Genetics of Congenital Heart Diseases

by

WINCARS Association

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&

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• Introduction
• Embryology in brief
• General genetics approach to CHD
• Chromosomal disorders
• Microdeletion/ duplication disorders
• Single gene disorders
• Pathway disorders
Introduction

- CHD: 1/3rd of all major congenital abnormalities
- Affects 2 to 3 children per 100 live births
- Polygenic: Environmental and genetic
- Knowledge about genetics is essential in reproductive counseling of patients with CHD
Evidence for genetic basis of CHD

- Specific type of CHDs are more common in specific chromosomal abnormalities
- Multiple family members affected
- Increased RR in a family with an affected member
Timeline of genetic CHD discoveries

(JACC VOL. 69, NO. 7, 2017 FEBRUARY 21, 2017:859–70)
CHD

Genetic
- Syndromic (30%)
  - Chromosomal
  - Microdeletion/duplication
  - Single gene disorders
- Non Syndromic (70%)

Environmental
- Teratogens
- Infections
- Drugs
Non genetic causes

- Critical period of cardiac development: 2-7 weeks
- Infectious agents: Rubella
- Maternal diabetes
- Maternal exposure to alcohol, isotretinoin, thalidomide, AED
- Environmental teratogens (dioxins, pesticides)

<table>
<thead>
<tr>
<th>TABLE 46-3</th>
<th>Some Common Teratogens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Teratogenic Influence</strong></td>
<td><strong>Risk of Heart Defect (%)</strong></td>
</tr>
<tr>
<td>Maternal rubella</td>
<td>35</td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>3-5</td>
</tr>
<tr>
<td>Maternal phenylketonuria</td>
<td>25-50</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>20-40</td>
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<tr>
<td>Maternal alcohol abuse</td>
<td>25-30</td>
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<tr>
<td>Hydantoin</td>
<td>2-3</td>
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<tr>
<td>Trimethadione</td>
<td>15-30</td>
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<tr>
<td>Thalidomide</td>
<td>&lt;5</td>
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<tr>
<td>Lithium</td>
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<tr>
<td>Retinoic acid</td>
<td>10-20</td>
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<tr>
<td>Cocaine</td>
<td>5</td>
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</tbody>
</table>

Emery and Rimoin’s, 5th edition
Continuous spectrum

“Syndromic”:
extracardiac malformations

Down Syndrome
Trisomy 13, 18

Tbx5 mutation

Primary Ciliary Dyskinesia

Nkx2.5 mutation

“Isolated”:
Extracardiac malformations

Embryology

Field theory of cardiac development

Moss and Adams, 7th edition
Transcriptional factors

Moss and Adams, 7th edition
Factors influencing development of heart

<table>
<thead>
<tr>
<th>Factor</th>
<th>Examples</th>
<th>Diseases associated</th>
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</thead>
<tbody>
<tr>
<td>Transcriptional regulators</td>
<td>TBX5, NKX2-5 GATA4 TBX1 SALL4</td>
<td>Holt Oram Inherited ASD,VSD 22q deletion syndrome, Duane radial ray defects</td>
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<tr>
<td>Signalling pathway</td>
<td>Wnt RAS MAPK NOTCH, TGF beta Bmp, FGF</td>
<td>Rasopathies Robinow syndrome</td>
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<tr>
<td>Micro RNA</td>
<td>miR-11 and miR-1-2</td>
<td>Conduction defect, VSD</td>
</tr>
<tr>
<td>Epigenetic regulators</td>
<td>Smyd 1</td>
<td>Regulates cardiac chamber growth and differentiation</td>
</tr>
<tr>
<td>Hemodynamic factors</td>
<td>Primary outflow tract disorders can cause secondary structural defect</td>
<td></td>
</tr>
</tbody>
</table>
Isolated CHD

- Genetically heterogeneous
- More than 50 genes are implicated
- Bulk falls in some genes involved in development (NKX2-5, GATA4, NOTCH1)

Circ Res. 2013 February 15; 112(4)
<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Phenotypes*</th>
<th>OMIM</th>
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</thead>
<tbody>
<tr>
<td>ANKRD1</td>
<td>Ankyrin Repeat Domain</td>
<td>TAPVR</td>
<td>609599</td>
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<tr>
<td>CITED2</td>
<td>c-AMP Responsive Element- Binding Protein</td>
<td>ASD; VSD</td>
<td>602937</td>
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<tr>
<td>FO2G2/ZFPM2</td>
<td>Friend of GATA</td>
<td>TOF, DORV</td>
<td>603693</td>
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<tr>
<td>GATA4</td>
<td>GATA4 Transcription Factor</td>
<td>ASD, PS, VSD, TOF, AVSD, PAPVR</td>
<td>600576</td>
</tr>
<tr>
<td>GATA6</td>
<td>GATA6 Transcription Factor</td>
<td>ASD, TOF, PS, AVSD, PDA, OFT defects, VSD</td>
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<td>HAND2</td>
<td>Helix-Loop-Helix Transcription Factor</td>
<td>TOF</td>
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<tr>
<td>IRX4</td>
<td>Iroquois Homeobox 4</td>
<td>VSD</td>
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<tr>
<td>MED13L</td>
<td>Mediator Complex Subunit 13- like</td>
<td>TGA</td>
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<tr>
<td>NKX2-5/NKX2.5</td>
<td>Homeobox Containing Transcription Factor</td>
<td>ASD, VSD, TOF, HLH, CoA, TGA, DORV, IAA, OFT defects</td>
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<td>NKX2-6</td>
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<td>TBX1</td>
<td>T-Box 1 Transcription Factor</td>
<td>TOF, (22q11 deletion syndromes)</td>
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<td>TBX5</td>
<td>T-Box 5 Transcription Factor</td>
<td>AVSD, ASD, VSD, (Holt Oram syndrome)</td>
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<td>TBX20</td>
<td>T-Box 20 Transcription Factor</td>
<td>ASD, MS, VSD</td>
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<td>TFAP2B</td>
<td>Transcription Factor AP-2 Beta</td>
<td>PDA, (Char syndrome)</td>
<td>601601</td>
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<tr>
<td>ZIC3</td>
<td>Zinc Finger Transcription Factor</td>
<td>TGA, PS, DORV, TAPVR, ASD, HLH, VSD, Dextrocardia, L-R axis defects</td>
<td>300265</td>
</tr>
</tbody>
</table>

*Circ Res. 2013 February 15; 112(4)*
<table>
<thead>
<tr>
<th>Receptors, Ligands, and Signaling</th>
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<tbody>
<tr>
<td><strong>ACVR1/ALK2</strong></td>
<td>BMP Receptor</td>
<td>AVSD</td>
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<tr>
<td><strong>ACVR2B</strong></td>
<td>Activin Receptor</td>
<td>PS, DORV, TGA, Dextrocardia,</td>
<td>602730</td>
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<tr>
<td><strong>ALDH1A2</strong></td>
<td>Retinaldehyde Dehydrogenase</td>
<td>TOF</td>
<td>603687</td>
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<tr>
<td><strong>CFC1/CRYPTIC</strong></td>
<td>Cryptic Protein</td>
<td>TOF; TGA; AVSD; ASD; VSD; IAA; DORV</td>
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<tr>
<td><strong>CRELD1</strong></td>
<td>Epidermal Growth Factor-Related Proteins</td>
<td>ASD; AVSD</td>
<td>607170</td>
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<tr>
<td><strong>FOXH1</strong></td>
<td>Forkhead Activin Signal Transducer</td>
<td>TOF, TGA</td>
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<tr>
<td><strong>GDF1</strong></td>
<td>Growth Differentiation Factor-1</td>
<td>Heterotaxy, TOF, TGA, DORV</td>
<td>602880</td>
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<td><strong>GJA1</strong></td>
<td>Connexin 43</td>
<td>ASD, HLH, TAPVR, (Oculodentodigital dysplasia)</td>
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<tr>
<td><strong>JAG1</strong></td>
<td>Jagged-1 Ligand</td>
<td>PAS, TOF, (Alagille syndrome)</td>
<td>601920</td>
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<tr>
<td><strong>LEFTY2</strong></td>
<td>Left-Right Determination Factor</td>
<td>TGA, AVSD, IAA, CoA, L-R axis defects, IVC defects</td>
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<tr>
<td><strong>NODAL</strong></td>
<td>Nodal homolog (TGF-beta superfamily)</td>
<td>TGA, PA, TOF, DORV, Dextrocardia, IVC defect, TAPVR, AVSD</td>
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<tr>
<td><strong>NOTCH1</strong></td>
<td>NOTCH1 (Ligand of JAG1)</td>
<td>BAV, AS, CoA, HLH</td>
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<tr>
<td><strong>PDGFRα</strong></td>
<td>Platelet-Derived Growth Factor Receptor Alpha</td>
<td>TAPVR</td>
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<tr>
<td><strong>SMAD6</strong></td>
<td>MAD-related protein</td>
<td>BAV, CoA, AS</td>
<td>602931</td>
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<tr>
<td><strong>TAB2</strong></td>
<td>TGF-beta Activated Kinase</td>
<td>OFT defects</td>
<td>605101</td>
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<tr>
<td><strong>TDGF1</strong></td>
<td>Teratocarcinoma-Derived Growth Factor 1</td>
<td>TOF, VSD</td>
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<tr>
<td><strong>VEGF</strong></td>
<td>Vascular Endothelial Growth Factor</td>
<td>CoA, OFT defects</td>
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<table>
<thead>
<tr>
<th>Structural Proteins</th>
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<td><strong>ACTC</strong></td>
<td>Alpha Cardiac Actin</td>
<td>ASD</td>
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<td><strong>ELN</strong></td>
<td>Elastin</td>
<td>SVAS, PAS, PS, AS, (Williams-Beuren syndrome)</td>
<td>130160</td>
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<td><strong>MYH11</strong></td>
<td>Myosin Heavy Chain 11</td>
<td>PDA, Aortic Aneurysm</td>
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<tr>
<td><strong>MYH6</strong></td>
<td>Alpha Myosin Heavy Chain</td>
<td>ASD, Ta, AS, PFO, TGA</td>
<td>160710</td>
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<tr>
<td><strong>MYH7</strong></td>
<td>Beta Myosin Heavy Chain</td>
<td>Ebstein Anomaly, ASD, NVM</td>
<td>160760</td>
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</tbody>
</table>

*Circ Res. 2013 February 15; 112(4)*
Recurrence risk

- RR for siblings 1-6%
- If two siblings affected: 10%
- RR higher for offspring
- Higher if proband is mother
- Higher for left sided lesions (8-10%)

World J Cardiol 2016 February 26; 8(2): 180-191
When to consider genetic testing

- Facial dysmorphism
- Limb defects
- Growth delay
- Mental subnormality
- Abnormalities pertaining to other systems
- Family history of other affected members
Genetic syndromes with cardiac diseases

Chromosomal disorders

Microdeletion disorders

Monogenic disorders
Types of genetic testing

- Cytogenetics
- Molecular genetics
- Biochemical genetics
Cytogenetic testing
Karyotyping

5 mL venous blood
Add phytohemagglutinin and culture medium
Culture at 37°C for 3 days
Add colchicine and hypotonic saline
Cells fixed

Analyze “metaphase spread”
Digest with trypsin and stain with Giemsa
Spread cells onto slide by dropping

(http://medical-dictionary.thefreedictionary.com/karyotype)
Karyotyping

Metaphase spread
(100X magnification under microscope)
Karyotyping

46, XY. Normal male karyotype
When to do karyotyping?

- Clinical suspicion of a chromosomal disorder

Down syndrome: Trisomy 21
When to do karyotyping?

Edwards syndrome: Trisomy 18
When to do karyotyping?

- Clinical suspicion of a chromosomal disorder

Turner syndrome: 45,X
When to do karyotyping?

Any case of multiple malformation syndrome with/without idiopathic intellectual disability/global developmental delay: 3-5% yield
Molecular cytogenetic testing
Molecular cytogenetic studies

- Karyotyping not useful for sub-microscopic chromosomal abnormalities: microdeletion/microduplication

- Phenotype suggestive of a specific microdeletion syndrome

**Molecular cytogenetic testing**

- 2D Echo – Tetralogy of Fallot
- DiGeorge syndrome
22q Microdeletion

- 22q microdeletion: due to sub-microscopic deletion on long arm of chromosome 22

[Diagram showing 22q11.2 deletions, including genes TBX1, COMT, ZNF74, CRKL, UBE2L3, MAPK1, IGLC1, and GNAZ.]

http://www.genetics4medics.com/digeorge-syndrome.html
22q microdeletion

Deleted region too small to be detected in karyotype

Requires molecular cytogenetic tests:
- Fluorescent in-situ hybridization (FISH)
- Multiplex ligation-dependent probe amplification (MLPA)
- Cytogenetic microarray (CMA)
**Multiplex ligation dependent probe amplification (MLPA)**

1. **Denaturation and hybridization**
   - Target A
   - Target B
   - Genomic DNA

2. **Ligation**
   - If hybridized properly, the two parts are ligated by a thermostable ligase

3. **PCR of the ligated product**
   - PCR product of each probe set has a unique length, and can be separated by capillary electrophoresis

4. **Capillary Electrophoresis**

3 ml of EDTA blood
Patient’s MLPA result
Diagnosis: 22q microdeletion syndrome
Fluorescence in situ hybridization (FISH)

Denatured

Denatured

Hybridized

Viewed under a fluorescence microscope

3 ml of heparinized blood (green-top tube)
Fluorescence in situ hybridization

(www.nature.com)
Molecular genetic testing
Single gene disorders with CHD

Johanson Blizzard syndrome: 
*UBR1* gene mutation analysis
Molecular genetic studies

• **Single gene disorders**: Karyotyping / FISH/ MLPA not useful

• **DNA-based gene sequence analysis** - when a specific monogenic disorder is suspected
Polymerase chain reaction (PCR)
Polymerase chain reaction

- Carried out in a **thermocycler**
Polymerase chain reaction

Exponential amplification

<table>
<thead>
<tr>
<th>Cycles</th>
<th>Copies</th>
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<td>2</td>
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<tr>
<td>4</td>
<td>16</td>
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<tr>
<td>10</td>
<td>1,024</td>
</tr>
<tr>
<td>15</td>
<td>32,768</td>
</tr>
<tr>
<td>20</td>
<td>1,048,576</td>
</tr>
<tr>
<td>25</td>
<td>33,554,432</td>
</tr>
<tr>
<td>30</td>
<td>1,073,741,824</td>
</tr>
</tbody>
</table>

Cycles: 1 → 2 → 4 → 8 → 16 → 32 → 64 → 128 → 256 → 512 → 1,024 → 2,048 → 4,096 → 8,192 → 16,384 → 32,768 → 65,536 → 131,072 → 262,144 → 524,288 → 1,048,576 → 2,097,152 → 4,194,304 → 8,388,608 → 16,777,216 → 33,554,432 → 67,108,864 → 134,217,728 → 268,435,456 → 536,870,912 → 1,073,741,824
Molecular genetic tests

- PCR - RFLP
- ARMS - PCR
- Multiplex - PCR
- MLPA
DNA sequence analysis

DNA Sequencer

Sequence chromatogram
DNA sequence analysis

Mutation detected
DNA sequence analysis

Normal

Carrier

Affected
Metabolic genetic testing
Inborn Errors of Metabolism

Salient features:
- Motor developmental delay
- Floppiness & arreflexia
- Hepatomegaly
- Growth retardation
- Cardiomegaly
- Hypertrophic cardiomyopathy
- Similarly affected sibling

Pompe Disease
Case Scenario

- Alpha glucosidase enzyme assay (acarbose inhibition): 3 nmol/hr/mg (ref: 60-120 nmol/hr/mg)

- GAA gene mutation analysis: c.1465 G>A/ c.1799 G>A
Molecular genetic studies

What if the features do not fit into a clinically identifiable syndrome?
Molecular genetic studies

- Chromosomal Microarray:
  - Scans entire genome for microdeletions/microduplications
  - For multiple malformation conditions without an identifiable syndromic association/etiology
Molecular genetic studies

Exome sequencing:

- Scans all coding portions of all genes (exome) for sequence variants
- For multiple malformation conditions without an identifiable syndromic association/etiology
- For multiple malformation conditions with overlapping phenotypes/genetically heterogeneous
Whole exome/genome sequencing

- Next generation sequencing: massively parallel sequencing strategy that can be used to sequence entire genome/ entire coding portion of genome

- Being used as a final resort testing for all undiagnosed conditions with suspected etiology
If the features do not fit into a clinically identifiable syndrome?

Chromosomal microarray ➞ if inconclusive

Exome sequencing
## Chromosomal disorders

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>% CHD</th>
<th>CHD type</th>
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<tbody>
<tr>
<td><strong>Chromosome aneuploidy</strong></td>
<td></td>
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<tr>
<td>Trisomy 21</td>
<td>44</td>
<td>AVSD (complete, partial), VSD, ASD, TOF</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>83</td>
<td>VSD, ASD, TOF, DORV, AVSD, CoA</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>51–64</td>
<td>Conotruncal CHD: TOF, DORV; VSD, ASD, AVSD; valvular anomalies</td>
</tr>
<tr>
<td>45X (Turner syndrome)</td>
<td>38</td>
<td>Left-sided cardiac structures: bicuspid aortic valve, AS, CoA, mitral valve anomalies, HLHS, aortic dilation, dissection</td>
</tr>
<tr>
<td><strong>Chromosome deletion</strong></td>
<td></td>
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</tr>
<tr>
<td>22q11.2 deletion syndrome (DiGeorge syndrome, velocardiofacial syndrome)</td>
<td>75–80</td>
<td>“Conotruncal anomalies”: interrupted aortic arch type B, truncus arteriosus, TOF, TGA, perimembranous VSD, isolated aortic arch anomalies</td>
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<tr>
<td>7p11.23 microdeletion (Williams–Beuren syndrome)</td>
<td>82</td>
<td>Supravalvular aortic and pulmonary stenosis, peripheral pulmonary stenosis</td>
</tr>
<tr>
<td>1p36 deletion syndrome</td>
<td>35</td>
<td>VSD, ASD, TOF, CoA, PDA</td>
</tr>
<tr>
<td>11q23 deletion syndrome (Jacobson syndrome)</td>
<td>56</td>
<td>VSD, left heart anomalies</td>
</tr>
</tbody>
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## Frequency of CHD in various chromosomal disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency of CHD</th>
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<tbody>
<tr>
<td>Trisomy 13</td>
<td>50%</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>95%</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>40%</td>
</tr>
<tr>
<td>Turner</td>
<td>25%</td>
</tr>
<tr>
<td>1p36 deletion</td>
<td>35%</td>
</tr>
<tr>
<td>3p25 deletion</td>
<td>25%</td>
</tr>
<tr>
<td>3q duplication</td>
<td>75%</td>
</tr>
<tr>
<td>4p16 deletion</td>
<td>30-50%</td>
</tr>
<tr>
<td>William syndrome (7p13 deletion)</td>
<td>75%</td>
</tr>
<tr>
<td>Smith Magenis syndrome (17p11.2 deletion)</td>
<td>10%</td>
</tr>
<tr>
<td>22 q deletion</td>
<td>75-85%</td>
</tr>
</tbody>
</table>

Moss and Adams, 7th edition
Down syndrome

- 44% have CHD (Freeman et al)
- AVSD: most common
- Flat facial profile
- Thyroid abnormalities
- Developmental delay
- 95%: Non disjunction
- 4%: Translocation
- 1%: Mosaicism
CHD in Down syndrome

- AVCD: 45%
- Isolated VSD: 35%
- ASD: 8%
- PDA 7%
- TOF: 5%
- In older patients: MVP, MR, AR
- Pulmonary hypertension is common
Trisomy 13
Trisomy 13

- Maternal history of severe preeclampsia
- Post axial polydactyly of hands and feet
- Microcephaly
- Anophthalmia/microophthalmia
- Scalp defects: 50%
- Renal abnormality
- Heart defect: 50%; VSD, PDA
- Holoprosencephaly: 66%
Trisomy 18
Trisomy 18

- Polyhydramnios
- Hypertonia
- Large septal defects, PDA, TOF
- Median survival is 1-2 weeks
- 90% die by 6 months of age
Turner syndrome
Most common: Bicuspid aortic valve, followed by coarctation of aorta

Others: PAPVR, ASD, VSD

10% have clinically detected heart disease

10% have ECHO abnormalities

Emery and Rimoin’s, 5th edition
• More than 30% are hypertensive
• Aortic dissection at around 35 years of age
• Increased risk of CV event
• Need regular follow up from Cardiologist
22q deletion syndrome

- Most common microdeletion syndrome
- Learning impairment
- Palate abnormalities
- Thymic hypoplasia
- Hypocalcemia
<table>
<thead>
<tr>
<th>Cardiac Finding</th>
<th>% of Affected Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetralogy of Fallot (TOF)</td>
<td>20%</td>
</tr>
<tr>
<td>Interrupted aortic arch (IAA)</td>
<td>13%</td>
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<tr>
<td>Ventricular septal defect (VSD)</td>
<td>14%</td>
</tr>
<tr>
<td>Truncus arteriosus (TA)</td>
<td>6%</td>
</tr>
<tr>
<td>Vascular ring</td>
<td>5.5%</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>3.5%</td>
</tr>
<tr>
<td>VSD; ASD</td>
<td>4%</td>
</tr>
<tr>
<td>Other 1</td>
<td>10%</td>
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<tr>
<td>Normal</td>
<td>24%</td>
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</tbody>
</table>

McDonald-McGinn et al [2010b]
William syndrome

- Heterozygous deletion at 7q11.3
- Mild intellectual disability in 75%
- Overfriendliness
- Idiopathic hypercalcemia: 15-50%
- Elastin arteriopathy: 75-80%
- MC is supravalvular AS
- PPS, MR, hypertension
Indian Pediatr 2014;51: 411-412
1p36 deletion syndrome

- Developmental delay
- Hypotonia
- Eye/ hearing abnormalities
- Skeletal, renal abnormalities
- Typical facial features
1p36 deletion syndrome

- Cardiovascular abnormalities in 43-71%
- ASD, VSD, Valvular abnormalities
- PDA, TOF
- Cardiomyopathy in 23%
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Cardiac disease</th>
<th>Distinctive features</th>
</tr>
</thead>
<tbody>
<tr>
<td>3p25 deletion</td>
<td>ASD, Assorted CHD</td>
<td>Ptosis, abnormal ears, postaxial polydactyly</td>
</tr>
<tr>
<td>3q duplication</td>
<td>Assorted CHD</td>
<td>Craniosynostosis, cleft palate, clinodactyly</td>
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<tr>
<td>4p16 deletion</td>
<td>OS ASD, PS, VSD</td>
<td>Greek helmet facies</td>
</tr>
<tr>
<td>Wolfe Hisrchhorn</td>
<td></td>
<td>Cleft lip/palate</td>
</tr>
<tr>
<td>Deletion 5p15</td>
<td>Assorted CHD</td>
<td>Cleft lip/palate</td>
</tr>
<tr>
<td>(Cri du chat syndrome)</td>
<td></td>
<td>Abnormal cat cry</td>
</tr>
<tr>
<td>17p11.2 deletion</td>
<td>Assorted CHD’s</td>
<td>Self injurious behaviour</td>
</tr>
<tr>
<td>Smith Magenis syndrome</td>
<td></td>
<td>Abnormal eyes, ears</td>
</tr>
<tr>
<td>Tetrasomy 22p</td>
<td>TAPVC, PAPVC, Assorted</td>
<td>Coloboma, anorectal anomalies, GU</td>
</tr>
<tr>
<td>Cat eye syndrome</td>
<td>CHD’s</td>
<td>abnormalities</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Cardiac Anomalies</td>
<td>Other Clinical Features</td>
</tr>
<tr>
<td>---------------</td>
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<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Noonan Syndrome</td>
<td>PS with dysplastic pulmonary valve, AVSD, HCM, CoA</td>
<td>Short stature, webbed neck, shield chest, developmental delay, cryptorchidism, abnormal facies</td>
</tr>
<tr>
<td>Costello Syndrome</td>
<td>PS, HCM, cardiac conduction abnormalities</td>
<td>Short stature, developmental delay, coarse facies, nasolabial papillomata, increased risk of solid organ carcinoma</td>
</tr>
<tr>
<td>LEOPARD Syndrome</td>
<td>PS and cardiac conduction abnormalities</td>
<td>Lentigines, hypertelorism, abnormal genitalia, growth retardation, sensorineural deafness</td>
</tr>
<tr>
<td>Alagille Syndrome</td>
<td>PS, TOF, ASD, peripheral pulmonary stenosis</td>
<td>Bile duct paucity, cholestasis, typical facies, butterfly vertebrae, ocular anomalies, growth delay, hearing loss, horseshoe kidney</td>
</tr>
<tr>
<td>Marfan Syndrome</td>
<td>Aortic root dilatation and dissection, mitral valve prolapse</td>
<td>Tall stature, arachnodactyly, pectus abnormality, scoliosis, ectopia lentis, spontaneous pneumothorax, striae, dural ectasia</td>
</tr>
<tr>
<td>Holt-Oram Syndrome</td>
<td>ASD, VSD, AVSD, progressive AV conduction system disease</td>
<td>Preaxial radial ray malformations (thumb abnormalities, radial dysplasia)</td>
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<tr>
<td>Heterotaxy Syndrome</td>
<td>DILV, DORV, d-TGA, AVSD</td>
<td>intestinal malrotation</td>
</tr>
<tr>
<td>Char Syndrome</td>
<td>PDA</td>
<td>Dysmorphic facies and digit anomalies</td>
</tr>
<tr>
<td>CHARGE Syndrome</td>
<td>ASD, VSD, valve defects</td>
<td>Coloboma, choanal atresia, developmental delay, genital and/or urinary anomalies</td>
</tr>
</tbody>
</table>

(Curr Cardiol Rev. 2010; 6(2): 91–97)
Neuro-Cardio-Facial-Cutaneous syndromes

RAS-MAP Kinase Pathway Disorders:

- Noonan syndrome
- Costello syndrome
- Cardio-Facio-Cutaneous syndrome
- LEOPARD syndrome
- Legius syndrome
- Neurofibromatosis I
RAS-MAP Kinase Pathway

RTK → GRB2 → SOS1 → SHP2 → RAS-GTP → Raf → MEK → MAPK → Gene transcription in nucleus

- Noonam Syndrome
- LEOPARD Syndrome
- CFC Syndrome
- Costello Syndrome
- NF1 like syndrome

GDP to GTP: NF1

GTP to GDP: SPRED
Features common to most Neuro-cardio-facial-cutaneous (NCFC) syndromes are:

- variable degree of mental retardation or learning disabilities
- cardiac defects (particularly pulmonary valve stenosis and hypertrophic cardiomyopathy)
- facial dysmorphism with downslanting eyes
- short stature
- relative macrocephaly
- skin abnormalitie &
- an increased risk for malignancy

Reason for overlap: Genes involved act through a common pathway – the RAS MAPK pathway
Neuro-Cardio-Facial-Cutaneous Syndromes

Noonan syndrome

Cardio-Facio-Cutaneous syndrome
(From: Internet Journal of Pediatrics and Neonatology. 2006 Vol 6, No. 2)

Costello syndrome
(From: London Medical Database)
Genetic counseling

- After genetic testing and confirmation of genetic etiology, genetic counseling is provided regarding:
  - Diagnosis, natural history, prognosis and management
  - Recurrence risk for subsequent offspring
  - Prenatal testing options for future pregnancies

- Denovo chromosomal abnormalities/microdeletions have risk of recurrence of <1%

- Familial chromosomal rearrangements – 5–30% risk of recurrence

- In single gene disorders, risk of recurrence will vary according to mode of inheritance: AD/AR/XL
Autosomal dominant disorders
**Autosomal dominant disorders**

- Only 1 copy of abnormal gene required to produce phenotype
- Passed from one generation to the next
- Both males and females equally affected
- May be transmitted to offspring of either sex
- Risk of recurrence in offspring is 50%

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   D   D
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 D  DD  DD
 d  Dd  Dd
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Autosomal recessive disorders

Died at 1 yr

3 yrs

P 9 mths
Autosomal recessive disorders

- Both copies of a gene should be mutated to produce disease phenotype
- Parents of an affected individual, though usually asymptomatic, are obligate carriers
- Horizontal pedigree pattern with 1 or more siblings affected
- Both males and females are equally affected
- Risk of recurrence in siblings is 25%
X-linked recessive disorders

- Died at 18 yrs
- Died at 20 yrs
- 9 yrs
- 7 yrs
- 3 yrs
**X-linked recessive disorders**

- Mostly males affected; females usually normal carriers or only mildly affected
- For a carrier mother, risk of male offspring being affected is 50% and chance of female offspring being carrier is 50%.

<table>
<thead>
<tr>
<th></th>
<th>(X_A)</th>
<th>(X_a)</th>
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<tbody>
<tr>
<td>(X_A)</td>
<td>(X_A)</td>
<td>(X_A) (X_a)</td>
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<tr>
<td>(Y)</td>
<td>(X_A) (Y)</td>
<td>(X_a) (Y)</td>
</tr>
</tbody>
</table>
Summing up....

- Congenital heart disease can be a component of many genetic syndromes
- Detailed family history and thorough dysmorphology evaluation essential in every case with CHD
- Genetic test to be done depends on clinical diagnosis – no single test for all types of genetic disorders
- Karyotyping informative only for chromosomal disorders
- Accurate genetic diagnosis essential for appropriate management, genetic counseling and prenatal diagnosis