SYNDROMES AND GENETICS IN CARDIOLOGY
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INTRODUCTION

- 30 minutes to cover an ENORMOUS topic
- I am NOT a genetics expert
- Remember – exams targeted toward GENERAL PAEDIATRICIANS
- Focus on congenital heart disease, not discussing:
  - Cardiac disease in metabolic disorders
  - Cardiomyopathies
  - Channelopathies (Brugada, Long QT syndrome)
- Likely more relevant for clinical exams – so keep this handy for later

Genetic syndromes - defined as a consistent pattern of malformation caused by a genetic alteration

- Change in chromosome number (WHOLE CHROMOSOME)
- Deletion/duplication of specific chromosome regions (SMALL PART OF CHROMOSOME)
- Single gene mutations (EVEN SMALLER PART OF CHROMOSOME)

CHD in association with other anomalies or syndrome in 25-40%

WHOLE CHROMOSOME

Aneuploidy
- Extra or missing whole chromosome
- 30% have CHD
  - Trisomies (21, 13 & 18)
  - ‘Missing X’ (Turner syndrome)
  - ‘Extra X’ (Klinefelter syndrome)

Tested by…
- Karyotype
TRISOMY 21

Clinical Features:
- Low set/small ears
- Flat facial features
- Upslanting palpebral fissures
- Transverse palmar crease
- Clinodactyly
- Hypotonia
- Widely spaced 1st & 2nd toes
- etc, etc...

50% have CHD

Clinical Features:
- ASD
- AV canal defect
- VSD
- Tetralogy of Fallot
- Coarctation of the aorta

50% have CHD

QUESTION

What is the most common congenital heart defect in trisomy 21?

a. ASD
b. AV canal defect
c. VSD
d. Tetralogy of Fallot
e. Coarctation of the aorta

AV canal defects

40% in trisomy 21
75% with AV canal defects have trisomy 21

Usually complete AV canal defects, but don’t forget partial defects
Often no murmur
Characteristic ECG – superior axis

Other left-to-right shunts:
- ASD
- VSD
- PDA

Other Issues:
- High risk of pulmonary hypertension
- Initially protective
- Develop irreversible pulmonary hypertension early
- Worsened by airway/lung disease
- Eisenmenger’s syndrome
- Goal – early surgical repair

Cyanotic CHD:
- Tetralogy of Fallot – 10%
- More complex lesions – palliative procedures not always offered

TRISOMY 13

Patau Syndrome

Clinical Features:
- Holoprosencephaly
- Cleft aplasia
- Midline defects
- Microphthalmia
- Coloboma
- Polydactyly/clenched hand
- Severe mental retardation

80% have CHD
- ASD/VSD
- PDA
- HLHS

80% die within first year of life

Other Issues:
- High risk of pulmonary hypertension
- Initially protective
- Develop irreversible pulmonary hypertension early
- Worsened by airway/lung disease
- Eisenmenger’s syndrome
- Goal – early surgical repair
**TRISOMY 18**

Edwards Syndrome

1 in 8,000 live births

**Clinical Features:**
- Hypertonia/arthrogryposis
- Rocker-bottom feet
- Overlapping fingers
- Omphalocele/diaphragmatic hernia
- Severe mental retardation

90-100% have CHD
- ASD/VSD
- PDA
- DORV/TToF/CoA

Median lifespan 5-15 days, 8% live beyond 1 year (CHD not life-limiting)

**TURNER SYNDROME (XO)**

1 in 2,000

**Clinical Features:**
- Short stature
- Broad chest
- Low posterior hairline
- Webbed neck
- Cubitus valgus
- Infertility

Usually not apparent until late childhood/adolescence

35% with CHD

**QUESTION**

What is the most common congenital heart defect in Turner syndrome?

a. AV canal defect
b. Tetralogy of Fallot
c. Coarctation of the aorta
d. Bicuspid aortic valve
e. Hypoplastic left heart syndrome

**Left Heart Lesions**
- Bicuspid aortic valve (15%)
- Aortic stenosis (10%)
- CoA (10%)
- Mitral valve anomalies (<5%)
- HLHS (rare)

- Early – aortic stenosis
- Later – aortic root dilatation and aortic regurgitation

- Long-term surveillance

**KLINEFELTER SYNDROME (47XXY)**

1 in 1,000

**Clinical Features:**
- Tall stature (reduced US:LS)
- Low IQ/behaviour problems
- Hypergonadostrophic hypogonadism (small testes 100% infertile)
- Gynaecomastia

Can go undetected

50% have CHD
- ASD
- PDA
**PART OF CHROMOSOME**

- Microdeletion of part of a chromosome
  - 22q11 microdeletion
  - William's syndrome

**22q11 MICRODELETION**

- 1 in 4,000
- 10% inherited, 90% sporadic

**Clinical Features (CATCH 22):**
- Cardiac anomalies
  - Abnormal facies (low-set/notched/rotated ears, short palpebral fissures, micrognathia, narrow nose, upslanting eyes)
  - Thymic aplasia/hypoplasia (1% complete)
  - Cleft palate, bifid uvula
  - Hypocalcaemia/hypoparathyroidism

- 30-fold increase risk of schizophrenia
- 75% have CHD

**QUESTION**

What is the most common congenital heart defect in 22q11 microdeletion?

- a. Tetralogy of Fallot
- b. VSD
- c. AV canal defect
- d. Hypoplastic left heart syndrome
- e. D-TGA

**WILLIAMS SYNDROME**

- 1 in 20,000
- 90% have 7q11.23 deletion

**Clinical Features:**
- Elf-like facies
- Widely spaced teeth
- Flat nasal bridge
- Long philtrum
- Developmental delay (strong language skills)
- Infantile hypercalcaemia (15% - self-resolving)

- 50-85% have CHD

**Other Issues:**

- VSD (15%)
- Vascular anomalies (50%)
  - R) aortic arch
  - L) SVC
  - Vascular ring

- Cardiac issues related to deletion of Elastin gene
**QUESTION**

What congenital heart lesion is commonly seen in Williams syndrome?

- a. VSD
- b. ASD
- c. Coarctation of the aorta
- d. Aortic root dilatation
- e. Peripheral pulmonary stenosis

**Supravalvar Problems:**
- Supravalvar aortic stenosis (usually progressive)
- Supravalvar pulmonary stenosis
- Peripheral pulmonary stenosis
- Early murmur – take note of where it radiates
- Careful look at the ECG
- Beware coronaries – very high risk sedation/GA

Non-Williams elastin gene mutations

**Supravalvar Problems:**

**NOTES:**
- Supravalvar aortic stenosis (usually progressive)
- Supravalvar pulmonary stenosis
- Peripheral pulmonary stenosis
- Early murmur – take note of where it radiates
- Careful look at the ECG
- Beware coronaries – very high risk sedation/GA

Non-Williams elastin gene mutations

**QUESTION**

What cardiac problem does this patient with Noonan syndrome have?

- a. Tetralogy of Fallot
- b. Pulmonary stenosis
- c. Hypertrophic cardiomyopathy
- d. Dilated cardiomyopathy
- e. Not sure
### ALAGILLE SYNDROME

1 in 100,000
AD loss of function JAG1 mutation – 94%

**Clinical Features:**
- Bile duct paucity
- Abnormal facies (broad forehead, deep-set widely spaced eyes, long straight nose, short pointed chin)
- Butterfly-shaped vertebrae
- 80% have CHD
- Branch/pulmonary stenosis (70%)
- Tetralogy of Fallot in (10%)
- ASD/VSD
- Aortic stenosis
- Coarctation of the aorta

### MARFAN SYNDROME

1 in 5,000
AD Fibrillin (FBN1) gene mutation (Ch15)

**Cardiac associations:**
- Aortic root dilatation
- Mitral valve prolapse

**Diagnosis made using modified Ghent criteria 2010:**
- Family history
- Aortic root
- FBN1 gene mutation
- Ectopia lentis
- Systemic score

**Negative family history:**
1. Aortic root dilatation + ectopia lentis
2. Aortic root dilatation + FBN1 mutation
3. Aortic root dilatation + systemic score ≥7
4. Ectopia lentis + FBN1 mutation (known to have aortic root dilatation)

**Positive family history:**
5. Ectopia lentis
6. Systemic score ≥7
7. Aortic root dilatation

**Surveillance**

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Deletion/Duplication</th>
<th>Gene Affected</th>
<th>% Affected</th>
<th>Associated Congenital Heart Disease</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion 1p36</td>
<td>35%</td>
<td>TOF/PA, PDA, Ebstein's, DCM, non-compaction</td>
<td>Obesity, cleft lip/palate, epilepsy, hearing loss, brachydactyly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deletion 3p25</td>
<td>33%</td>
<td>Primum ASD, AVSD</td>
<td>Pena, abnormal ears, hearing loss, congenital hypothyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duplication 3q</td>
<td>75%</td>
<td>Various CHD</td>
<td>Craniosynostosis, short neck, GU abnormalities, cleft palate, cicatricial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deletion 4p16</td>
<td>WHSC1/WHSC2</td>
<td>30-50%</td>
<td>Secundum ASD, valvar PS, VSD</td>
<td>Abnormal ears, cleft lip/palate, GU abnormalities, seizures, hearing loss</td>
<td></td>
</tr>
<tr>
<td>Deletion 4q12</td>
<td>40%</td>
<td>RVOT obstruction, PS</td>
<td>Abnormal pinnae, cleft palate, Pierre-Robin sequence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deletion 5p15</td>
<td>20%</td>
<td>VSD, PDA, ToF</td>
<td>Cataract, cleft lip/palate, abnormal ears, presacral tags</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deletion 8p23</td>
<td>GATA4</td>
<td>65-80%</td>
<td>PS, secundum ASD, AVSD, VSD, LV non-compaction</td>
<td>GU abnormalities, abnormal ears, diaphragmatic hernia</td>
<td></td>
</tr>
<tr>
<td>Duplication 8q</td>
<td>45%</td>
<td>Conotruncal defects (ToF, DORV, truncus arteriosus)</td>
<td>Shunt 5th finger, hypertelorism, hirsutism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deletion 9p</td>
<td>35%</td>
<td>Various CHD</td>
<td>Trigonocephaly, hypertelorism, abnormal ears</td>
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### Chromosome Deletion/Duplication

<table>
<thead>
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<tr>
<td>Deletion 10p</td>
<td></td>
<td>50%</td>
<td>VSD, ASD, PDA</td>
<td>Hearing loss, renal anomalies, DiGeorge phenotype</td>
</tr>
<tr>
<td>Deletion 11q23 (Jacobsen Syndrome)</td>
<td></td>
<td>55%</td>
<td>VSD, LVOT obstruction, HLHS</td>
<td>Thyrombocytopenia, undescended testes, renal anomalies</td>
</tr>
<tr>
<td>Deletion 17p11.2 (Smith-Magenis)</td>
<td>RAI1</td>
<td>10%</td>
<td>Various CHD</td>
<td>Brachycephaly-aggressive, self-injurious behaviour, sleep disturbances, eye/ear anomalies</td>
</tr>
<tr>
<td>Deletion 18q</td>
<td></td>
<td>15-30%</td>
<td>PS, ASD, VSD</td>
<td>Widely spaced nipples, cleft palate, GU abnormalities, auricular atresia, brain dysmyelination</td>
</tr>
<tr>
<td>Tetrasomy 22p (cat eye syndrome)</td>
<td></td>
<td>50%</td>
<td>TAPVD/PAVPD</td>
<td>Rectoanal anomalies, coloboma, presacral tag/pit, GU anomalies</td>
</tr>
</tbody>
</table>

### Syndrome Gene Affected % Affected Associated Congenital Heart Disease Other Features

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<tr>
<td>Char syndrome</td>
<td>TFAP2J</td>
<td>20-70%</td>
<td>PDA, muscular VSD</td>
<td>Supernumery nipples, anomalies of 5th finger</td>
</tr>
<tr>
<td>Cornelia de Lange syndrome</td>
<td>NIPBL/SMC1A</td>
<td>25%</td>
<td>VSD, ASD, PS, HCM</td>
<td>Upper limb deficiency, GI anomalies</td>
</tr>
<tr>
<td>Costello syndrome</td>
<td>HRAS</td>
<td>85%</td>
<td>Valvar PS, HCM, atrial tachycardia, aortic dilatation</td>
<td>Skin/soft tissue laxity, fine/curly hair, ulnar deviation, scoliosis, pectus</td>
</tr>
<tr>
<td>Holt-Oram syndrome</td>
<td>TBX5</td>
<td>75%</td>
<td>ASD, VSD, PAVPD, conduction defect</td>
<td>Upper limb abnormalities</td>
</tr>
<tr>
<td>Kabuki syndrome</td>
<td>MLH2</td>
<td>45-55%</td>
<td>ASD, VSD, LVOT obstruction</td>
<td>Long palpebral fissures, cleft lip/palate, skeletal abnormalities</td>
</tr>
<tr>
<td>LEOPARD syndrome</td>
<td>PRPNI/RAFI</td>
<td>70-100%</td>
<td>Valvar PS, HCM, conduction defect</td>
<td>Café au lait macules, lentigines, deafness, ear anomalies</td>
</tr>
<tr>
<td>NF</td>
<td>NFI</td>
<td>2%</td>
<td>Valvar PS, valvar AS, CoA, HCM</td>
<td>Café au lait macules, optic glioma, scoliosis, pseudosarcothrosis</td>
</tr>
<tr>
<td>Rubinstein-Taybi syndrome</td>
<td>CREBBP/EP300</td>
<td>40%</td>
<td>PDA, ASD, VSD, CoA, HLHS</td>
<td>Broad thumbs/great toes</td>
</tr>
<tr>
<td>Townes-Brocks syndrome</td>
<td>SALL1</td>
<td>25%</td>
<td>Truncus arteriosus, ToF, ASD, VSD</td>
<td>Thumb malformations, ear anomalies, imperforate anus</td>
</tr>
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<tr>
<td>Ellis-van Creveld syndrome</td>
<td>EVC/EVC2</td>
<td>70%</td>
<td>AVSD</td>
<td>Short limbs, polydactyly, hypoplastic nails, dental anomalies</td>
</tr>
<tr>
<td>Keutel syndrome</td>
<td>MGP</td>
<td>70%</td>
<td>Peripheral PS</td>
<td>Short digits, mixed hearing loss, cartilage calcification</td>
</tr>
<tr>
<td>McKusick-Kaufman syndrome</td>
<td>MKKS</td>
<td>15-50%</td>
<td>AVSD</td>
<td>Hydrometrocolpos, postaxial polydactyly</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome</td>
<td>DHCR7</td>
<td>45%</td>
<td>Secundum ASD, VSD</td>
<td>2-3 toe syndactyly, cleft palate, lung anomalies, genital anomalies</td>
</tr>
<tr>
<td>Simpson-Golabi-Behmahl syndrome</td>
<td>GPC3</td>
<td>25%</td>
<td>Secundum ASD, VSD, variable cardiomyopathy</td>
<td>Macrocrania, cleft palate, supernumery nipples, hypoplasia, polysismyactyly</td>
</tr>
</tbody>
</table>

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</thead>
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<tr>
<td>PHACES syndrome</td>
<td></td>
<td>90%</td>
<td>CoA, interrupted arch type A, R</td>
<td>Posterior fossa malformation, haemangiomatous, eye anomalies</td>
</tr>
<tr>
<td>Goldenhar syndrome</td>
<td></td>
<td></td>
<td>Conotruncal defects, esp ToF</td>
<td>Microtia, ear tag/pit, hypoplastic face, vertebral anomalies, radial deficiency, GU anomalies</td>
</tr>
<tr>
<td>VATER/VACT ERLS association</td>
<td></td>
<td>50%</td>
<td>Various CHD</td>
<td>Vertebral anomalies, Anorectal anomalies, Tracheoesophageal fistula, Renal anomalies, Limb/radial deficiency, Single umbilical artery</td>
</tr>
</tbody>
</table>
WHAT HAVE I GOT?

Alagille syndrome
Peripheral pulmonary stenosis

WHAT ABOUT ME?

22q11 microdeletion
Blue – Tetralogy of Fallot
Failure – Truncus arteriosus

AND DON’T FORGET ME…

Williams Syndrome
Supravalvar aortic stenosis
My poor coronary arteries…
don’t sedate me

OR ME…

Alagille syndrome AGAIN!!
HETERO TX SYNDROME

Situs classification:
- Situs solitus – normal configuration of thoracic and abdominal viscera
- Situs inversus – inverted configuration of thoracic and abdominal viscera (complete mirror image)
- Situs ambiguous – intermediate configuration of thoracic and abdominal viscera = Heterotaxy syndrome

Heterotaxy ≠ cardiac disease

- Situs solitus and inversus – atrial situs corresponds to visceral situs
- Situs ambiguous – duplication of left or right sided thoracic/abdominal viscera (right/left atrial isomerism)

Situs ambiguous associated with gut malrotation

Situs inversus:
- Associated with dextrocardia
- 3-5% have CHD – usually L-TGA
- 20% have Kartagener’s syndrome

Left atrial isomerism (polyphenia):
- Bilateral left atria and left lungs
- Multiple small spleens (non-functioning)
- Central/transverse liver
- Interrupted IVC (azygous/hemi-azygous continuation)
- CHD – less common (50%) and simple scimitar or abnormal rhythms (including complete heart block)

Right atrial isomerism (asplenia):
- Bilateral right atria and right lungs
- Absent spleen
- Central/transverse liver
- CHD – extremely common (90%) and complex cyanotic + anomalous pulmonary venous return

FINAL TIPS

- Trisomy 21 = AV canal defect AND AV canal defect = Trisomy 21
- Blue trisomy 21 = Tetralogy of Fallot
- Turner’s = Left heart lesions (bicuspid aortic valve)
- 22q11 = Conotruncal defects
- Williams = Supravalvar problems (AS/PS/peripheral PS)
- Noonan’s and superior axis = HCM
- Stretched Marfan = stretched aorta and/or mitral valve

- Tetralogy of Fallot and truncus arteriosus – rule out 22q11
- What happened to D-TGA? – rarely seen in genetic syndromes
- If all else fails – ASD or VSD

BEST OF LUCK TO YOU ALL!