From Genes to Syndromes: Changes in Management

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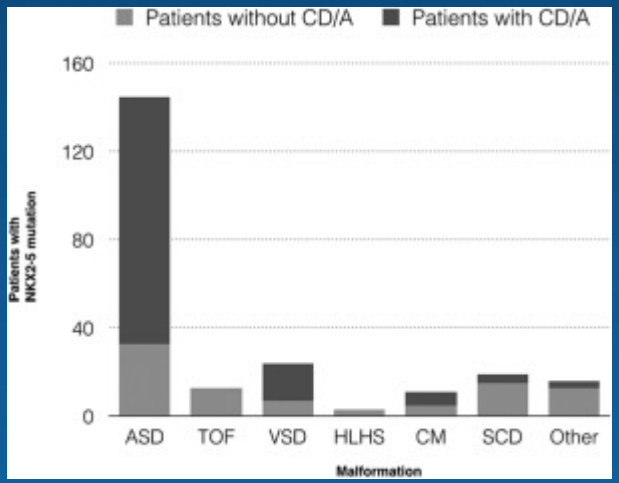
Background

- As you've heard lots of developments in genetics
- A few examples of genetic influencing our management

NKX 2.5

- NKX 2.5- a transcription factor key in the development of the AV Node
- Found in potentially 9% of all familial ACHD
- Autosomal dominant



NKX 2.5

- Conduction abnormalities seen in 74%
- Sudden cardiac death seen in 15% of familial NKX 2.5 cases
- Important pick up in ACHD clinic

NKX 2.5

- 33 yr old male referred from DGH with palps
- Large ASD seen and also had 1st degree AV block
- Given the association- decided to insert a PPM at the time of out-patient surgery for the ASD
- Subsequent genetics positive for a novel NKX 2.5 mutation- wider family history of ASD established

Notch 1

- Bicuspid aortic valve is the most common congenital cardiac lesion
- 1-2% of population affected
- Associated with earlier valve dysfunction and thoracic aortic aneurysm
- Familial inheritance could be up to 30%

Notch 1

- Codes for a transmembrane protien important in cell differentiation
- Rate of aortic dilatation is fives time as high as patient without a Notch 1 mutation
- Would potentially affect our screening intervals and advice to women in pregnancy with a BAV

Noonan's

- Systemic disorder
- Most common gene involved in PTPN11 which is involved in the RAS/MAPK signalling pathway
- Autosomal dominant

Noonan's

- Most common lesion is PS
- There is subset of patient with a hypertrophic cardiomyopathy phenotype
- Important to know as the long term outcome is much better compared to standard HCM
- Also need surveillance for leukaemias

Alagille

- JAG1 mutation-protein binds to NOTCH1 and is important in transcription/cell differentiation
- Can be syndromic with a typical facial appearance but can also be quite subtle
- Causes branch PS

Alagille

- Important to pick up as is associated with bile duct abnormalities and causes liver failure requiring transplant potentially

Holt-Oram

- Classic triad of radial/thumb bone abnormalities, septal defect and conduction abnormalities
- Autosomal dominant
- TBX5 mutation in 75%- transcription factor important in embryogenesis

Holt-Oram

- Sometimes the bony abnormality can be subtle
- Familial penetration can be varaiable

Holt-Oram

- Male late 40s- repaired VSD and complete heart block. Also had short left radial bone and abnormal fingers left hand
- Admitted as an emergency for pacemaker failure
- On discussion-one son has multiple VSDs and possibly an abnormal thumb and the other has cardiac conduction abnormalities at a young age
- All referred to genetics