Genetics of Congenital Heart Diseases

by
WINCARS Association

Dr Prajnya Ranganath
(MD Pediatrics, DM Medical Genetics)
Associate Professor & Head

&

Dr Dhanya Lakshmi N
MD(Pediatrics),DCH,DNB,DM (Medical Genetics)
Assistant Professor

Dept of Medical Genetics
Nizam’s Institute of Medical Sciences, Hyderabad
- 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

(Figure 1: Timeline of CHD Genetic Discoveries and the Genetic Technologies and Study Designs Used)

First report on CHD genetics (Campbell, 1949)
First multifactorial inheritance hypothesis (Nora, 1968)
Empiric RR in CHD (Nora, 1970)
Epidemiology of CHD - BWIS first report (Ferencz, 1985)
First single-gene mutation associated with nonsyndromic CHD (NKK2-S) (Schott, 1998)
First single-gene mutation associated with syndromic CHD (TBX5) (Basson, 1997)
GATA4 gene associated with CHD (Garg, 2003)
CHD gene panel (Blue, 2014)
CNV analysis in CHD (Thiendepont, 2007)
GWAS in CHD (Cordell, 2013)
Somatic mutations (Reamon-Buettner, 2004)
De novo variants in sporadic CHD (Zaidi, 2013)
ES in familial CHD (Arrington, 2012)
ES in CHD & NDD (Homsy, 2015)
ES in AVSD (Priest, 2016)
Clinical ES in familial CHD (LaHaye, 2016)
ES in sCHD vs nsCHD (Sifrim, 2016)

Linkage analysis → CMA → GWAS → MPS

(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)

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>
</tr>
</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>
</tr>
<tr>
<td>Signalling pathway</td>
<td>Wnt, RAS MAPK, NOTCH, TGF beta Bmp, FGF</td>
<td>Rasopathies, Robinow syndrome</td>
</tr>
<tr>
<td>Micro RNA</td>
<td>miR-1-1 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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transcription Factors and Co-factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANKRD1</td>
<td>Ankyrin Repeat Domain</td>
<td>TAPVR</td>
<td>609599</td>
</tr>
<tr>
<td>CITED2</td>
<td>c-AMP Responsive Element- Binding Protein</td>
<td>ASD; VSD</td>
<td>602937</td>
</tr>
<tr>
<td>FOG2/ZFPM2</td>
<td>Friend of GATA</td>
<td>TOF, DORV</td>
<td>603693</td>
</tr>
<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>
<td>601656</td>
</tr>
<tr>
<td>HAND2</td>
<td>Helix-Loop-Helix Transcription Factor</td>
<td>TOF</td>
<td>602407</td>
</tr>
<tr>
<td>IRX4</td>
<td>Iroquois Homeobox 4</td>
<td>VSD</td>
<td>606199</td>
</tr>
<tr>
<td>MED13L</td>
<td>Mediator Complex Subunit 13- like</td>
<td>TGA</td>
<td>608771</td>
</tr>
<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>
<td>600584</td>
</tr>
<tr>
<td>NKX2-6</td>
<td>Homeobox Containing Transcription Factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBX1</td>
<td>T-Box 1 Transcription Factor</td>
<td>TOF, (22q11 deletion syndromes)</td>
<td>602054</td>
</tr>
<tr>
<td>TBX5</td>
<td>T-Box 5 Transcription Factor</td>
<td>AVSD, ASD, VSD, (Holt Oram syndrome)</td>
<td>601620</td>
</tr>
<tr>
<td>TBX20</td>
<td>T-Box 20 Transcription Factor</td>
<td>ASD, MS, VSD</td>
<td>606061</td>
</tr>
<tr>
<td>TFAP2B</td>
<td>Transcription Factor AP-2 Beta</td>
<td>PDA, (Char syndrome)</td>
<td>601601</td>
</tr>
<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>
<th>Structural Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACVR1/ALK2</strong> BMP Receptor</td>
<td><strong>ACTC</strong> Alpha Cardiac Actin</td>
</tr>
<tr>
<td><strong>ACVR2B</strong> Activin Receptor</td>
<td><strong>ELN</strong> Elastin</td>
</tr>
<tr>
<td><strong>ALDH1A2</strong> Retinaldehyde Dehydrogenase</td>
<td><strong>MYH11</strong> Myosin Heavy Chain 11</td>
</tr>
<tr>
<td><strong>CFC1/CRYPTIC</strong> Cryptic Protein</td>
<td><strong>MYH6</strong> Alpha Myosin Heavy Chain</td>
</tr>
<tr>
<td><strong>CRELD1</strong> Epidermal Growth Factor-Related Proteins</td>
<td><strong>MYH7</strong> Beta Myosin Heavy Chain</td>
</tr>
<tr>
<td><strong>FOXH1</strong> Forkhead Activin Signal Transducer</td>
<td></td>
</tr>
<tr>
<td><strong>GDF1</strong> Growth Differentiation Factor-1</td>
<td></td>
</tr>
<tr>
<td><strong>GJA1</strong> Connexin 43</td>
<td></td>
</tr>
<tr>
<td><strong>JAG1</strong> Jagged-1 Ligand</td>
<td></td>
</tr>
<tr>
<td><strong>LEFTY2</strong> Left-Right Determination Factor</td>
<td></td>
</tr>
<tr>
<td><strong>NODAL</strong> Nodal homolog (TGF-beta superfamily)</td>
<td></td>
</tr>
<tr>
<td><strong>NOTCH1</strong> NOTCH1 (Ligand of JAG1)</td>
<td></td>
</tr>
<tr>
<td><strong>PDGFRA</strong> Platelet-Derived Growth Factor Receptor Alpha</td>
<td></td>
</tr>
<tr>
<td><strong>SMAD6</strong> MAD-related protein</td>
<td></td>
</tr>
<tr>
<td><strong>TAB2</strong> TGF-beta Activated Kinase</td>
<td></td>
</tr>
<tr>
<td><strong>TGF1</strong> Teratocarcinoma-Derived Growth Factor 1</td>
<td></td>
</tr>
<tr>
<td><strong>VEGF</strong> Vascular Endothelial Growth Factor</td>
<td></td>
</tr>
</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%)

Table 2 Recurrence risks for non-syndromic congenital heart disease in first-degree relatives

<table>
<thead>
<tr>
<th>Type of non-syndromic CHD</th>
<th>Recurrence risk of same CHD in first-degree relatives (%)</th>
<th>Recurrence risk of discordant CHD in first-degree relatives (%)</th>
<th>Recurrence risk of any CHD in first-degree relatives (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASVD</td>
<td>1.10</td>
<td>2.2</td>
<td>3.30</td>
</tr>
<tr>
<td>ASD</td>
<td>0.88</td>
<td>2.4</td>
<td>3.28</td>
</tr>
<tr>
<td>VSD</td>
<td>0.67</td>
<td>1.9</td>
<td>2.57</td>
</tr>
<tr>
<td>ASD and VSD</td>
<td>0.24</td>
<td>2.2</td>
<td>2.44</td>
</tr>
<tr>
<td>Conotruncal defect¹</td>
<td>1.30</td>
<td>2.4</td>
<td>3.70</td>
</tr>
<tr>
<td>Right ventricular outflow tract obstruction²</td>
<td>1.70</td>
<td>3.0</td>
<td>4.70</td>
</tr>
<tr>
<td>Left sided obstructions³</td>
<td>0.79</td>
<td>2.4</td>
<td>3.19</td>
</tr>
</tbody>
</table>

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

Diagram showing the relationship between DNA, genes, proteins, and cellular functions.
Cytogenetic testing
Karyotyping

1. 5 mL venous blood
2. Add phytohemagglutinin and culture medium
3. Culture at 37°C for 3 days
4. Add colchicine and hypotonic saline
5. Cells fixed
6. Spread cells onto slide by dropping
7. Digest with trypsin and stain with Giemsa
8. Analyze “metaphase spread”

(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

![22q11.2 deletions (Schematic diagram depicting the deletion and some of the genes in this region)](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

2. Ligation

3. PCR of the ligated product

4. Capillary Electrophoresis

PCR primer sequence F
PCR primer sequence R
Stuffer sequence; different for each probe sets

Hybridization sequences

If hybridized properly, the two parts are ligated by a thermostable ligase

PCR product of each probe set has a unique length, and can be separated by capillary electrophoresis

3 ml of EDTA blood
Patient’s MLPA result
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
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
DNA Amplification Using Polymerase Chain Reaction

1. **FIRST CYCLE**
   - Reaction mixture contains target DNA sequence to be amplified, two primers (P1, P2) and heat-stable Taq polymerase.
   - Reaction mixture is heated to 98°C to denature target DNA. Subsequent cooling to 37°C allows primers to hybridize to complementary sequences in target DNA.
   - When heated to 72°C, Taq polymerase extends complementary strands from primers.
   - First synthesis cycle results in two copies of target DNA sequence.

2. **SECOND CYCLE**
   - DENATURE DNA
   - HYBRIDIZE PRIMERS
   - EXTEND NEW DNA STRANDS
   - Second synthesis cycle results in four copies of target DNA sequence.
Polymerase chain reaction

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

Exponential amplification

<table>
<thead>
<tr>
<th>Cycles</th>
<th>Copies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
</tr>
<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>
Molecular genetic tests
DNA sequence analysis

DNA Sequencer

Sequence chromatogram
DNA sequence analysis

PCR amplification

Sequencing

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 1 Chromosome abnormality syndromes associated with CHD

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>% CHD</th>
<th>CHD type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chromosome aneuploidy</strong></td>
<td></td>
<td></td>
</tr>
<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>
<td></td>
</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>
</tr>
<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>
</table>

## Frequency of CHD in various chromosomal disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency of CHD</th>
</tr>
</thead>
<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>22q 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
# Cardiac abnormalities

<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>
</tr>
<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>
</tr>
<tr>
<td>Normal</td>
<td>24%</td>
</tr>
</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
1p36 deletion syndrome

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

- Cardiovascular abnormalities in 43-71%
- ASD, VSD, Valvular abnormalities
- PDA, TOF
- Cardiomyopathy in 23%
### Less common deletion/duplication syndromes

<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>
</tr>
<tr>
<td>4p16 deletion</td>
<td>OS ASD, PS, VSD</td>
<td>Greek helmet facies, Cleft lip/palate</td>
</tr>
<tr>
<td>Wolfe Hisrchhorn</td>
<td></td>
<td>Cleft lip/palate, Abnormal cat cry</td>
</tr>
<tr>
<td>Deletion 5p15</td>
<td>Assorted CHD</td>
<td>Cleft lip/palate, Abnormal cat cry</td>
</tr>
<tr>
<td>(Cri du chat syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17p11.2 deletion</td>
<td>Assorted CHD’s</td>
<td>Self injurious behaviour, Abnormal eyes, ears</td>
</tr>
<tr>
<td>Smith Magenis syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrasomy 22p</td>
<td>TAPVC, PAPVC, Assorted CHD’s</td>
<td>Coloboma, anorectal anomalies, GU abnormalities</td>
</tr>
<tr>
<td>Cat eye syndrome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Single gene disorders associated with CHDs

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Cardiac Anomalies</th>
<th>Other Clinical Features</th>
<th>Causative Gene(s)</th>
</tr>
</thead>
<tbody>
<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>
<td>PTPN11, KRAS, RAF1, SOS1</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>
<td>HRAS</td>
</tr>
<tr>
<td>LEOPARD Syndrome</td>
<td>PS and cardiac conduction abnormalities</td>
<td>Lentigines, hypertelorism, abnormal genitalia, growth retardation, sensorineural deafness</td>
<td>PTPN11, RAF1</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>
<td>JAG1, NOTCH2</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>
<td>FBLN, TGFB1, TGFB2</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>
<td>TBX5</td>
</tr>
<tr>
<td>Heterotaxy Syndrome</td>
<td>DILV, DORV, d-TGA, AVSD</td>
<td>intestinal malrotation</td>
<td>ZIC3, CFC1</td>
</tr>
<tr>
<td>Char Syndrome</td>
<td>PDA</td>
<td>Dysmorphic facies and digit anomalies</td>
<td>TFAP2b</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>
<td>CHD7, SEMA3E</td>
</tr>
</tbody>
</table>

(Curr Cardiol Rev. 2010; 6(2): 91–97)
RAS-MAP Kinase Pathway Disorders:

- Noonan syndrome
- Costello syndrome
- Cardio-Facio-Cutaneous syndrome
- LEOPARD syndrome
- Legius syndrome
- Neurofibromatosis I
RAS-MAP Kinase Pathway
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 downsloping eyes
- short stature
- relative macrocephaly
- skin abnormalities &
- 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)
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%

\[
\begin{array}{ccc}
D & D & D \\
D & DD & DD \\
d & Dd & Dd \\
\end{array}
\]
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%

<table>
<thead>
<tr>
<th></th>
<th>D</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>DD</td>
<td>Dd</td>
</tr>
<tr>
<td>d</td>
<td>Dd</td>
<td>dd</td>
</tr>
</tbody>
</table>
X-linked recessive disorders

P

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>
</tr>
</thead>
<tbody>
<tr>
<td>(X_A)</td>
<td>(X_A X_A)</td>
<td>(X_A X_a)</td>
</tr>
<tr>
<td>(X_a)</td>
<td>(X_A Y)</td>
<td>(X_a Y)</td>
</tr>
</tbody>
</table>
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
THANK YOU

www.nims.edu.in