td>Haemangiomas</td>
<td>11/27</td>
<td>3/3</td>
<td>1/2</td>
<td>47</td>
</tr>
<tr>
<td>Red itchy skin</td>
<td>11/28</td>
<td>3/4</td>
<td>1/2</td>
<td>44</td>
</tr>
<tr>
<td>Ichthyosis</td>
<td>7/23</td>
<td>1/2</td>
<td>0/2</td>
<td>30</td>
</tr>
<tr>
<td>Café-au-lait macules</td>
<td>7/27</td>
<td>0/4</td>
<td>2/2</td>
<td>27</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>5/21</td>
<td>2/3</td>
<td>0/2</td>
<td>27</td>
</tr>
<tr>
<td>Cutaneous lymphangioma</td>
<td>2/29</td>
<td>0/3</td>
<td>0/2</td>
<td>6</td>
</tr>
</tbody>
</table>
Costello Syndrome

- Complex developmental disorder
  - Characteristic craniofacial features
  - Neurocognitive delay
  - Failure to thrive
  - Endocrine and skeletal disease
  - Predisposition to neoplasias
  - Cardiac disease
Costello Syndrome

- Many different types of heart disease seen
  - Malformations
  - Tachyarrhythmias
  - Cardiac hypertrophy
    - May be isolated to the left ventricle (LV), both ventricles, or may result in a dilated cardiomyopathy
# Costello Syndrome

## TABLE II. Cardiovascular Malformations in 28 Patients With Costello Syndrome

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>New patients</th>
<th>Literature</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>27</td>
<td>67</td>
<td>94</td>
</tr>
<tr>
<td>Cardiovascular malformation, total*</td>
<td>4 (14%)</td>
<td>24 (36%)</td>
<td>28 (30% all patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(50% any abn)</td>
</tr>
<tr>
<td>Right-sided obstruction</td>
<td>3</td>
<td>10</td>
<td>13 (46%)</td>
</tr>
<tr>
<td>Pulmonic stenosis, valvar or NOS</td>
<td>1</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Pulmonic stenosis, ASD</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary artery stenoses</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Right and left sided obstruction</td>
<td>0</td>
<td>1</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Pulmonic stenosis, BAV, AS, MS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left-sided obstruction</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Septal defect</td>
<td>0</td>
<td>9</td>
<td>9 (32%)</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Not specified</td>
<td>1</td>
<td>4</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>Conotruncal</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atrioventricular canal</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Single ventricle</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heterotaxy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AS, aortic stenosis; BAV, bicuspid aortic valve; CVM, cardiovascular malformation; MS, mitral stenosis; NOS, not otherwise specified.

*Additional mitral valve abnormalities: prolapse, myxomatous or redundant [new patients 3 and 23; Martin and Jones, 1991], thick mitral and/or aortic valve tips [new patient 4; Suri and Carrott, 1998, patient 1; Izumikawa et al., 1993, patient 1]; regurgitation without mitral valve abnormality [new patient 22], unspecified murmur [Torrello et al., 1995].
Costello Syndrome

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>New patients</th>
<th>Literature</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>27</td>
<td>67</td>
<td>94</td>
</tr>
<tr>
<td>Cardiac hypertrophy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 (22%)</td>
<td>26 (39%)</td>
<td>32 (34% all pts)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(54% any abs)</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>5</td>
<td>11</td>
<td>16 (50%)</td>
</tr>
<tr>
<td>Definite HCM&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Possible HCM</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Probably not HCM, concentric</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>LVH +/− subAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVH NOS</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Biventricular hypertrophy, LV &gt; RV</td>
<td>1</td>
<td>3</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Definite HCM</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Possible HCM</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Definitely not HCM</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Not specified, unclear</td>
<td>0</td>
<td>12</td>
<td>12 (38%)</td>
</tr>
</tbody>
</table>

## TABLE IV. Rhythm Disturbances in 31 Patients With Costello Syndrome

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>New patients</th>
<th>Literature</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>27</td>
<td>67</td>
<td>94</td>
</tr>
<tr>
<td>Rhythm disturbance</td>
<td>8 (30%)</td>
<td>23 (34%)</td>
<td>31 (33% all pts) (56% any abn)</td>
</tr>
<tr>
<td>Atrial, primary tachycardia</td>
<td>5 (62%)</td>
<td>18 (78%)</td>
<td>23 (74%)</td>
</tr>
<tr>
<td>SVT, +/- PACs</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>MAT, +/- PACs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>“Multifocal SVT”, PACs, PVCs</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chaotic atrial rhythm</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Atrial, NOS</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia NOS, probably atrial</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Fibrillation, flutter</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fibrillation, “conduction defects”</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Premature atrial contractions</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Premature nodal contractions</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ventricular, total</td>
<td>2</td>
<td>2</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Premature ventricular contractions</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Neonatal VT and multifocal PVCs, persistent atrial fibrillation</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Complete heart block, “VT”</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Not otherwise specified</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

MAT, multifocal tachycardia; NOS, not otherwise specified; PAC, premature atrial contraction; PVC, premature ventricular contraction; SVT, supraventricular tachycardia; VT, ventricular fibrillation.
# Genetics of Syndromic Associated Cardiovascular Disease

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Cardiac anomalies</th>
<th>Causative gene(s)</th>
<th>Gene MIM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(A) Disease genes for syndromic cardiovascular malformations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alagille syndrome</td>
<td>PS, TOF, ASD, peripheral pulmonary stenosis</td>
<td>JAG1, NOTCH2</td>
<td>601920, 600275</td>
</tr>
<tr>
<td>Char syndrome</td>
<td>PDA</td>
<td>TFAP2B</td>
<td>601601</td>
</tr>
<tr>
<td>CHARGE syndrome</td>
<td>ASD, VSD, valve defects</td>
<td>CHD7, SEMA3E</td>
<td>608892, 608116</td>
</tr>
<tr>
<td>Costello syndrome</td>
<td>PS, HCM, cardiac conduction abnormalities</td>
<td>HRAS</td>
<td>190020</td>
</tr>
<tr>
<td>Ellis van Creveld</td>
<td>ASD</td>
<td>EVC, EVC2</td>
<td>604831, 607261</td>
</tr>
<tr>
<td>Heterotaxy syndrome</td>
<td>DILV, DORV, d-TGA, AVSD</td>
<td>ZIC3, CFC1</td>
<td>300265, 605194</td>
</tr>
<tr>
<td>Holt-Oram syndrome</td>
<td>ASD, VSD, AVSD, progressive AV conduction system disease</td>
<td>TBX5</td>
<td>601620</td>
</tr>
<tr>
<td>LEOPARD syndrome</td>
<td>PS and cardiac conduction abnormalities</td>
<td>PTPN11, RAF1</td>
<td>176876, 164760</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>PS with dysplastic pulmonary valve, AVSD, HCM, CoA</td>
<td>PTPN11, KRAS, RAF1, SOS1</td>
<td>176876, 190070, 164760, 182530</td>
</tr>
<tr>
<td>Rubinstein Taybi</td>
<td>ASD, VSD</td>
<td>CREBBP, EP300</td>
<td>600140, 602700</td>
</tr>
<tr>
<td>Smith Lemli Opitz</td>
<td>VSD, ASD, AVSD</td>
<td>DHCR7</td>
<td>602858</td>
</tr>
</tbody>
</table>
Velocardofoacial Syndrome (VCFS)

- Learning disability (66%),
- Cleft palate or pharyngeal hypotonia (49%)
- Cardiac anomalies (74%) - TOF, Interrupted Aortic Arch Type B, etc
- Genitourinary abnormalities
- 22q11 deletion, 5-10% inherited
- DiGeorge Syndrome - hypocalcemia, thymic aplasia

Single Gene Disorders in Nonsyndromic Cardiovascular Disease

- The etiology of most nonsyndromic disease is unknown
- Last decade has seen an increase in identified genes
  - NKX2.5
  - GATA4
  - T box genes
  - NOTCH1
Morphologic Development of the Heart
Cardiac Lineages

- Second lineage progenitors lie medial and caudal to the first lineage progenitors of the crescent
  - PAM – pharyngeal arch mesoderm
  - DPM – dorsal pericardial mesoderm

First lineage: Cardiac crescent

Second lineage:
Contribution of Neural Crest
Contributions of the Cardiac Neural Crest
NKX2.5

- NK-homeobox transcription factor
- Plays a key role in cardiac chamber development
- Also important for conduction system morphogenesis
- Importance to myocardial function as well
- Associated with multiple structural lesions
NKX2.5

GATA4

- GATA4 is an essential transcription factor for cardiac morphogenesis
- Required for normal myocardial growth and right ventricular development
- Important for normal endocardial cushion derived tissue development (atrioventricular valves)
## GATA4

### Patient characteristics

<table>
<thead>
<tr>
<th>Cardiac lesion</th>
<th>Patients, # (%)</th>
<th>GATA4 alteration, # (%)</th>
<th>Proband with family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocardial cushion defects</td>
<td>42 (39)</td>
<td>2 (4.8)</td>
<td>0</td>
</tr>
<tr>
<td>Double inlet LV</td>
<td>9 (8)</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>ASD/VSD</td>
<td>8 (7)</td>
<td>1 (12.5)</td>
<td>1</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>48 (45)</td>
<td>0 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
<td>4 (3.7)</td>
<td></td>
</tr>
</tbody>
</table>

a GATA4 alteration is defined as a non-synonymous sequence alteration not found in control individuals.

b 24 of these patients were via personal communications from M. Sarkar, C. Seidman, and J. Seidman.
T Box Transcription Factors

- DNA consensus sequence TCACACCT
- T-box is a 180 amino acid DNA-binding domain, generally comprising about a third of the entire protein (17-26 kDa)
- Similarity to the DNA binding domain of Mus musculus (Mouse) Brachyury (T)
- Conserved from Drosophila Dorsocross complex
- 7 T-box transcription factors expressed in cardiac development – Tbx1,2,3,4,5,18,20
# Genotype-Phenotype Correlations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosomal location</th>
<th>Cardiac defect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK2</td>
<td>2q23-q24</td>
<td>Primum type ASD, MVP</td>
<td>Joziasse [52]</td>
</tr>
<tr>
<td>BMPR2</td>
<td>2q33</td>
<td>AVSD, ASD, PDA, PAPVR + PAH</td>
<td>Roberts [90]</td>
</tr>
<tr>
<td>CFC1/Cryptic</td>
<td>2q21.1</td>
<td>Heterotaxia, TGA, DORV, common AV canal, AA hypoplasia, pulmonary artresia, DIRV</td>
<td>Bamford [7, 41]</td>
</tr>
<tr>
<td>Cited2</td>
<td>6q23.3</td>
<td>TOF, VSD, ASD, anomalous pulmonary venous return, RVOT obstruction</td>
<td>Sperling [102]</td>
</tr>
<tr>
<td>CRELD1</td>
<td>22p13</td>
<td>AVSD, cleft mitral valve, ASD type I, heterotaxy</td>
<td>Sheffield [98]</td>
</tr>
<tr>
<td>Elastin</td>
<td>7q11.2</td>
<td>Supravalvular AoS</td>
<td>Robinson [91]</td>
</tr>
<tr>
<td>FOG2</td>
<td>8q23</td>
<td>TOF</td>
<td>Metcalfe [66]</td>
</tr>
<tr>
<td>GATA 4</td>
<td>8p23.1-p22</td>
<td>ASD, AVSD, pulmonary valve thickening, insufficiency of cardiac valves</td>
<td>Pizzuti [82]</td>
</tr>
<tr>
<td>JAG1</td>
<td>20p12</td>
<td>TOF, VSD with aortic dextroposition, PPS</td>
<td>Okubo [78]</td>
</tr>
<tr>
<td>KRAS</td>
<td>12p12.1</td>
<td>ASD, VSD, valvular PS, HCM, HOCM, MVP, IVP, LYH</td>
<td>Garg [35]</td>
</tr>
<tr>
<td>MYH6</td>
<td>14q12</td>
<td>Secundum ASD</td>
<td>Eldadah [29]</td>
</tr>
<tr>
<td>NKx2.5</td>
<td>5q34</td>
<td>ASD, VSD, TOF, AoS, VH Pulmonary atresia, Mitral valve anomalies, conduction disturbances</td>
<td>Schubbert [96]</td>
</tr>
<tr>
<td>NKx2.6</td>
<td>8p21</td>
<td>IA</td>
<td>Schott [95]</td>
</tr>
<tr>
<td>NOTCH1</td>
<td>9q34.3</td>
<td>Bicuspid aortic valve, mitral valve stenosis, TOF, VSD</td>
<td>König [57]</td>
</tr>
<tr>
<td>PROSIT240</td>
<td>12q24</td>
<td>TGA</td>
<td>Heathcote [43]</td>
</tr>
<tr>
<td>IBX1</td>
<td>22q11.2</td>
<td>Interrupted aortic arch, IA, other aortic arch anomalies</td>
<td>Garg [36]</td>
</tr>
<tr>
<td>TRX5</td>
<td>17q24.1</td>
<td>ASD, AVSD</td>
<td>Mohamed [70]</td>
</tr>
<tr>
<td>Zic3</td>
<td>Xq26.2</td>
<td>TGA, DORV, ASD, AVSD</td>
<td>Müncke [76]</td>
</tr>
</tbody>
</table>

Transcription Factor Gene Families

- Homeobox (NKX2.5, HOXA13)
- Paired-Box (PAX2, PAX6)
- Forkhead (FOXC2)
- T-Box (TBX1,3,5, 20)
- Zinc-finger (GLI3, ZIC2, ZIC3)
- GATA (GATA4)
**Tbx1 gene**

**b.** wild-type E10.5

**c.** Absence of the left fourth PAA in a *Tbx1*+/− embryo at E10.5

**d.** PAA morphology in a *Tbx1*−/− embryo

**e.** Compound heterozygous *Df(16)1/Tbx1tm1Bld* embryo

PAA, pharyngeal arch artery; AS, aortic sac; DA, dorsal aorta; IC, internal carotid artery.
Asymmetric Disposition of Visceral Organs in Humans

- **Situs Solitus**: normal disposition of organs
- **Right Isomerism (Asplenia Syndrome)**
- **Left Isomerism (Polysplenia Syndrome)**
- **Situs Inversus**: complete mirror-image reversal of organ asymmetry
- **Heterotaxy**: one or more of the individual organ systems with reversed L/R polarity
Heterotaxy Summary

- ZIC3 mutations in X-linked heterotaxy; also seen in 1% isolated CHD
- Sporadic males and an affected female observed
- ZIC3 mutation analysis is available
- Pedigrees show high rate of birth defects – isolated CHD, NTD, clubfoot, GI anomalies
- Other single gene defects have been identified, but collectively likely < 10% of cases, thus many genetic causes remain unidentified
- Association of heterotaxy cases with gestation diabetes, twin pregnancies, cocaine use
Conclusions

- Genetics increasingly recognized as having significant influence on cardiovascular disease
- Improving technologies provide opportunity for novel gene discovery
- Opportunity for better genotype-phenotype correlations
- Increasing utility of genetic testing in clinical practice to deliver more complete care to patients and their families