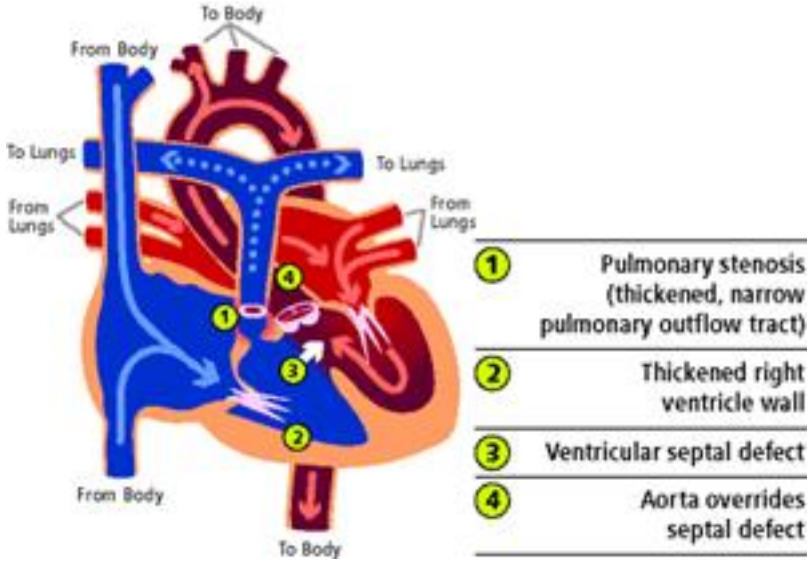
Congenital Heart Disease (CHD)



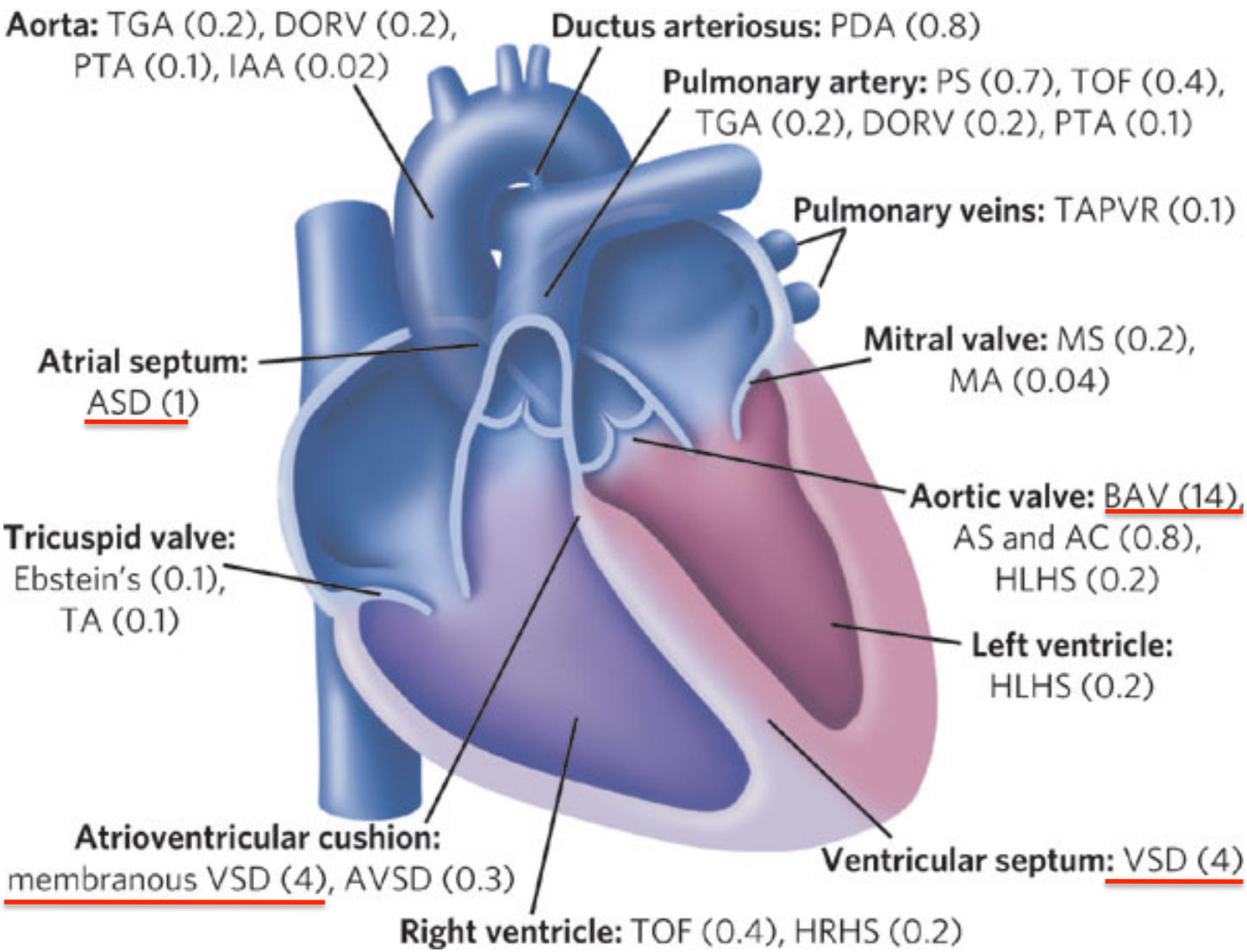
- Congenital heart disease (CHD) usually refers to abnormalities in the heart's structure or function that arises before birth.
- CHD affects 1–2% of all children and is the leading cause of death in infants under 1 year of age.
- At least 10% of the affected children will require surgery during infancy or childhood.

CHD

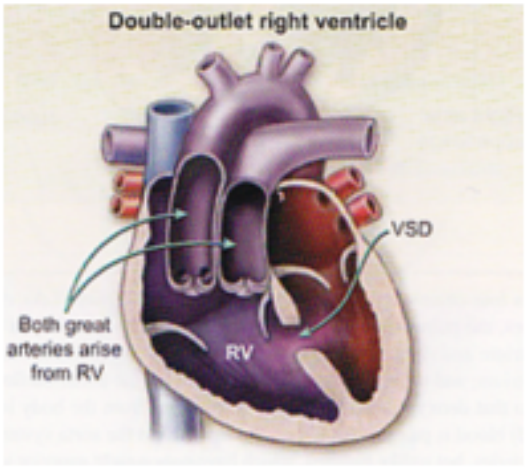
Disease causing mechanisms could be

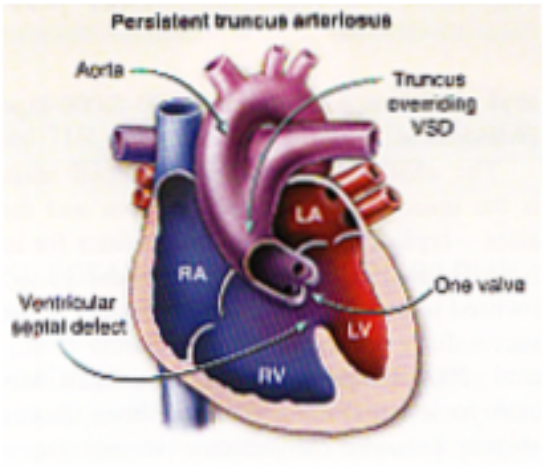
- chromosomal aberrations
  - Trisomy 21, 13, 18
  - Deletions such as those found in the Di George Syndrome
- Spontaneous mutations (Nkx2.5, GATA4, Tbx5)
- Environmental factors
  - alcoholism
  - retinoic acid, vitamin A, folic acid (vitamin B9)
  - obesity
  - hemodynamics
- infections
  - rubella
- pharmacological induced CHD
  - Lithium, Phenytoin, Cumarine
- unknown causes

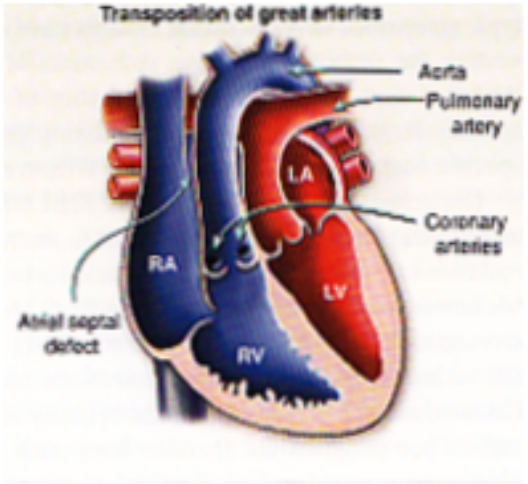
Types of CHD

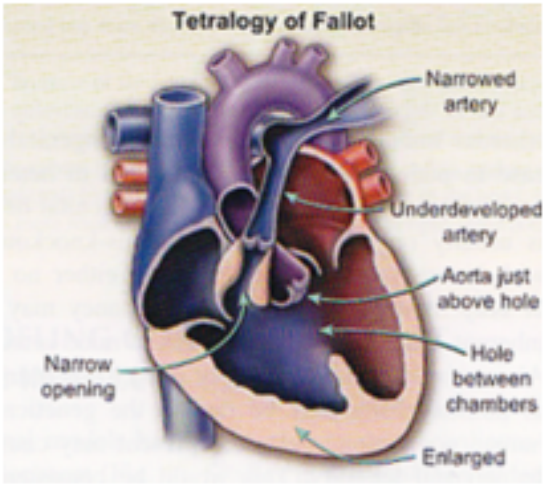

Aorta: TGA (0.2), DORV (0.2), PTA (0.1), IAA (0.02)
Ductus arteriosus: PDA (0.8)
Pulmonary artery: PS (0.7), TOF (0.4), TGA (0.2), DORV (0.2), PTA (0.1)
Pulmonary veins: TAPVR (0.1)
Atrial septum: ASD (1)
Mitral valve: MS (0.2), MA (0.04)
Aortic valve: BAV (14), AS and AC (0.8), HLHS (0.2)
Tricuspid valve: Ebstein's (0.1), TA (0.1)
Left ventricle: HLHS (0.2)
Atrioventricular cushion: membranous VSD (4), AVSD (0.3)
Ventricular septum: VSD (4)
Right ventricle: TOF (0.4), HRHS (0.2)

Cyanotic heart disease (blue baby) as a result of mixing oxygenated and deoxygenated blood









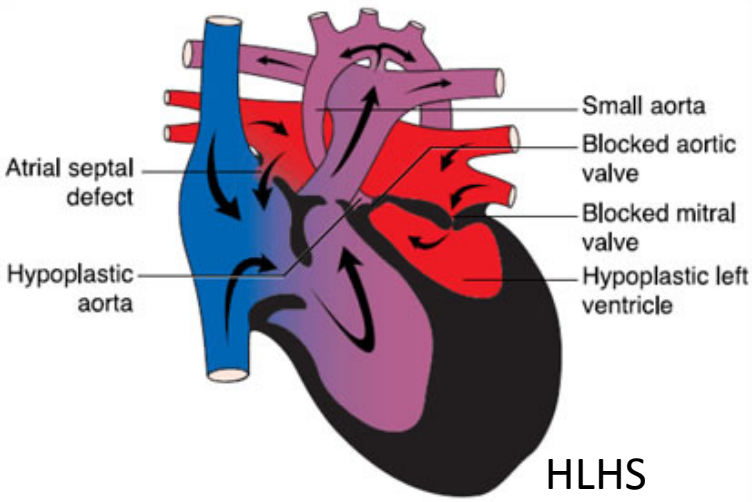
transposition of the great arteries (TGA)
tetralogy of Fallot (TOF)
tricuspid atresia
pulmonary atresia
Ebstein's anomaly of the tricuspid valve
double outlet right ventricle (DORV)
persistent truncus arteriosus (PTA)
total anomalous pulmonary venous connection

Tetralogy of Fallot

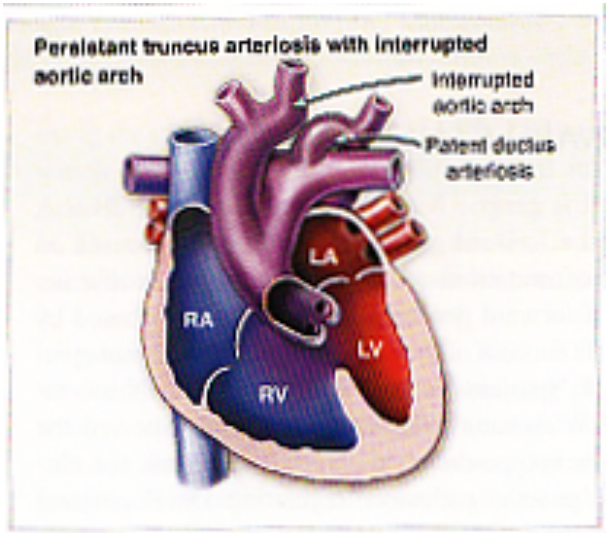
Malalignment of the aortico-pulmonary septum
Ventricular septum defect
Pulmonary stenosis
Overriding aorta
→ Right ventricular hypertrophy

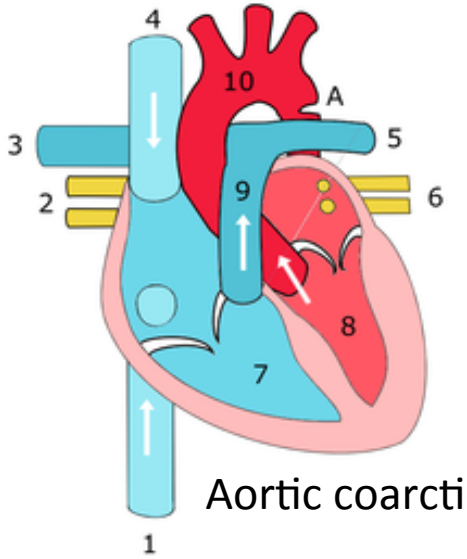
Left sided obstruction defects

hypoplastic left heart syndrome (HLHS)
mitral valve stenosis
aortic valve stenosis
aortic coarctation
interrupted aortic arch (IAA)



HLHS





Aortic coarction

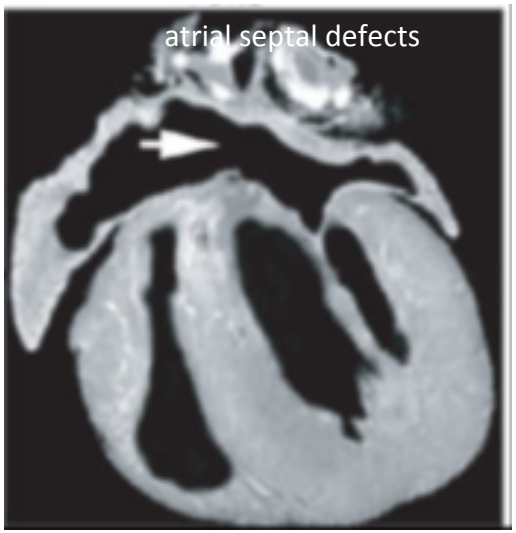
Septation defects

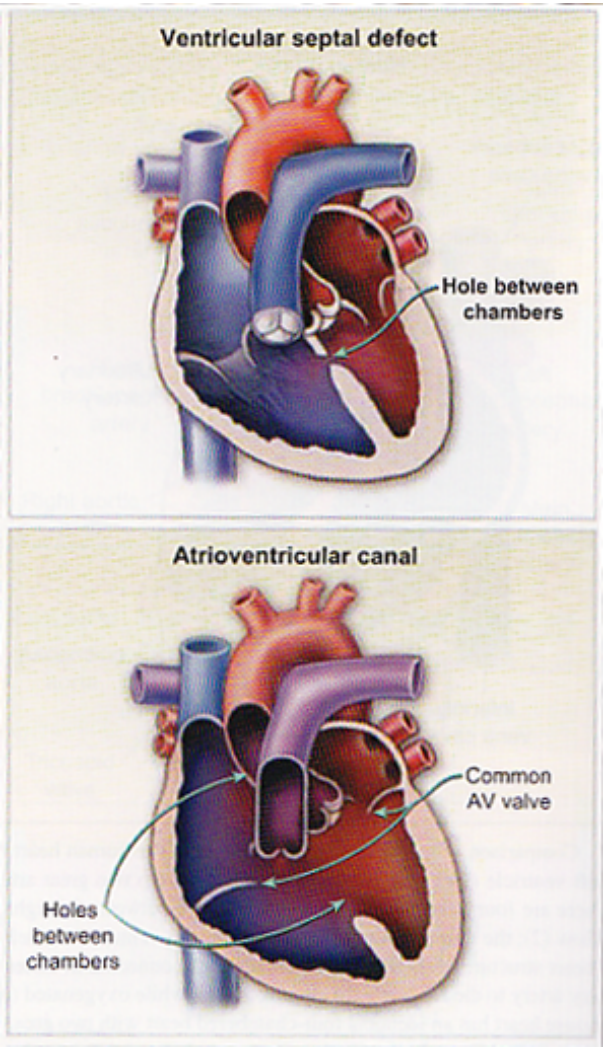
atrial septation defects, (ASDs),

ventricular septal defects (VSDs)

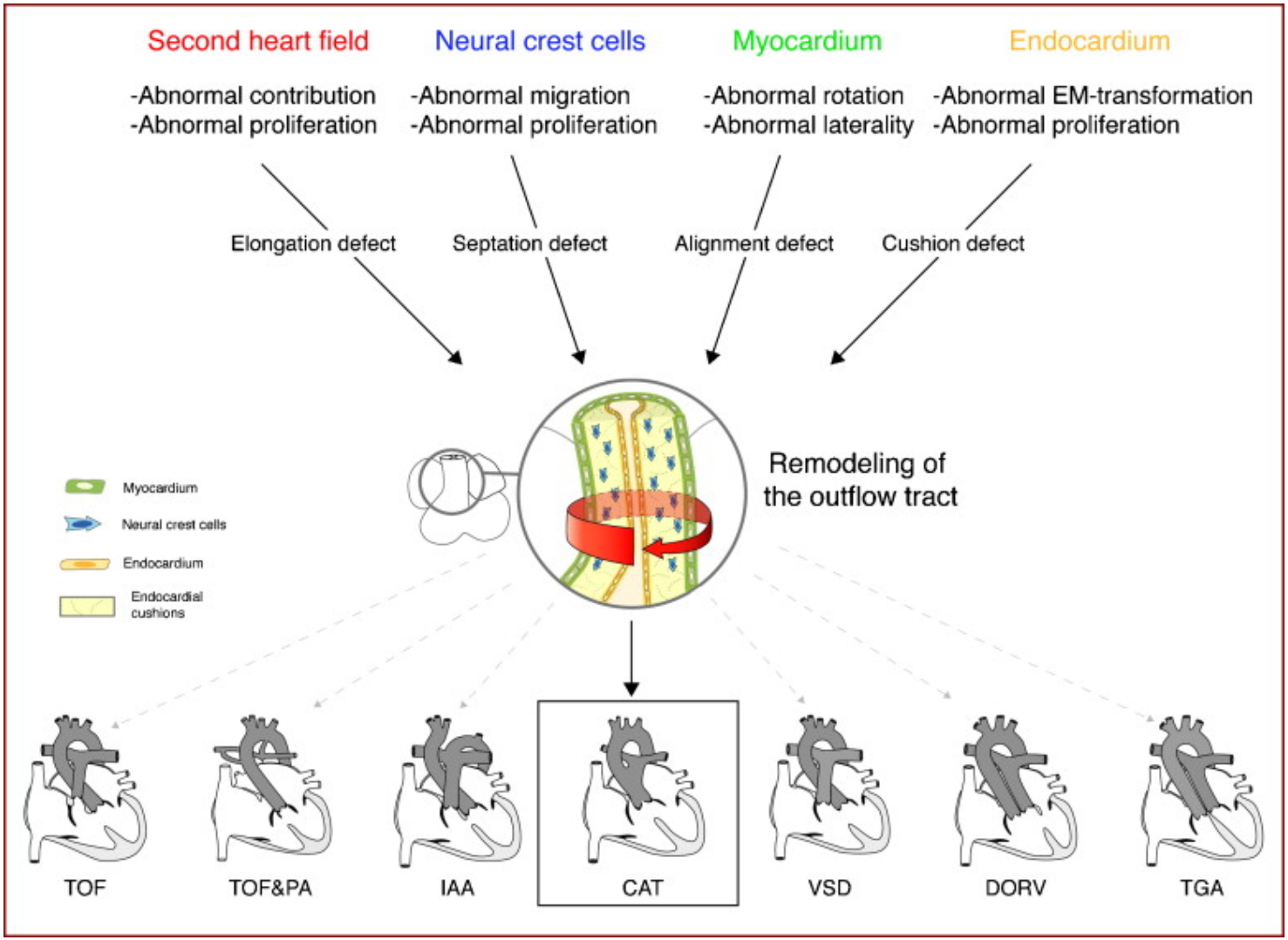
atrioventricular septal defects (AVSDs)

apart from bicuspid aortic valve anomaly septation defects are the most common forms of CHD.





Congenital heart disease is complex and multifactorial

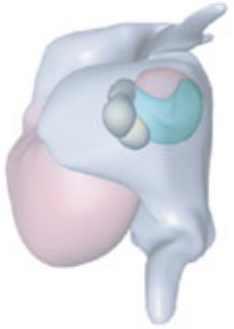


TOF - Tetralogy of Fallot; PA- Pulmonary Atresia, IAA – Interrupted Aortic Arch
CAT – Common Aortic Trunk, VSD - Ventricular Septum Defect,
DORV – Double Outlet Right Ventricle, TGA – Transposition of the Great Arteries

Molecular Basis of CHD

Mutations in the same gene can cause different forms of CHD
Mutations in different genes can cause a similar form of CHD

Atrial septation



ASD: *NKX2-5*
GATA4
TBX20
MYH6
TBX5

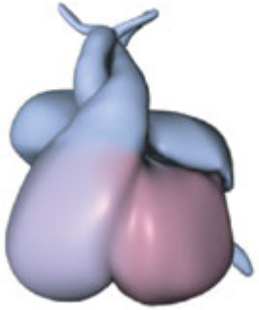
Ventricular septation and atrioventricular cushion formation

VSD: *NKX2-5*
GATA4
TBX20
TBX1
TBX5

AVSD: *PTPN11*
KRAS
SOS1
RAF1
CRELD1

Ebstein's, TA: *NKX2-5*

Great vessel formation and valvulogenesis



DORV, TGA: *NKX2-5*
THRAP2

PTA: *TBX1*

TOF: *NKX2-5,*
NOTCH1
TBX1
JAG1
NOTCH2

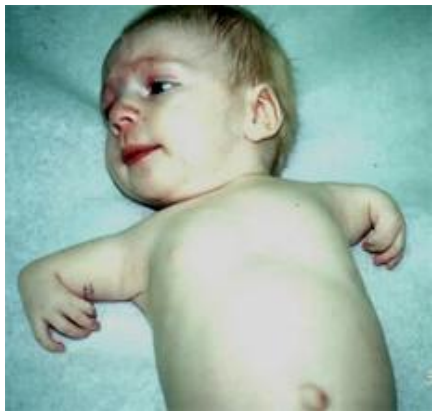
AS and AC: *NOTCH1*
PTPN11

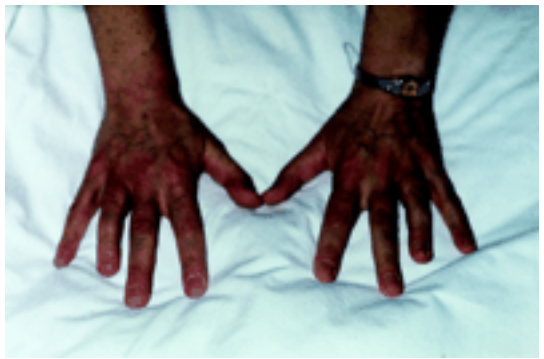
PS: *PTPN11*
JAG1
NOTCH2

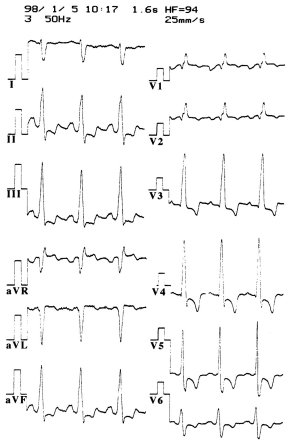
BAV: *NOTCH1*

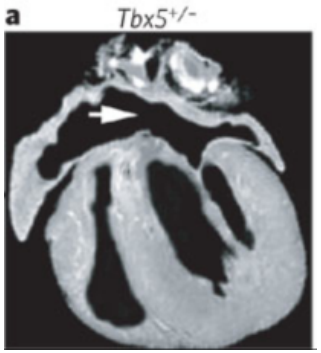
HLHS: *NOTCH1*

PDA: *TFAP2B*









Holt-Oram Syndrome

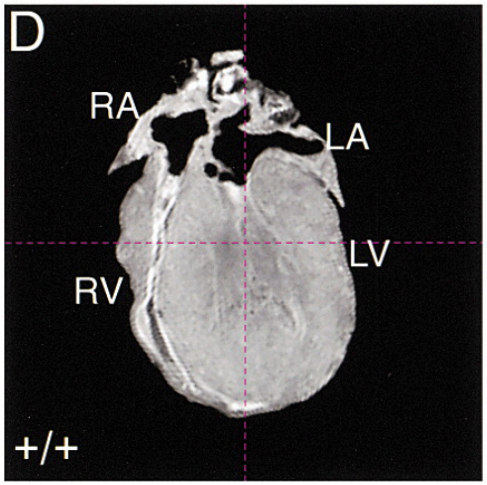
Holt Oram Syndrome (HOS)
is a disorder characterized by birth defects of the upper limbs and defects of the heart.

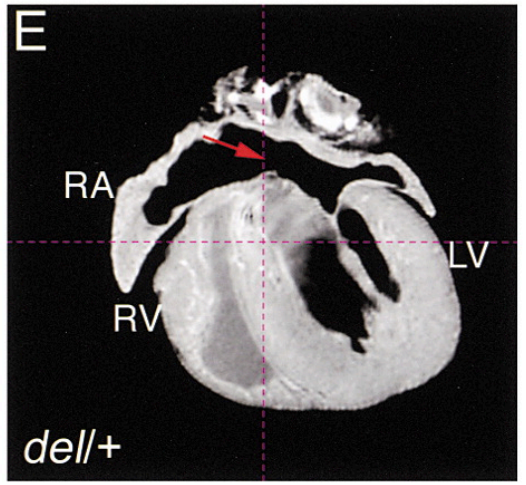
The most common heart defects observed in patients with HOS are atrial septal defects (ASD) and ventricular septal defects (VSD) but may also include electrocardiographic abnormalities, such as various degrees of atrioventricular block.

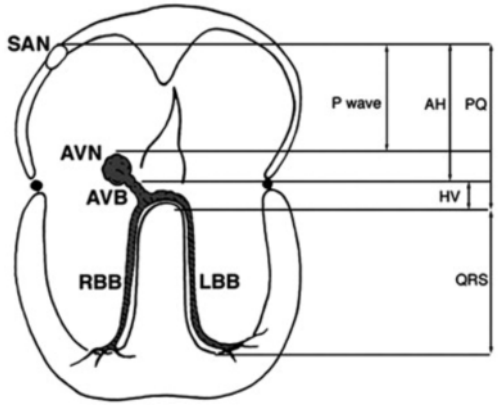
Limb defects observed in HOS range from absence of most of a limb to an extra bone in the thumb. Other limb defects include under-development of a limb, hand, or thumb and fusion of the bones of the wrist.

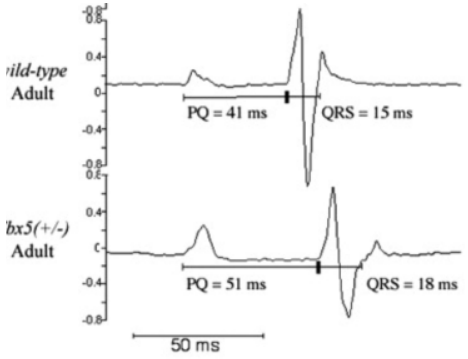
More than 70% of patients diagnosed with HOS have a mutation in Tbx5

Null mutation in mice affects limb and heart development





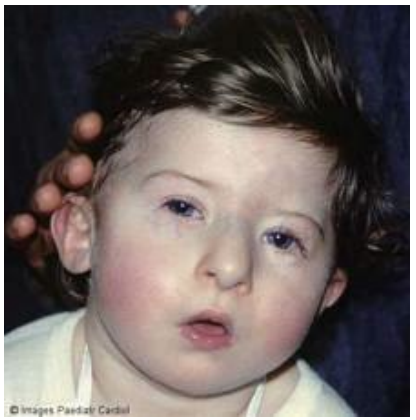


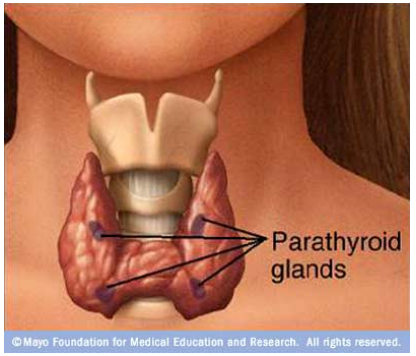


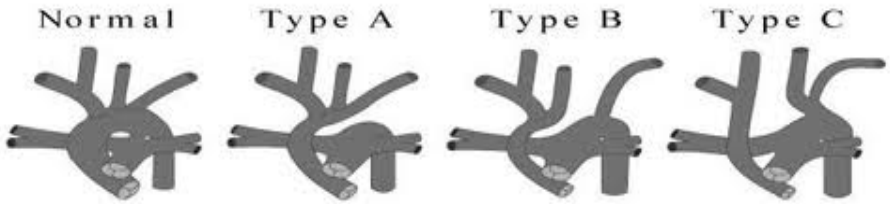
DiGeorge or 22q11 Syndrom

Syndrome with a wide variety of symptoms:
congenital heart disease mainly outflow tract and aortic arch
defects in the palate
learning disabilities
mild defects in facial features
recurrent infections due to impaired T-cell function
hypoplastic thymus
Defective parathyroid (low parathormone hypocalcemia)
Hypothyroidism

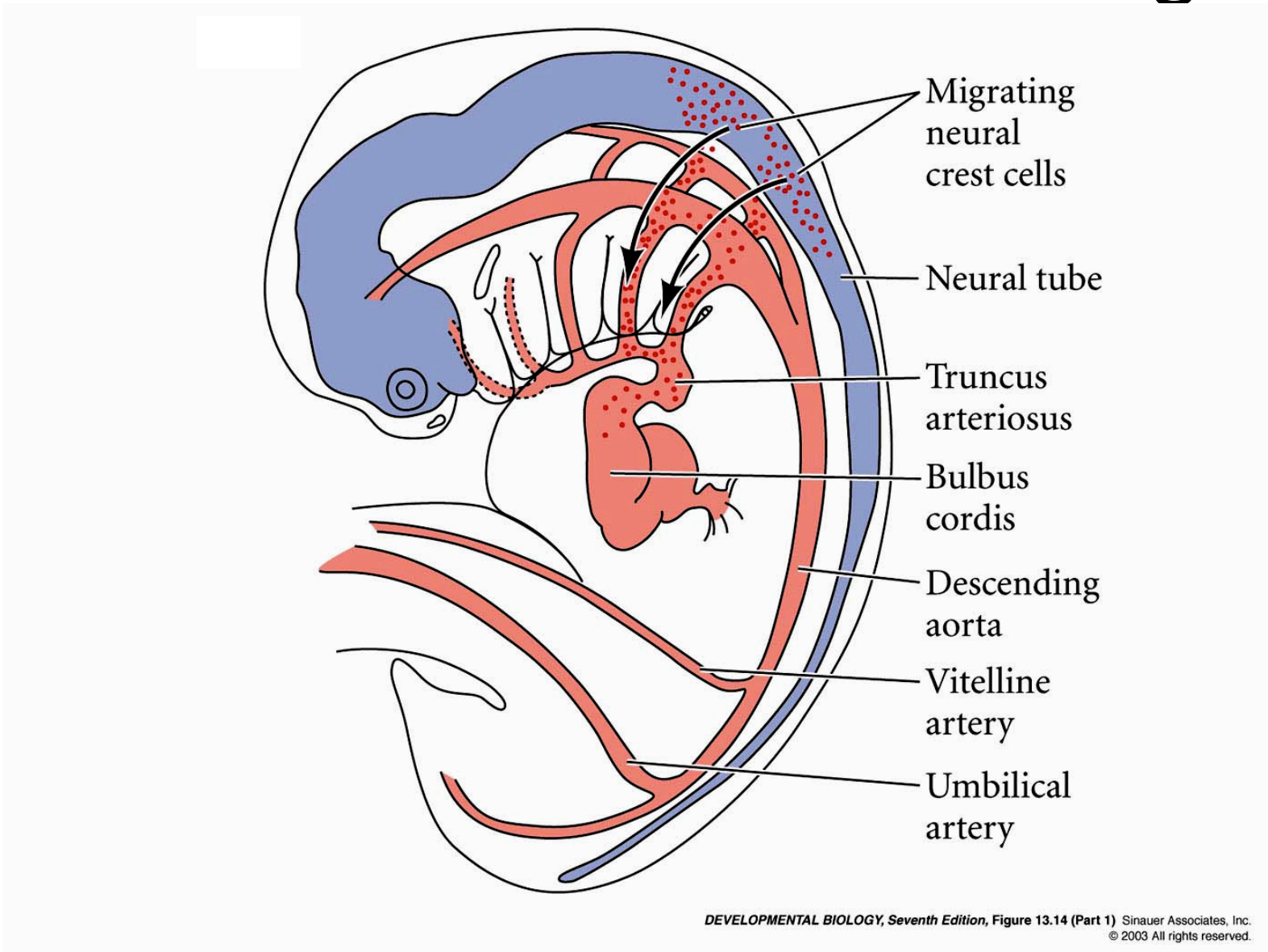
Deletions of 22q11.2





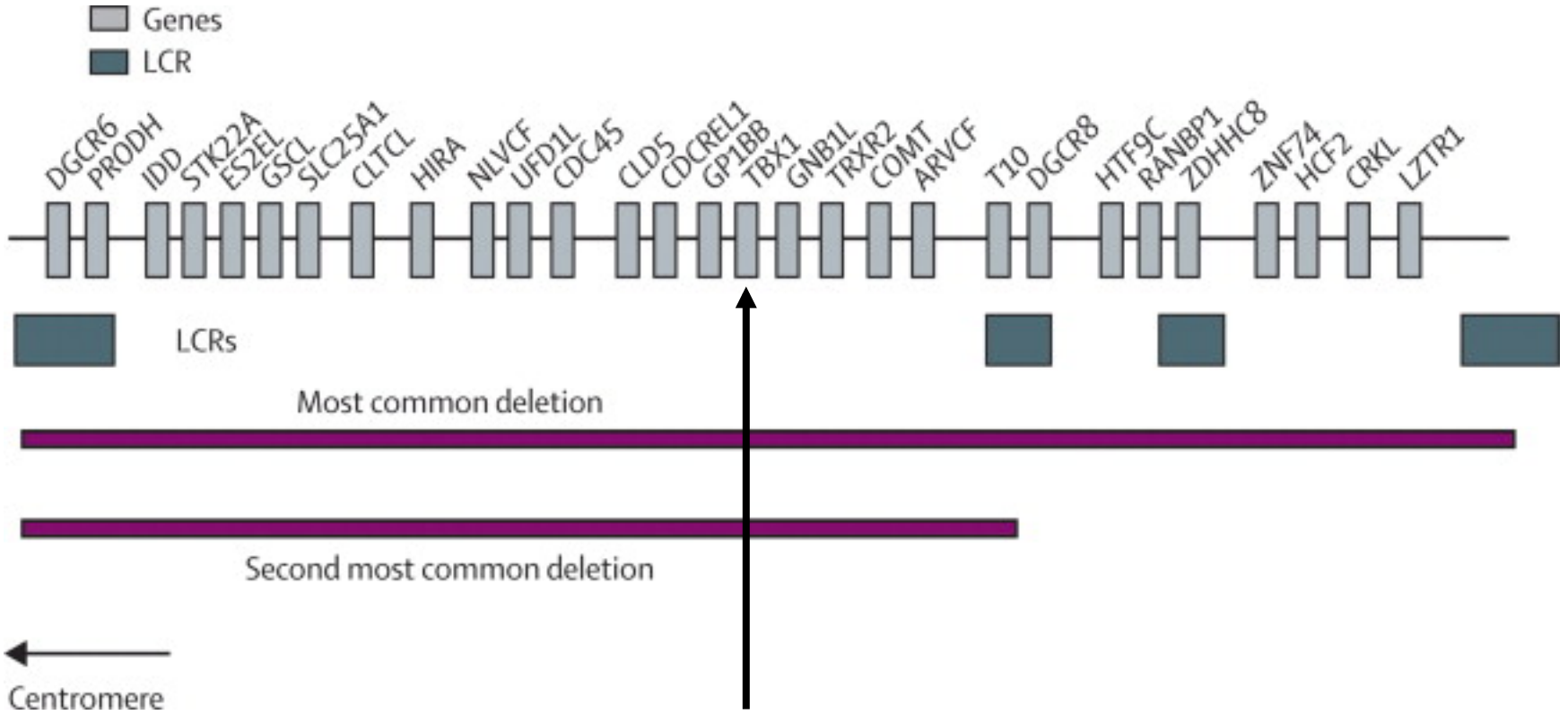


The cardiac neural crest lineage

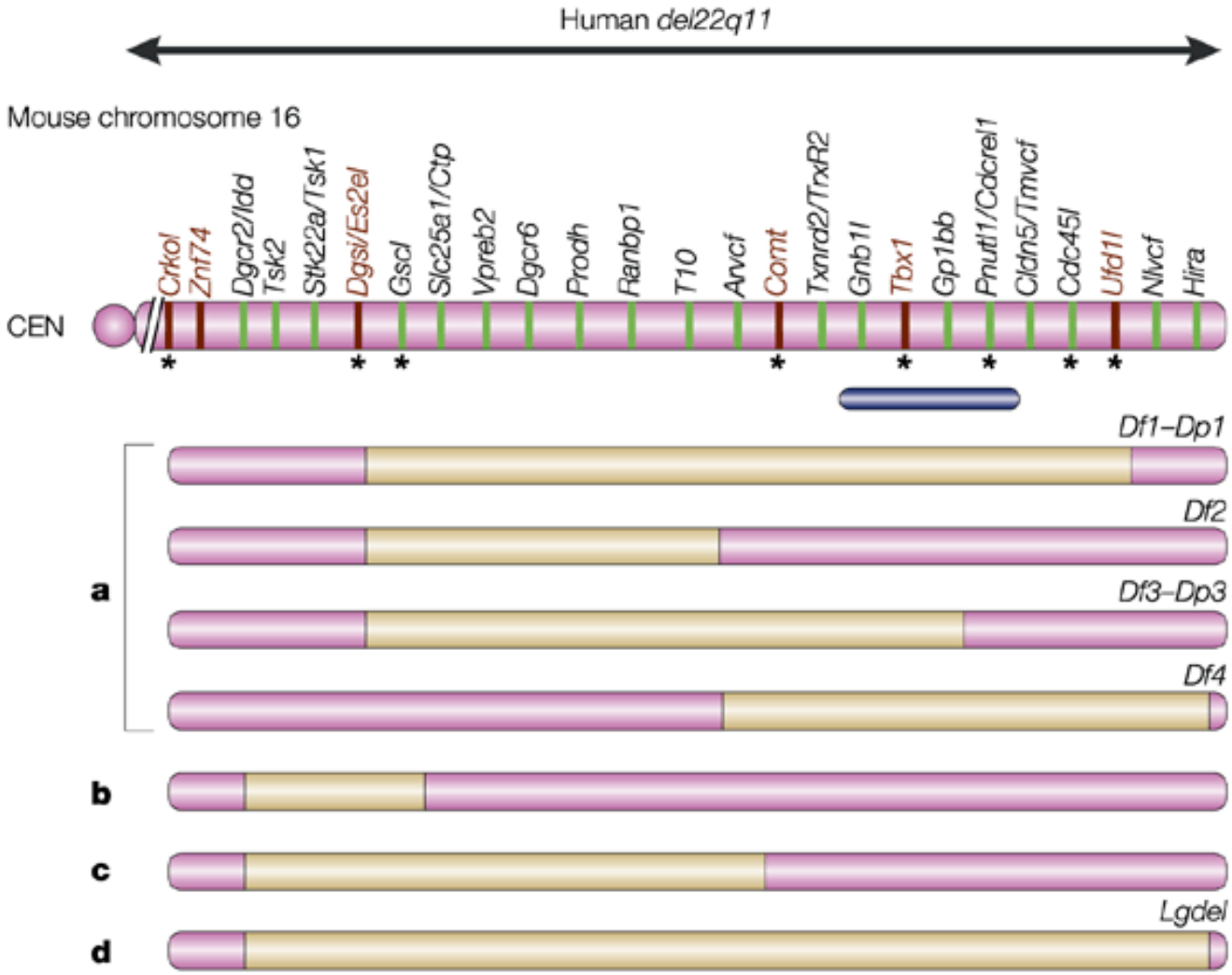


DEVELOPMENTAL BIOLOGY, Seventh Edition, **Figure 13.14 (Part 1)** Sinauer Associates, Inc.
© 2003 All rights reserved.

DiGeorge or 22q11 Syndrom

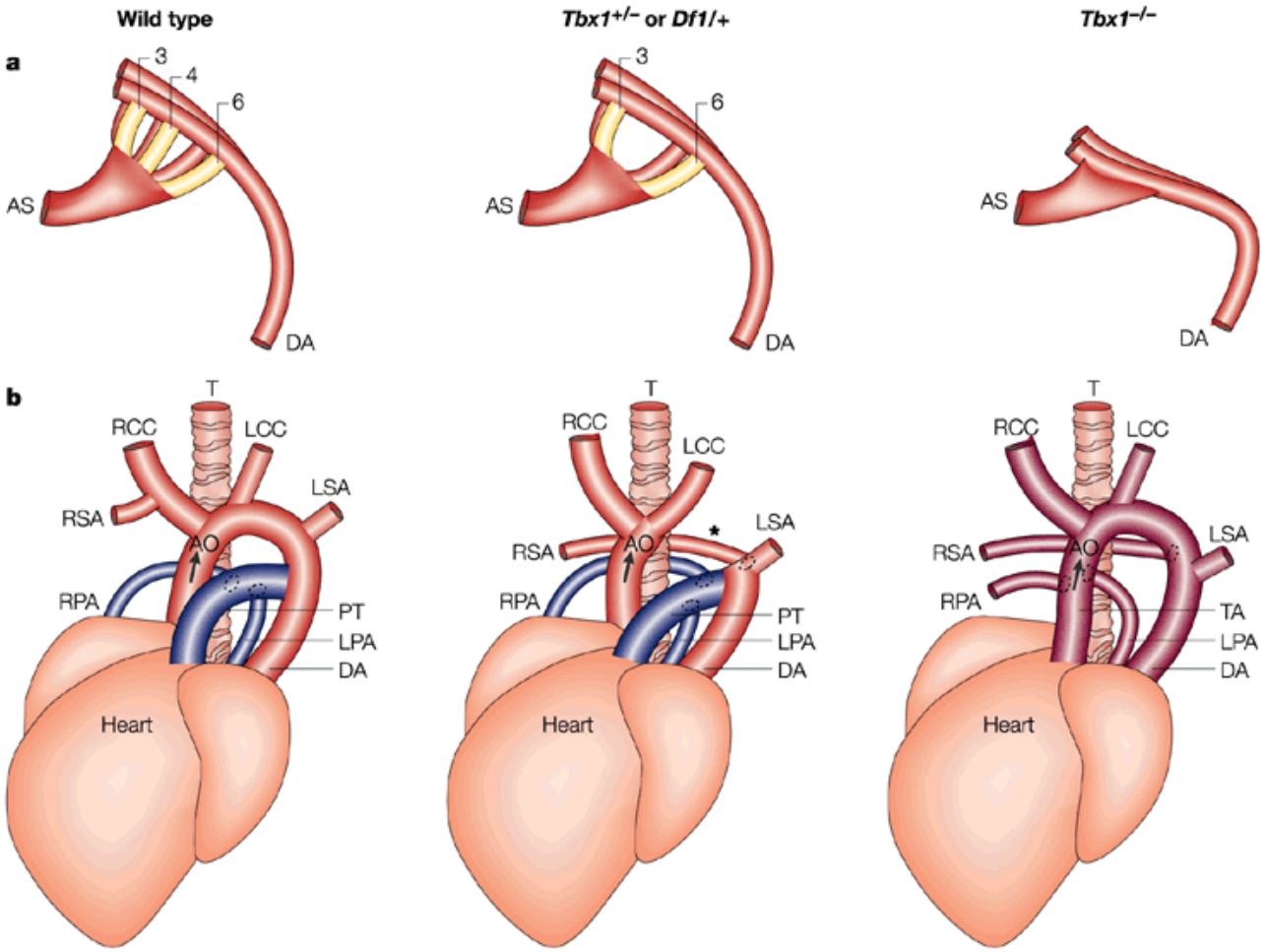


Chromosomal engineering in mice was utilized to mimic human microdeletion of 22q11



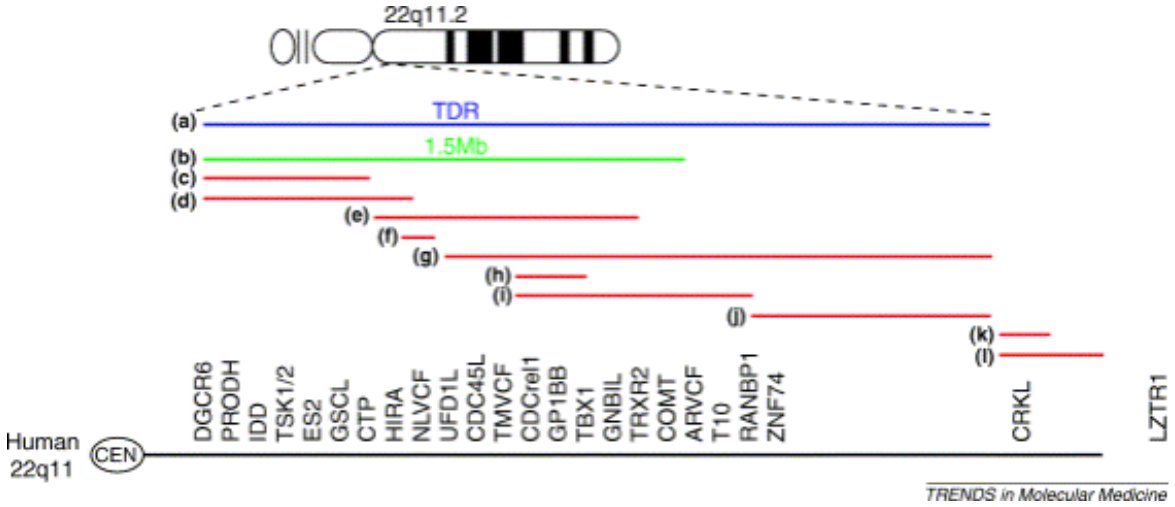
Nature Reviews | Genetics

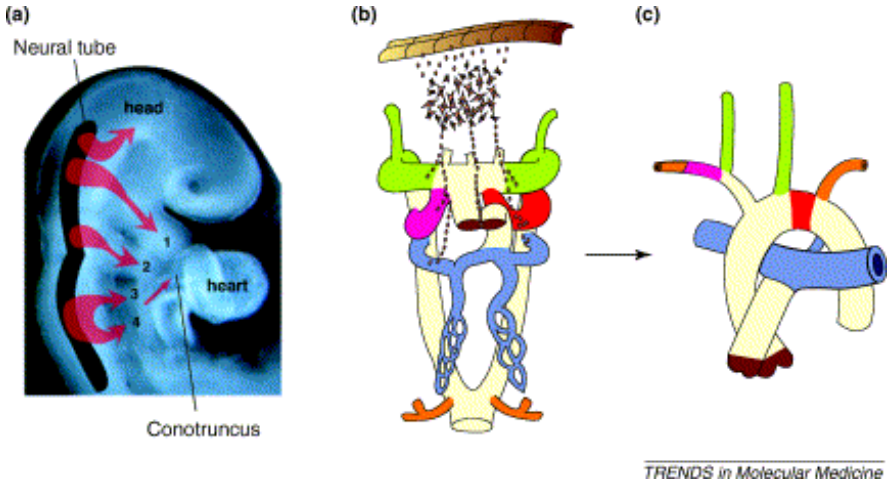
Mice with deletions of 22q11 and mutatins of Tbx1 have aortic arch abnormalities



Nature Reviews | Genetics

DiGeorge or 22q11 Syndrom





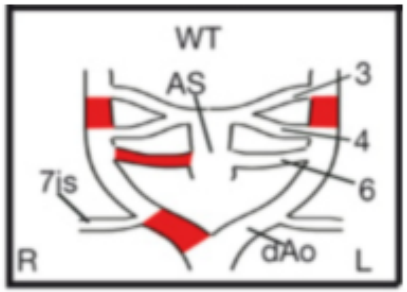
Epigenetic factors

hemodynamic flow
affects valve morphogenesis modulates aortic arch patterning

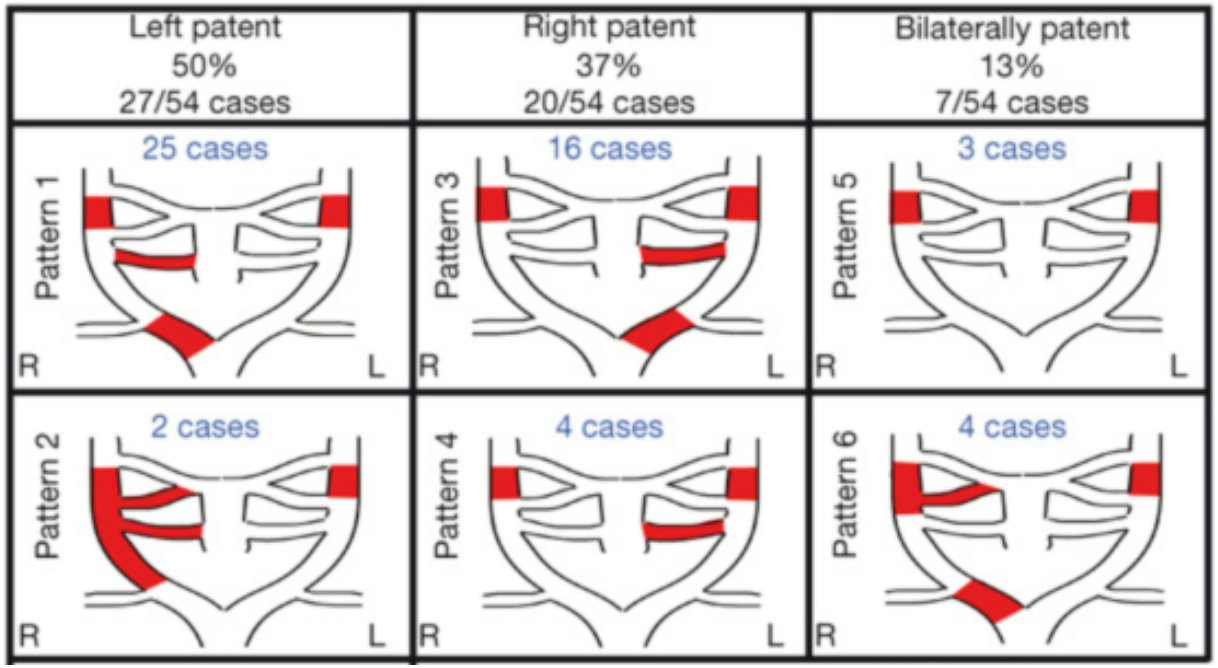
obesity
increased incidence of Tetralogy of Fallot if BMI (during pregnancy) > 40

Blood Flow as an epigenetic factor

WT



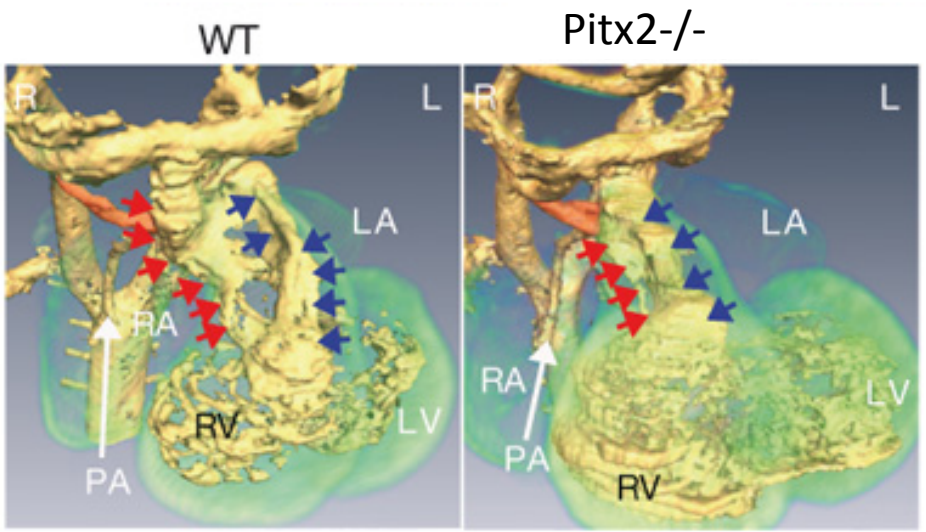
Pitx2-/-

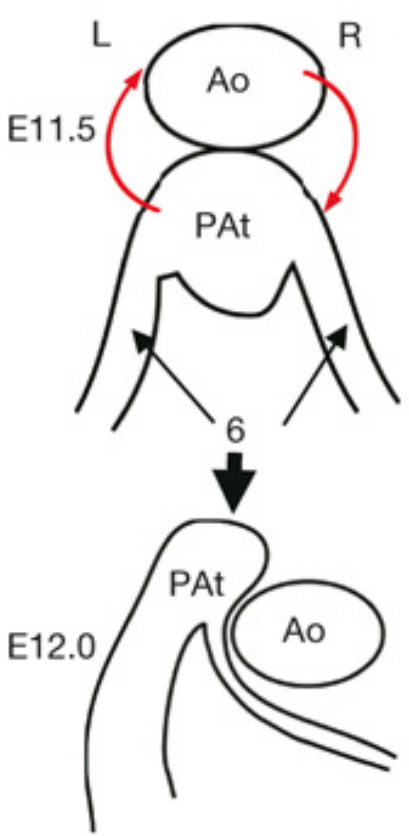


but there is no expression of Pitx2 in the branchial arches (non-cell autonomous)

Yashiro, et al. (2007) *Nature* ***450, 285-288***

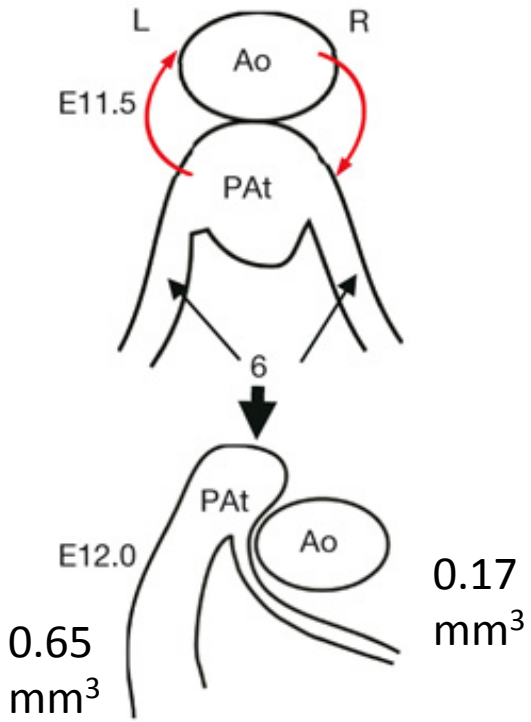
Pitx2 induces asymmetric aortic arch remodelling through an flow-dependent mechanism

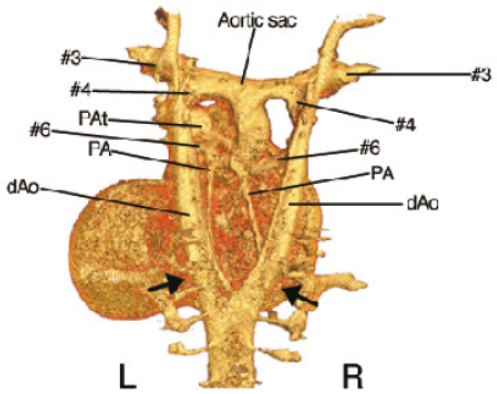




Yashiro, et al. (2007) *Nature* ***450, 285-288***

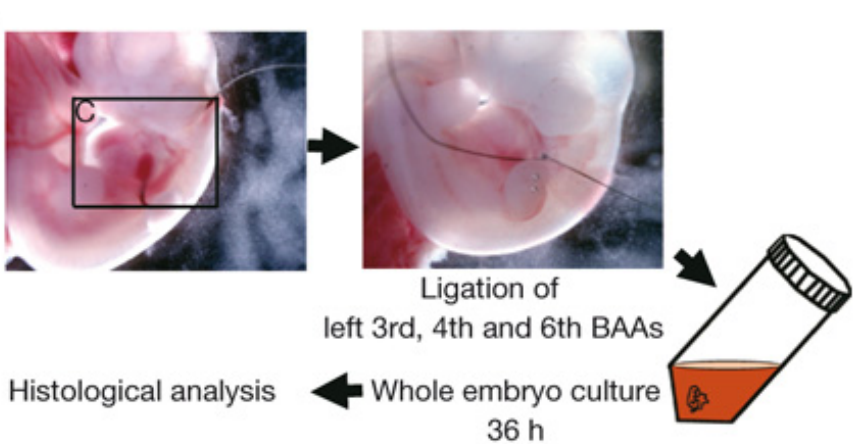
Blood flow through the aortic arch becomes asymmetric at E12.0 in the mouse embryo

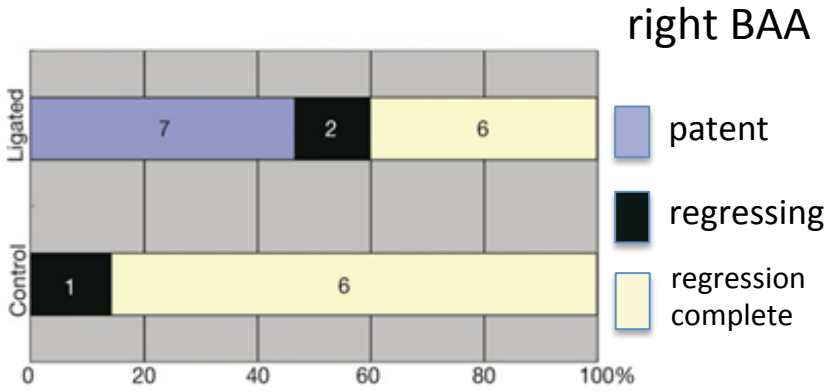


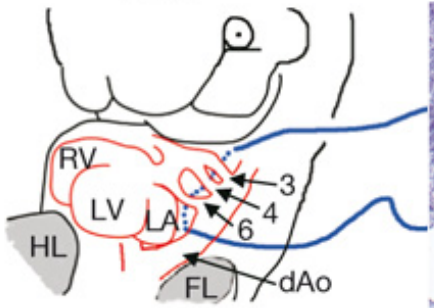


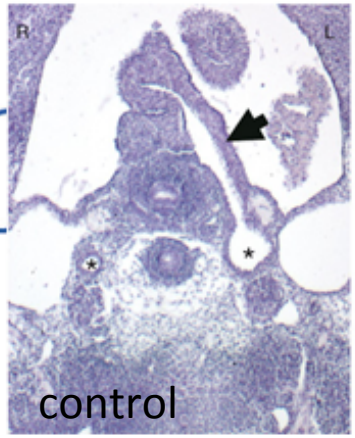
Yashiro, et al. (2007) *Nature* ***450, 285-288***

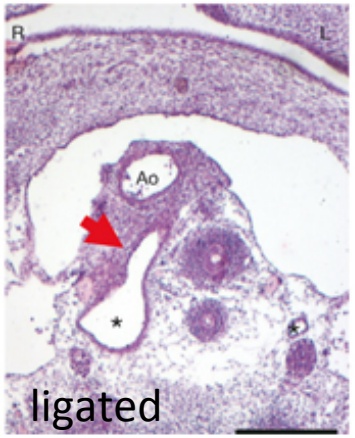
Manipulation of flow reverses aortic arch pattern











Summary

- Congenital heart disease (CHD) is very common and affects between 1 and 2% of babys that are born. The number rises to about 10% if the spontaneous abortions are included.

- There are multiple causes for CHD including chromosomal aberrations such as trisomies or deletions. Syndromic and non-syndromic forms have been mapped to single gene mutations in a wide variety of genes, which all make up a small number of cases. Well established examples are mutations in *TBX5* that induces Holt-Oram syndrome.

- Many mutations in *NKX2.5* have been found in non-syndromic cases of CHD which result in VSD, ASF, TOF, DORV or Ebstein's anomaly.

- Deletion of 22q11 is the cause for Di George syndrome (DGS). There are large number of genes located in this chromosomal region and *TBX1* is responsible for some of the cardiac malformations that are associated with DGS.

- Epigenetic factors also induces CHD such as blood flow or obesity. Pitx2 affects aortic arch remodelling through a flow dependent mechanism. Likewise flow affects endocardial cushion development.

References

Andelfinger G. (2008) Genetic factors in congenital heart malformation. Clin Genet 73:516-27.

Bruneau BG. (2008) The developmental genetics of congenital heart disease. Nature 451:943-8. 18288184.

Srivastava D. (2006) Genetic regulation of cardiogenesis and congenital heart disease. Annu Rev Pathol. 1:199-213.

Clark KL, Yutzey KE, Benson DW. (2006) Transcription factors and congenital heartdefects. Annu Rev Physiol. 68:97-121.