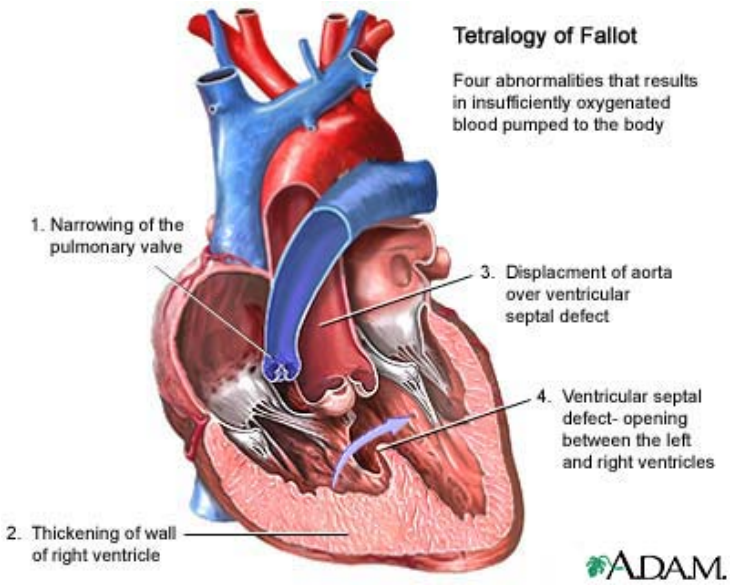
Congenital Heart Disease (CHD)



- 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. CHD is the cause for 30% of embryos or fetuses lost before birth.
- At least 10% of the affected children will require surgery during infancy or childhood.

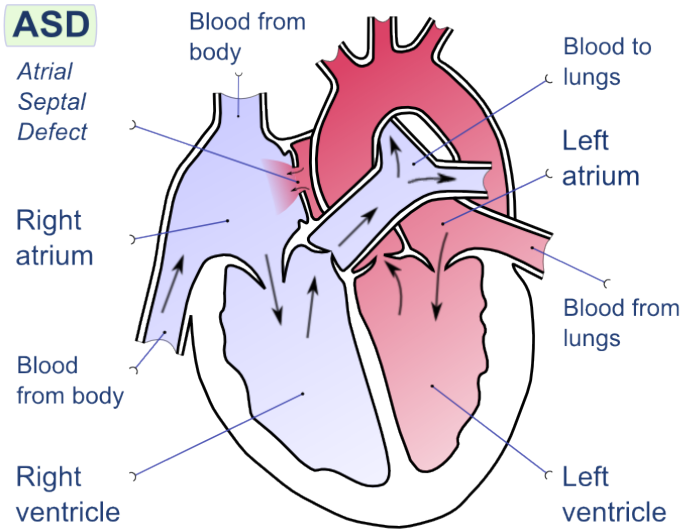
Disease Causing Mechanisms

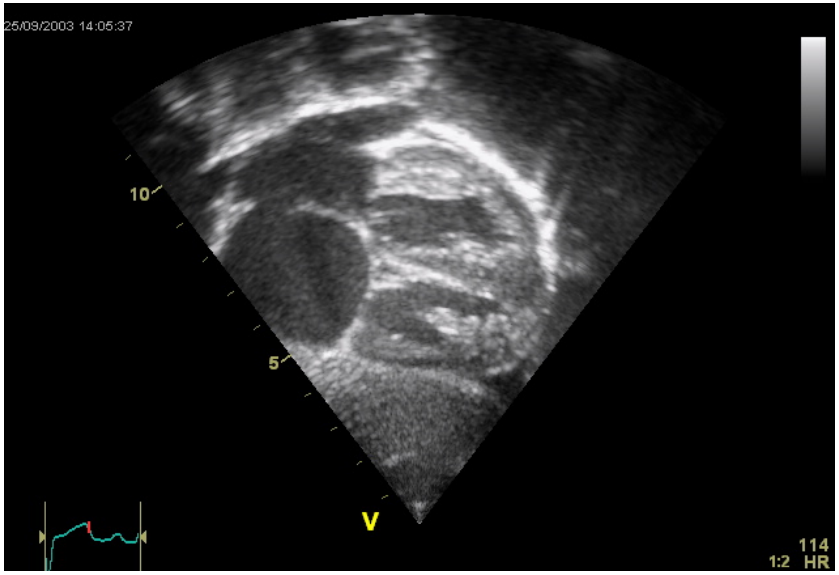
- **Chromosomal aberrations**
  - Trisomy 21, 13, 18
  - Deletions such as those found in the Di George Syndrome
- **Copy number variations**
- **Spontaneous mutations** (Nkx2.5, GATA4, Tbx5)
- **Environmental factors**
  - alcoholism
  - retinoic acid, vitamin A, folic acid (vitamin B9)
  - obesity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

Forms of CHD

Atrial Septal Defect

- **Atrial septal defect (ASD).** A congenital heart defect resulting from incomplete atrial septation.



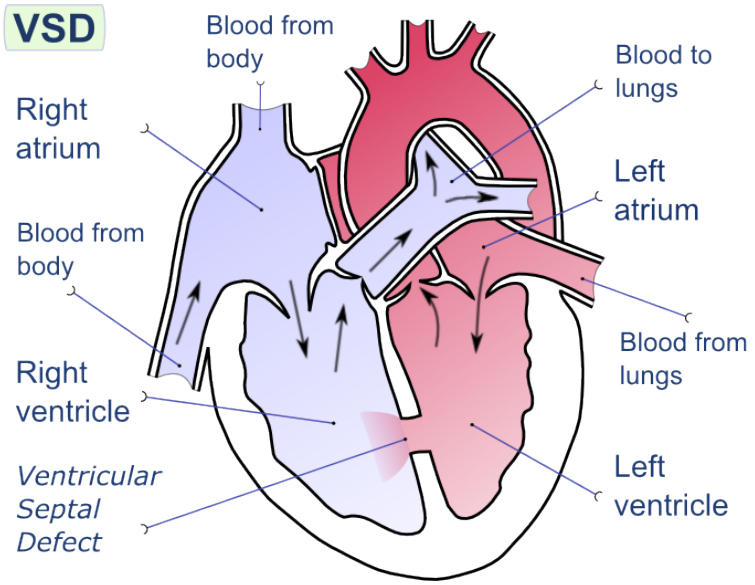


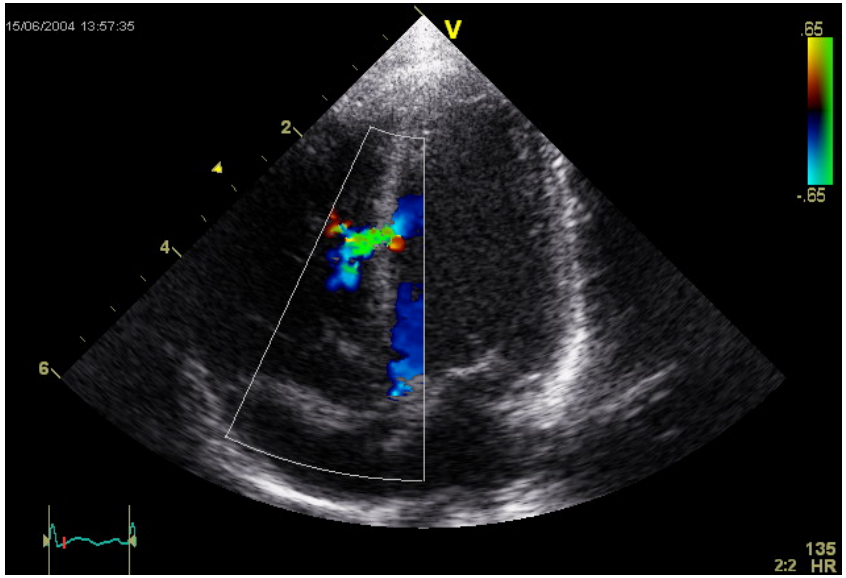
ASDs are detected in 1 child per 1500 live births. ASDs make up 30 to 40% of all congenital heart diseases that are seen in adults.

Forms of CHD

Ventricular Septal Defect (VSD)

Ventricular septal defect (VSD). A congenital heart defect resulting from incomplete ventricular septation



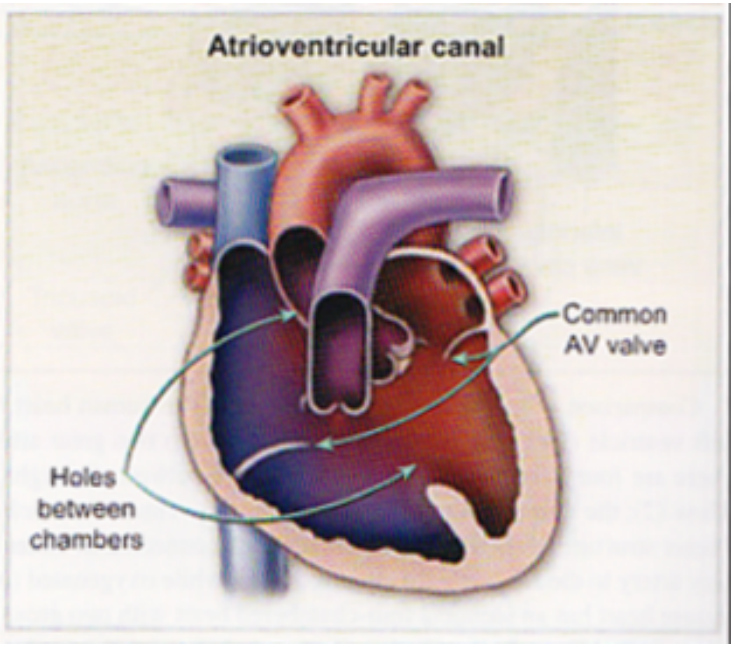


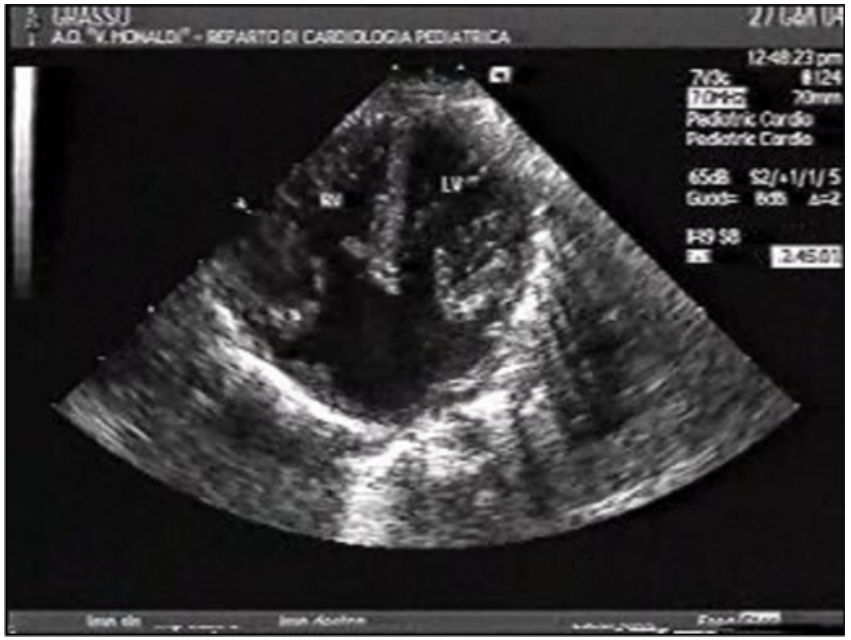
Membranous ventricular septal defects are more common than muscular ventricular septal defects, and are the most common congenital cardiac anomaly with approx. 4 cases per 1000 live births.

Forms of CHD

Atrioventricular septal defect (AVSD)

Atrioventricular septal defect (AVSD). A congenital heart defect resulting from incomplete septation of the atrioventricular canal.



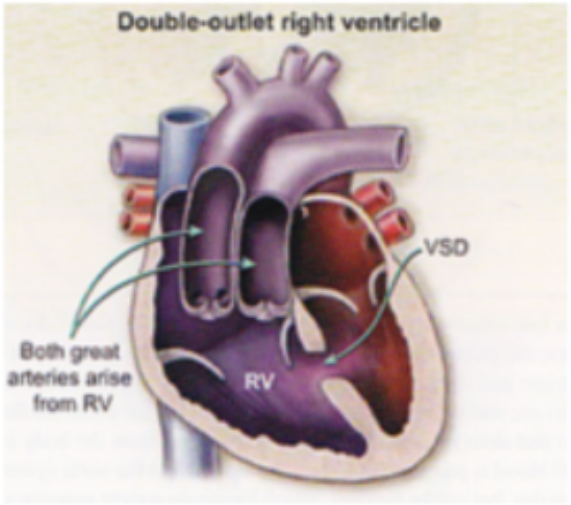


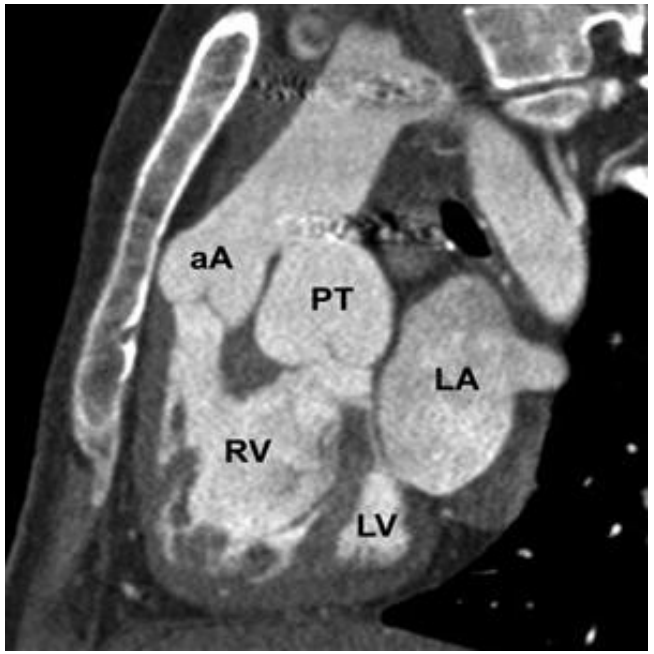
This type of congenital heart defect is associated with patients with Down syndrome (trisomy 21) or heterotaxy syndromes. 45% of children with Down syndrome have CHD of which 35-40% have AV septal defects.

Forms of CHD

Double Outlet Right Ventricle (DORV)

Double-outlet right ventricle (DORV). A congenital heart defect in which both aorta and pulmonary trunk arise from the right ventricle.



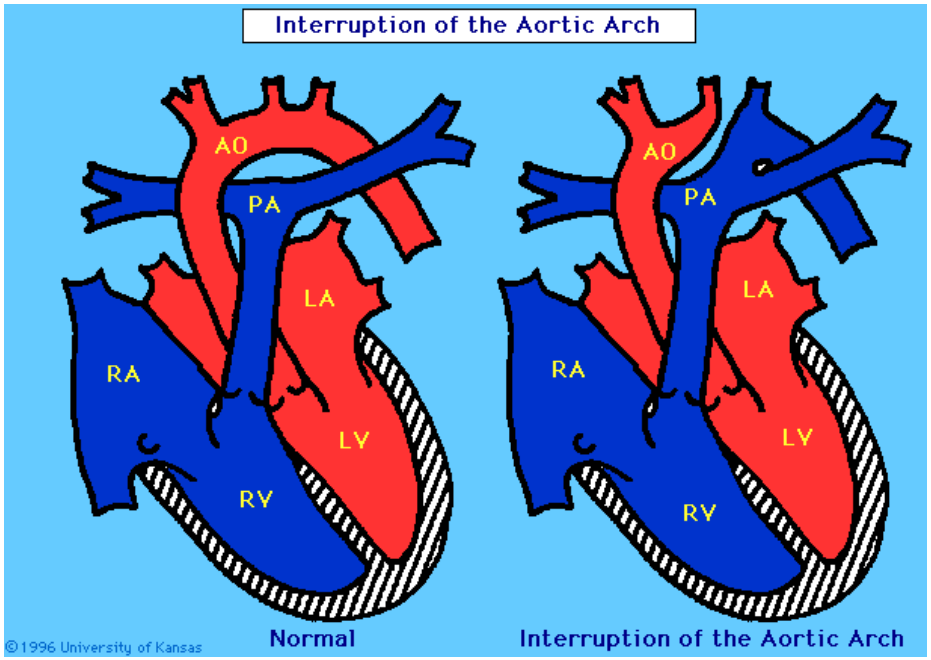


DORV affects between 1% and 3% of people born with CHD. Chromosomal aberrations are reported in 40% of the cases .

Forms of CHD

Interruption of the Aortic Arch (IAA)

Interruption of the aortic arch (IAA). A congenital heart defect in which a segment of the aortic arch is occluded or absent.

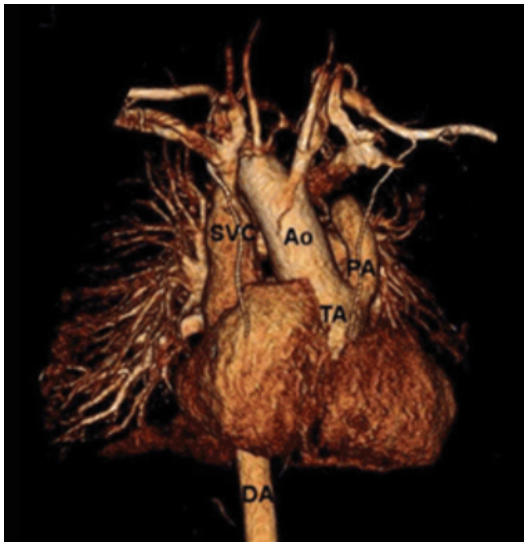


Rare defect affecting 3 per million life birth. Often caused by a deletion in chromosome 22q11 (Di George syndrome). The cardiac phenotype is caused by a deletion of Tbx1. But other genes in the network might also cause IAA.

Forms of CHD

Persistent truncus arteriosus (PTA)

Persistent truncus arteriosus (PTA). A congenital heart defect in which the aorta fails to separate from the pulmonary trunk, resulting in a single arterial trunk that emerges from the ventricles.

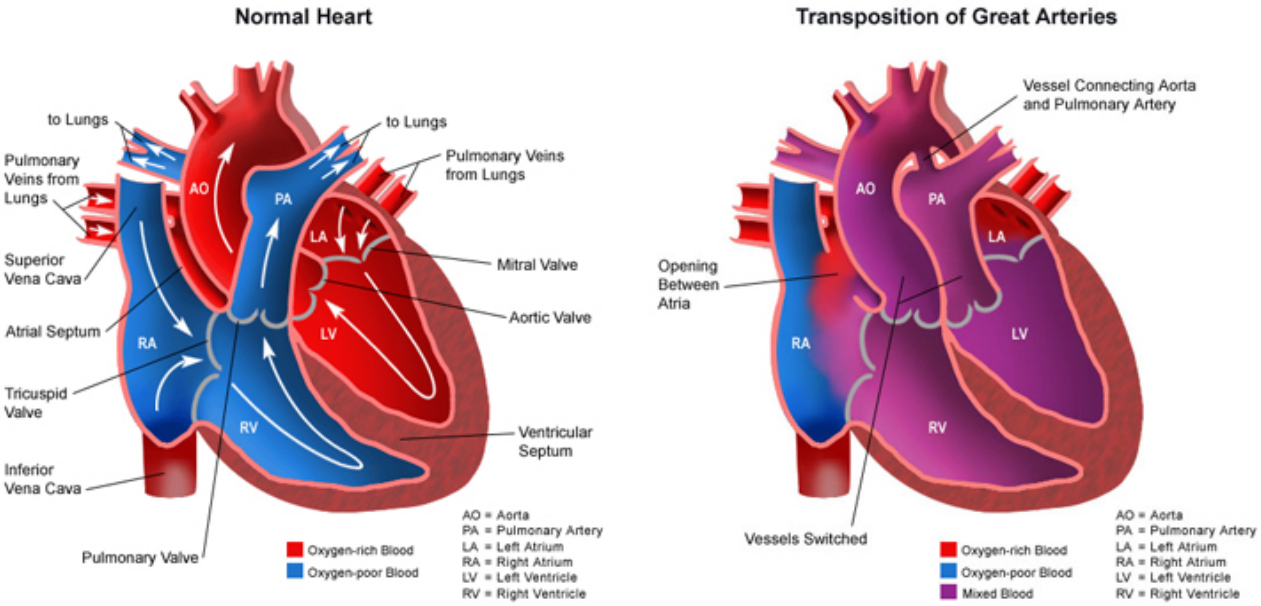


Genetic disorders and teratogens have been associated as possible causes. Up to 50% of cases are associated with chromosome 22q11 deletions. The cardiac neural crest directly contributes to the aorticopulmonary septum. Microablation of the cardiac neural crest in chick embryos and mutations affecting this population of cells in rodents results in PTA. Numerous genes have been associated with PTA, some of which include FGF8, BMP4, Tbox1, Nkx2.5, GATA4, as well as connexin 43.

Forms of CHD

Transposition of the great arteries

Transposition of the great arteries (TGA), is a rare congenital heart defect involving an abnormal spatial arrangement of the pulmonary artery and the aorta. the left ventricle of the heart is severely underdeveloped. Only compatible with life if in addition a septal defect or a patent DA is present.

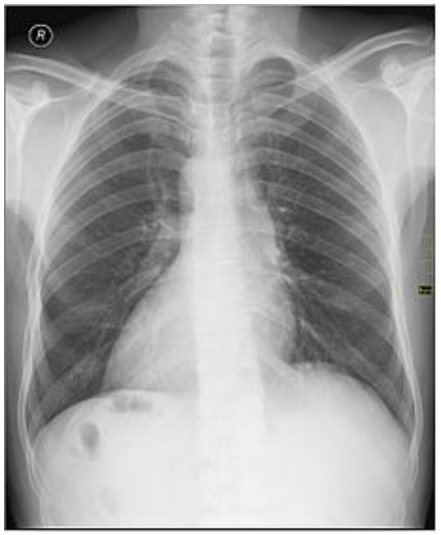


Transposition of the great arteries (TGA) is one of the commonest cyanotic congenital cardiac anomalies and can account for up to 7% of all congenital cardiac anomalies.

Forms of CHD

Dextrocardia

Dextrocardia. A congenital heart defect in which the heart is located on the right side of the body. There are two forms isolated dextrocardia or dextrocardia situs inversus.

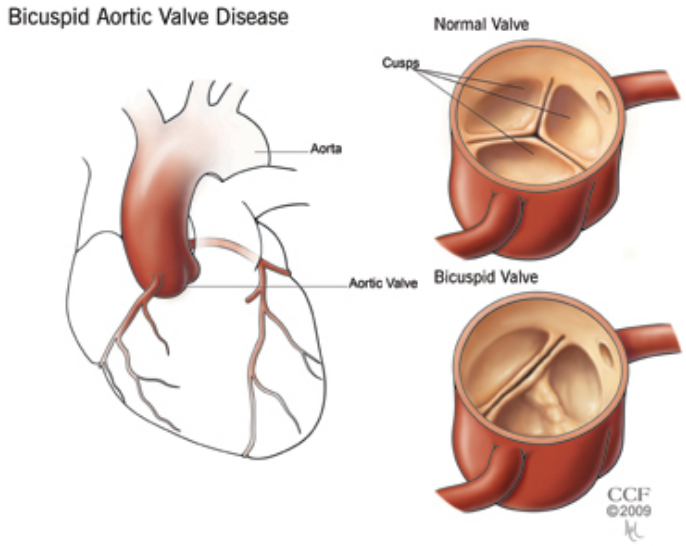


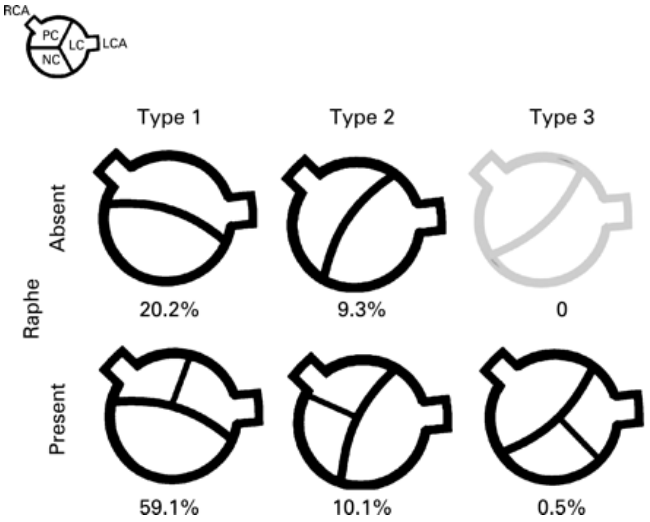
Dextrocardia is believed to occur in approximately 1 in 12,000 people. Kartagener's syndrome is present in 1 of 25 cases of situs inversus totalis and is caused by mutations in motor proteins that drive the nodal flow.

Forms of CHD

Bicuspid aortic valve (BAV)

Bicuspid aortic valve (BAV). A congenital heart defect in which the aortic valve has only two cusps. The term BAV is also used broadly to describe any malformation of the aortic valve cusps.



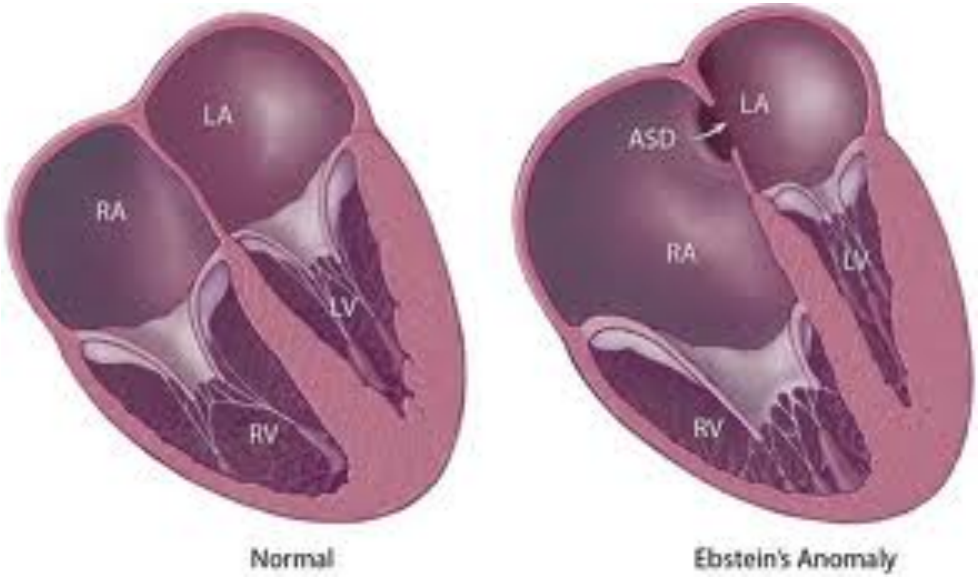


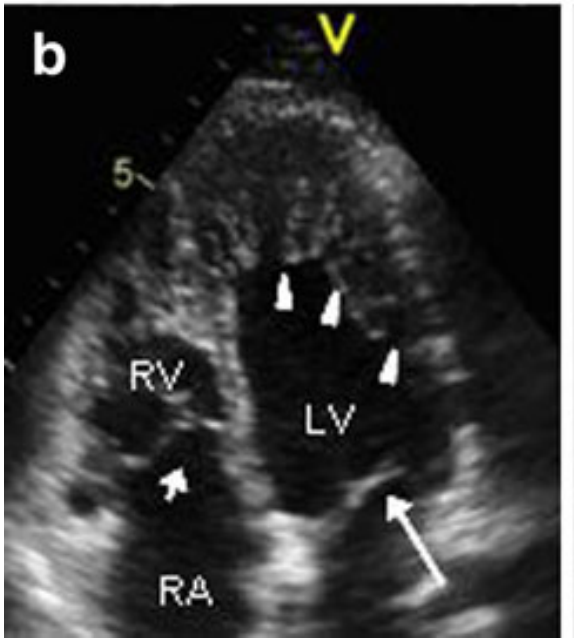
Bicuspid aortic valves are the most common cardiac valvular anomaly, occurring in 1-2% of the general population. It is twice as common in males as in females. BAV has been associated with mutations in Notch1. In animal models mutations in *Gata5*, *Nos3*, have been found cause BAV with reduced penetrance.

Forms of CHD

Ebstein's anomaly

Ebstein anomaly is a congenital heart defect in which the opening of the tricuspid valve is displaced towards the apex of the right ventricle.



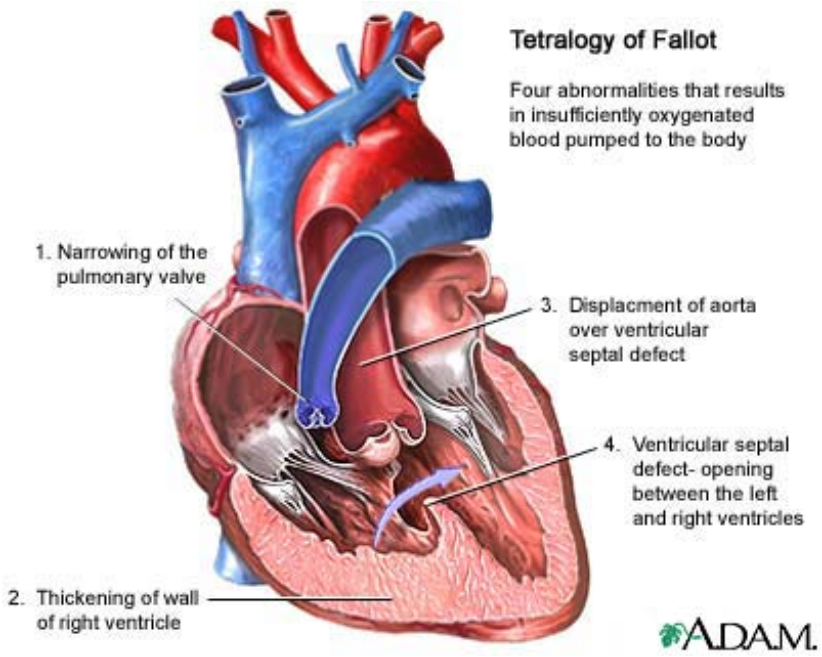


Ebstein's anomaly is a rare congenital heart malformation affecting about 1 in 200,000 live births. An association between mutations in beta-MHC (MYH7) and Epstein's anomaly has been found.

Forms of CHD

Tetralogy of Fallot

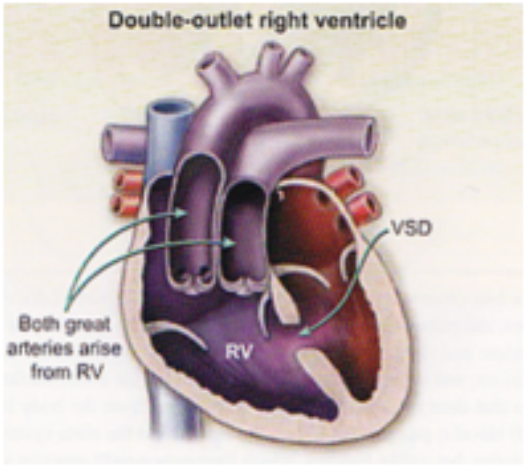
Tetralogy of Fallot (TOF) is a CHD which is classically understood to involve four anatomically different abnormalities. It is the most common cyanotic heart defect and common cause of blue baby syndrome.

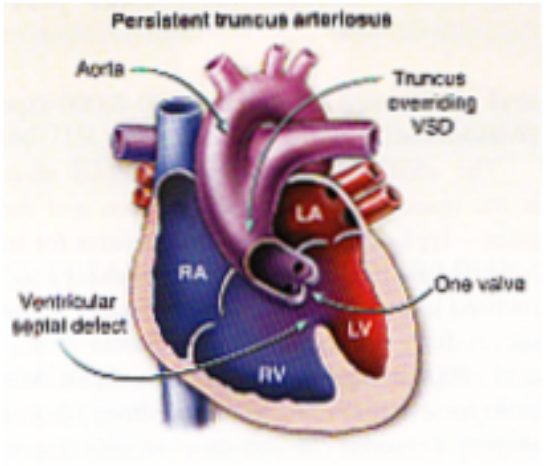


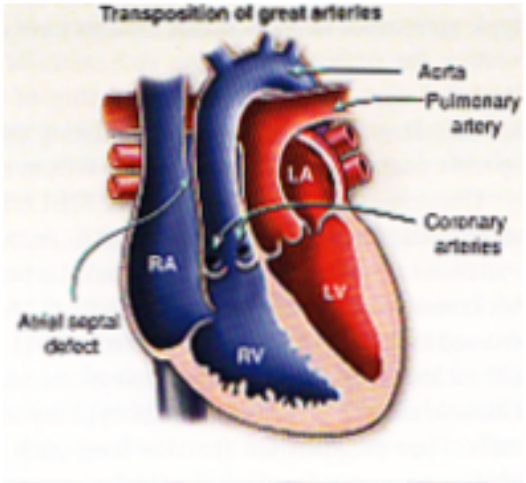
Malalignment of the aortico-pulmonary septum
Ventricular septum defect
Pulmonary stenosis
Overriding aorta
→ **Right ventricular hypertrophy**

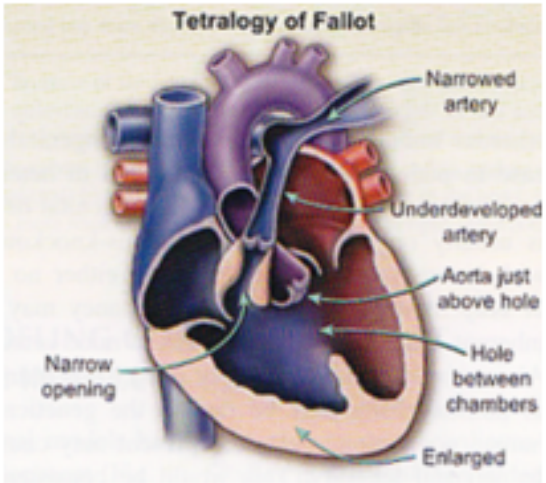
The cause of TOF is thought to be due to environmental or genetic factors or a combination. It is associated with chromosome 22 deletions and Di George syndrome. Specific genetic association have been found with JAG1, NKX2.5, ZFPM2 (FOG2), and VEGF.

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





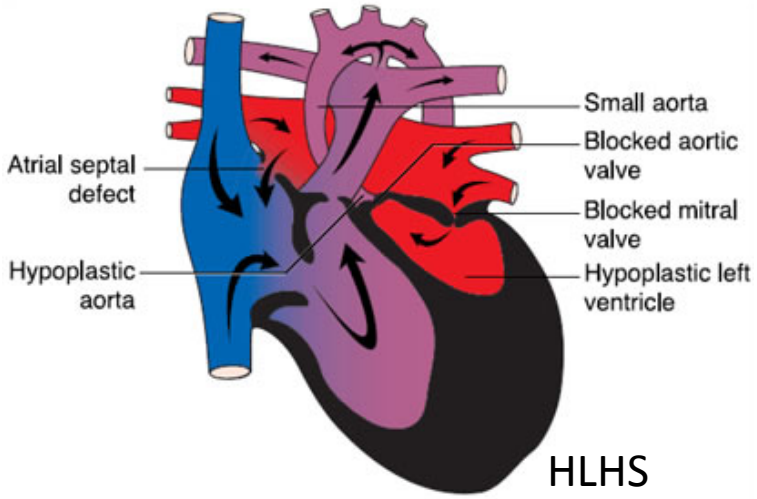




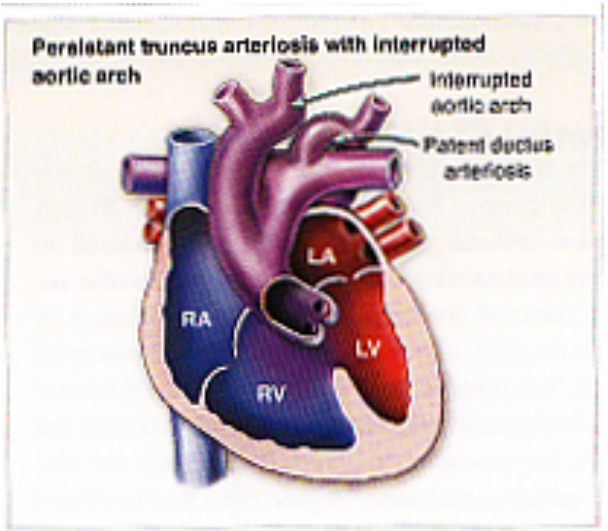
transposition of the great arteries (TGA)
tetralogy of Fallot (TOF)
tricuspid atresia
pulmonary atresia
Ebstein's anomaly
double outlet right ventricle (DORV)
persistent truncus arteriosus (PTA)
total anomalous pulmonary venous connection

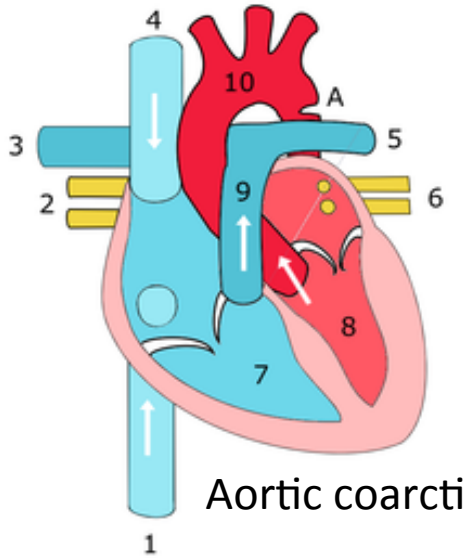
Left sided obstruction defects

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



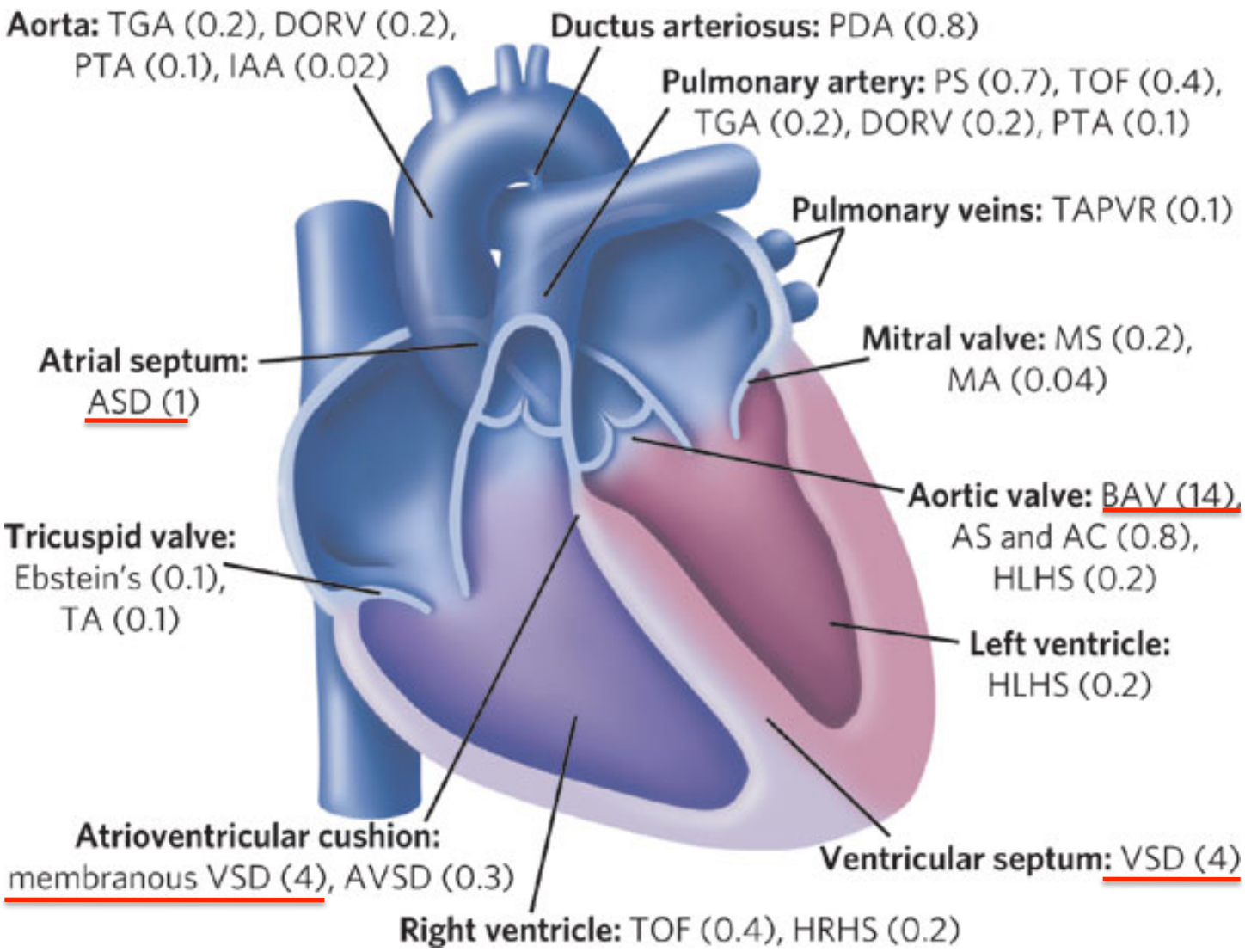
HLHS



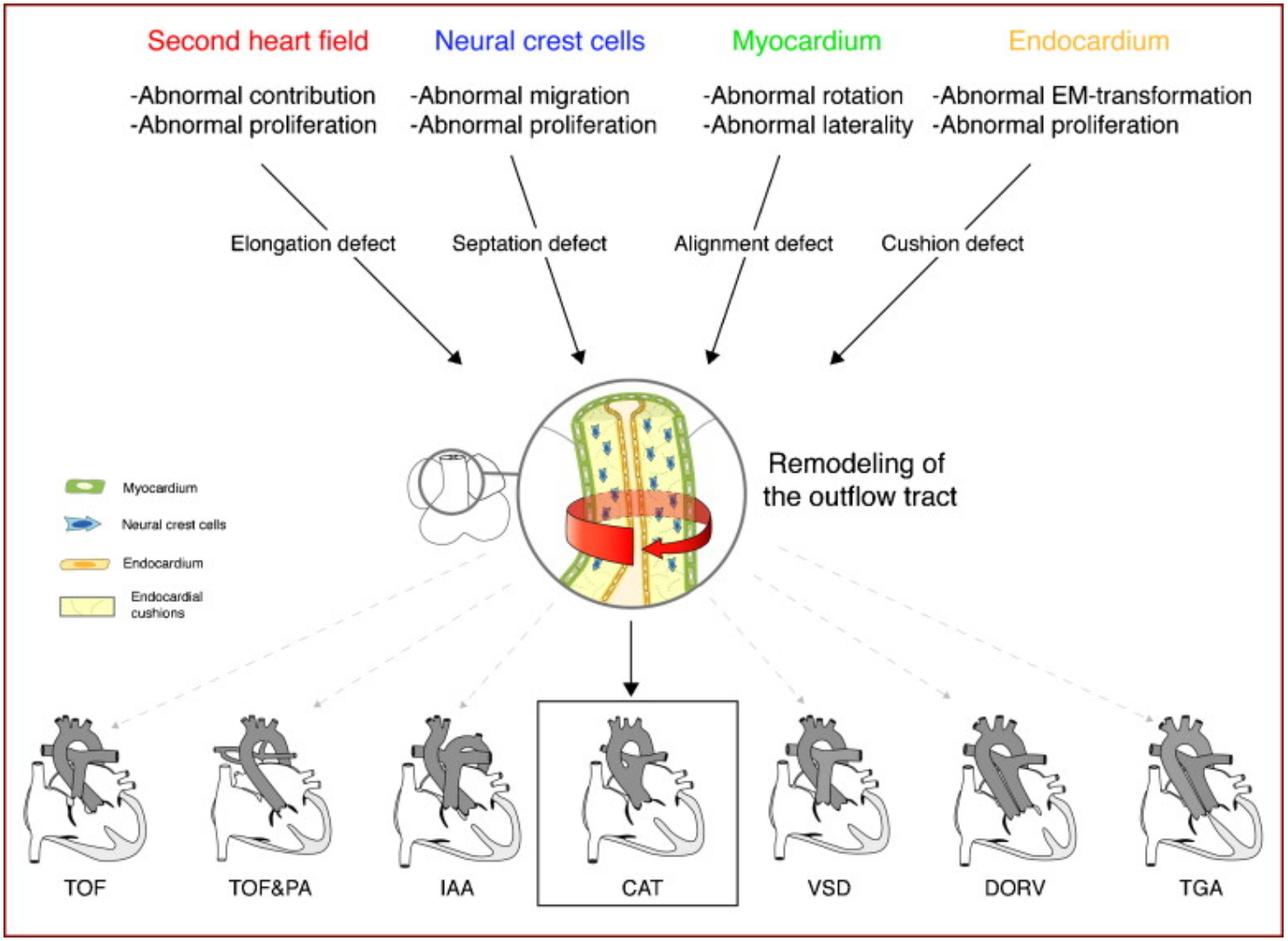


Aortic coarction

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)

Congenital heart disease is complex and multifactorial



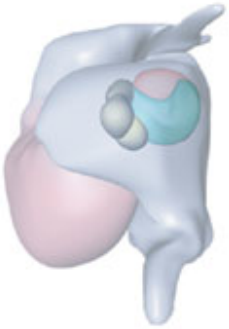
TOF - Tetralogy of Fallot; PA- Pulmonary Atresia, IAA – Interrupted Aortic Arch
CAT – Common Aortic Trunk, VSD - Ventricular Septum Defect,
DORV – Double Outlet Right Ventricle, TGA – Transposition of the Great Arteries

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

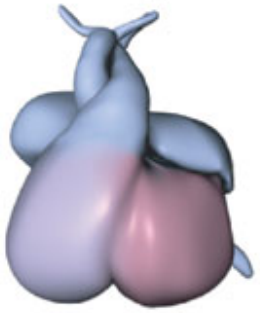
Ventricular septation and atrioventricular cushion formation

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

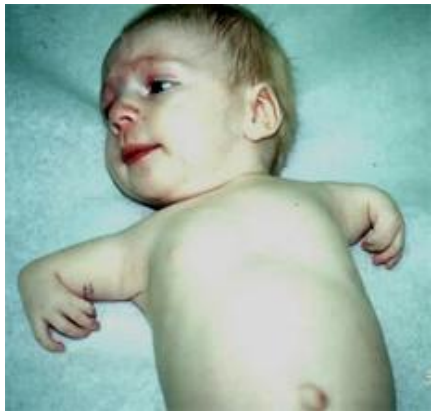
AS and AC: *NOTCH1*
PTPN11

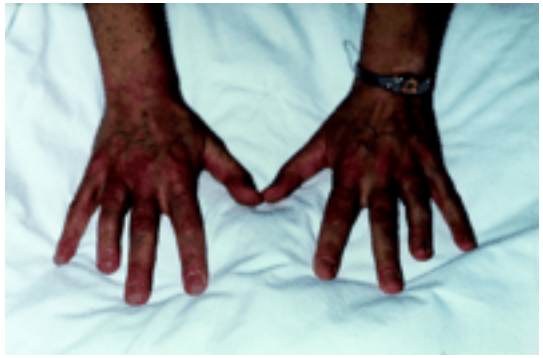
PS: *PTPN11*
JAG1
NOTCH2

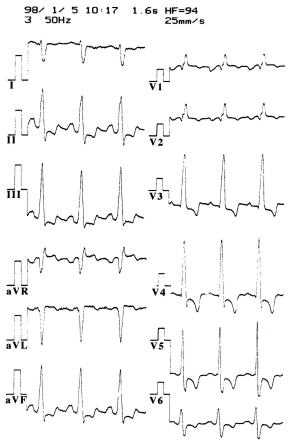
BAV: *NOTCH1*

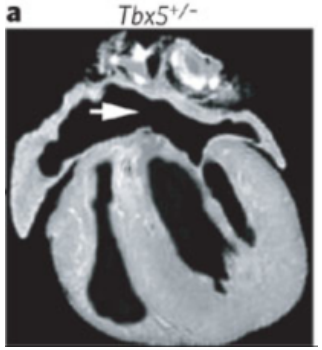
HLHS: *NOTCH1*

PDA: *TFAP2B*









Holt-Oram Syndrome

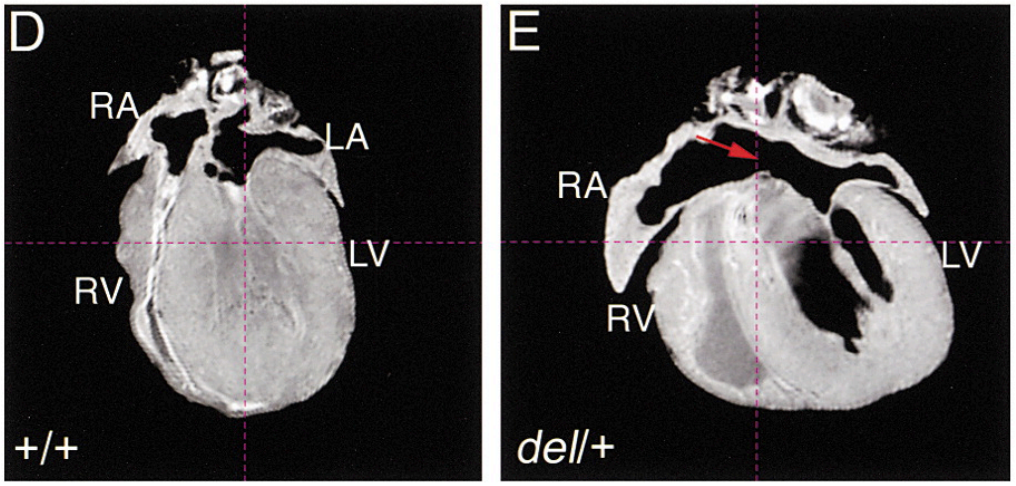
Holt Oram Syndrome (HOS)
is a disorder characterized by birth defects of the upper limbs and defects of the heart.

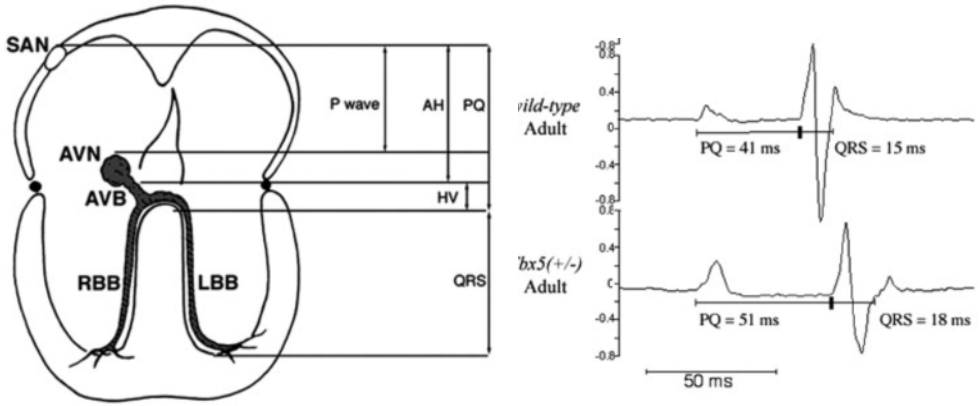
The most common heart defects observed in patients with HOS are atrial septal defects (ASD) and ventricular septal defects (VSD) but may also include electrocardiographic abnormalities, such as various degrees of atrioventricular block.

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

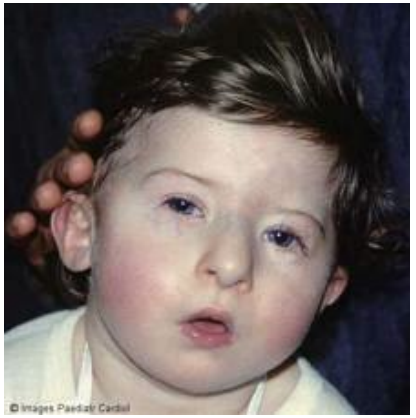


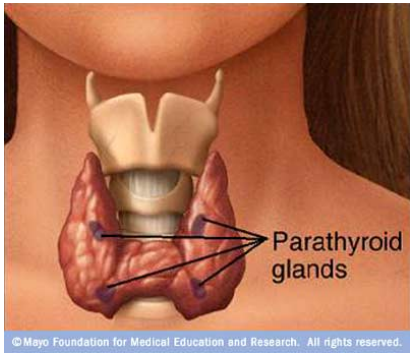


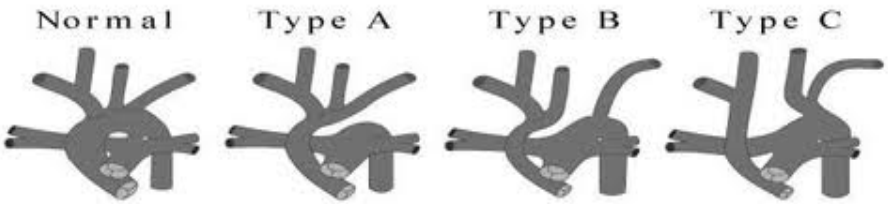
DiGeorge or 22q11 Syndrom

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

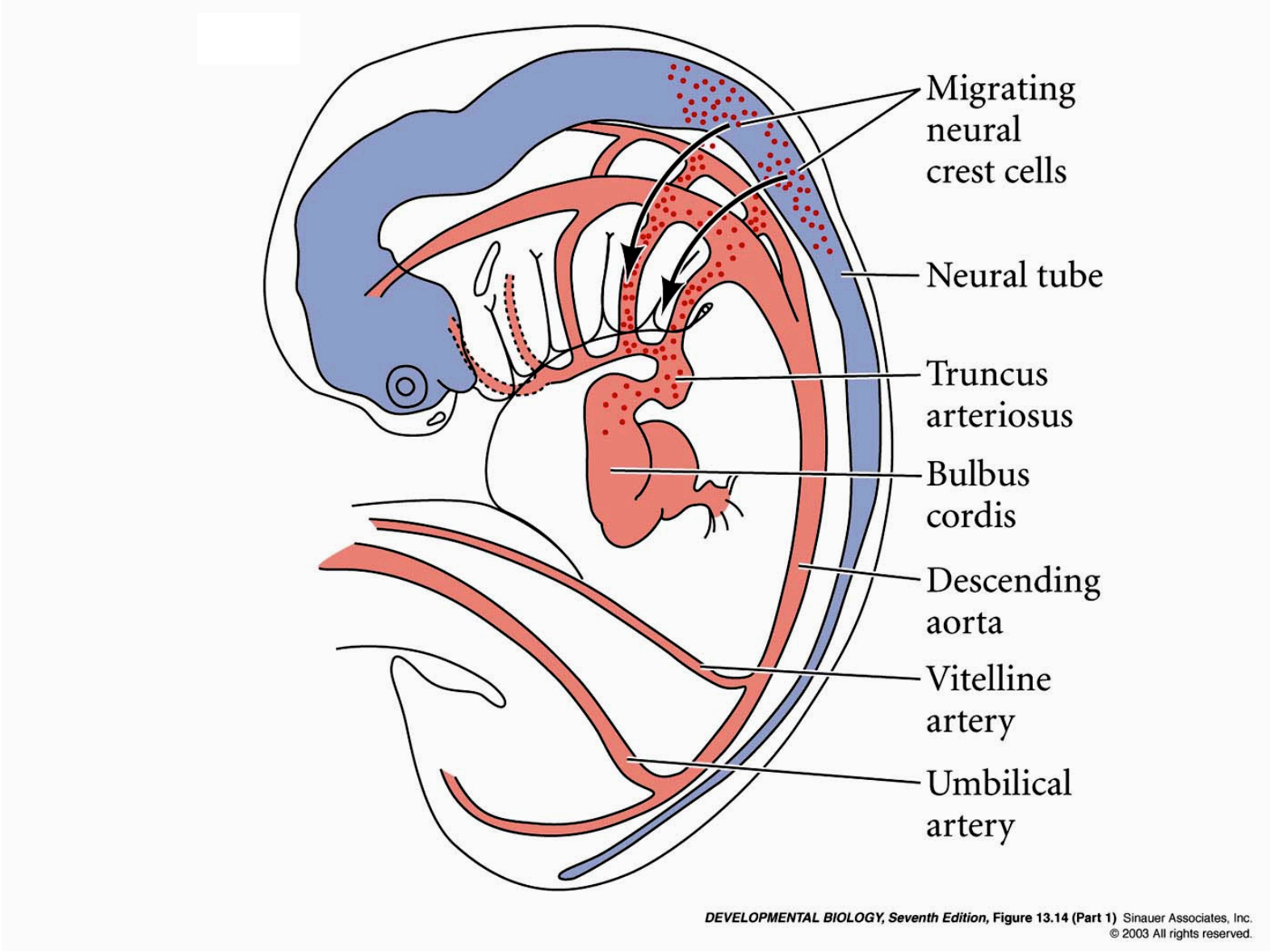
Deletions of 22q11.2





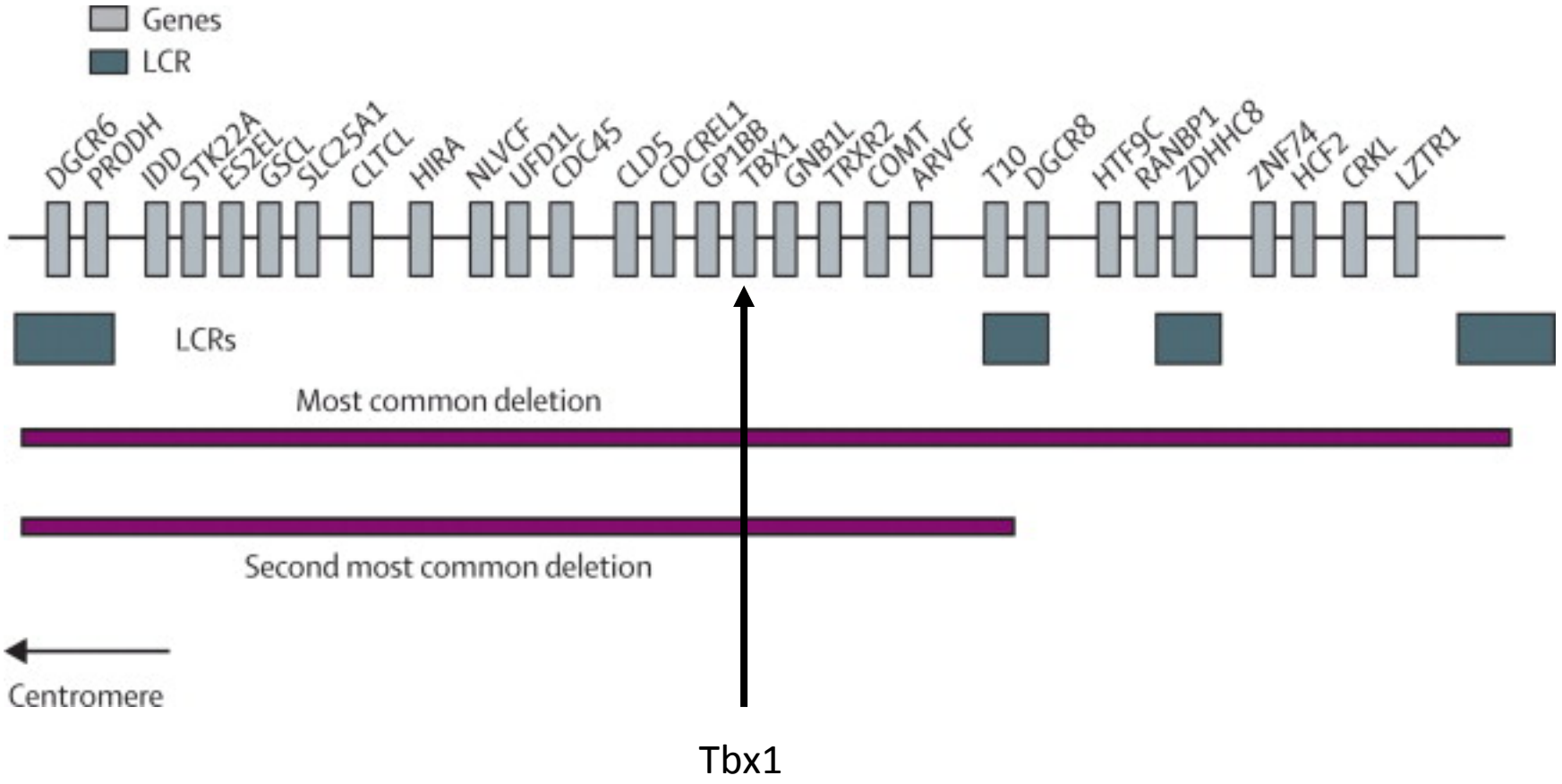


The cardiac neural crest lineage



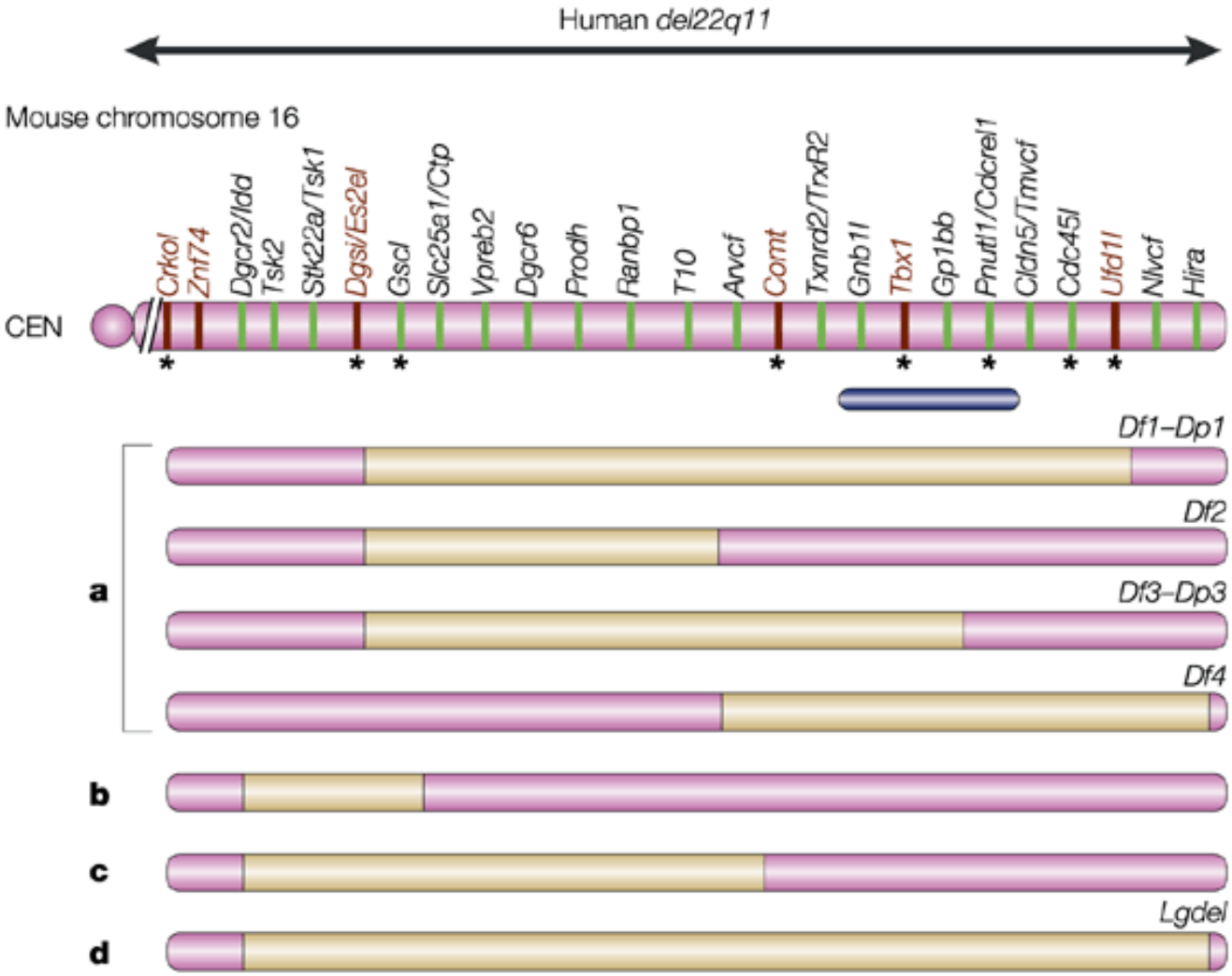
DEVELOPMENTAL BIOLOGY, Seventh Edition, **Figure 13.14 (Part 1)** Sinauer Associates, Inc.

DiGeorge or 22q11 Syndrom

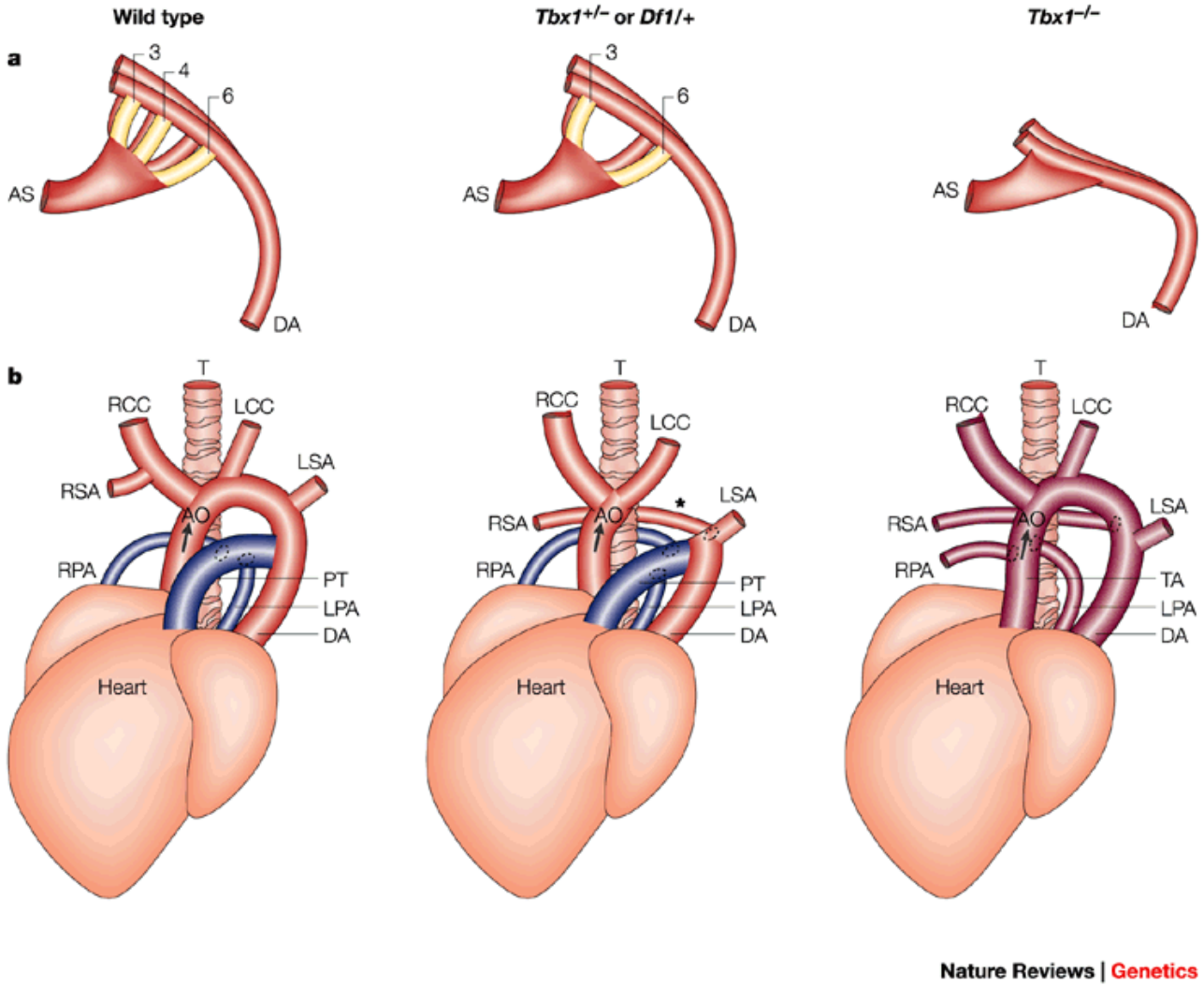


Tbx1

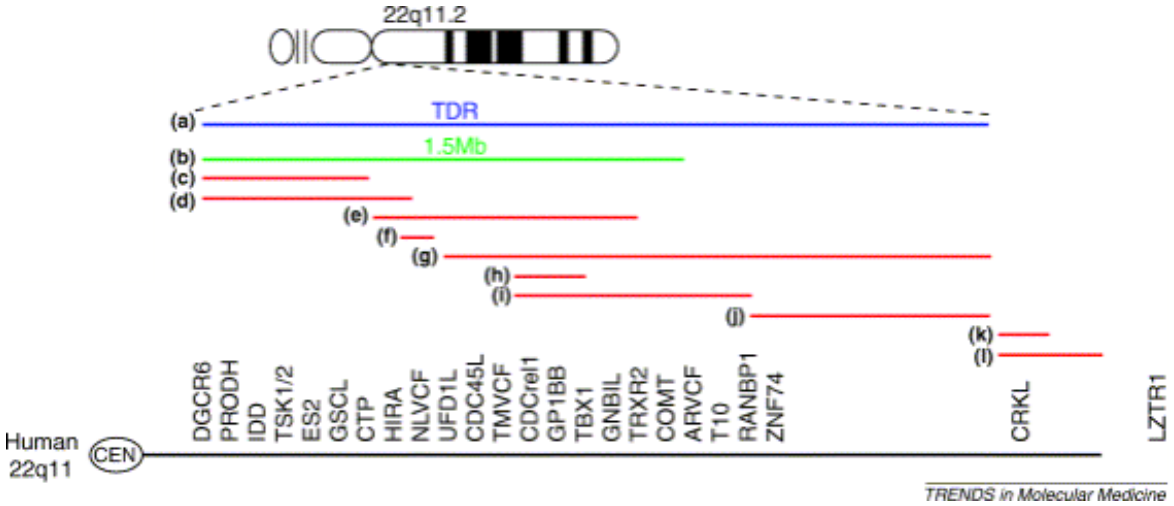
Chromosomal engineering in mice was utilized to mimic human microdeletion of 22q11

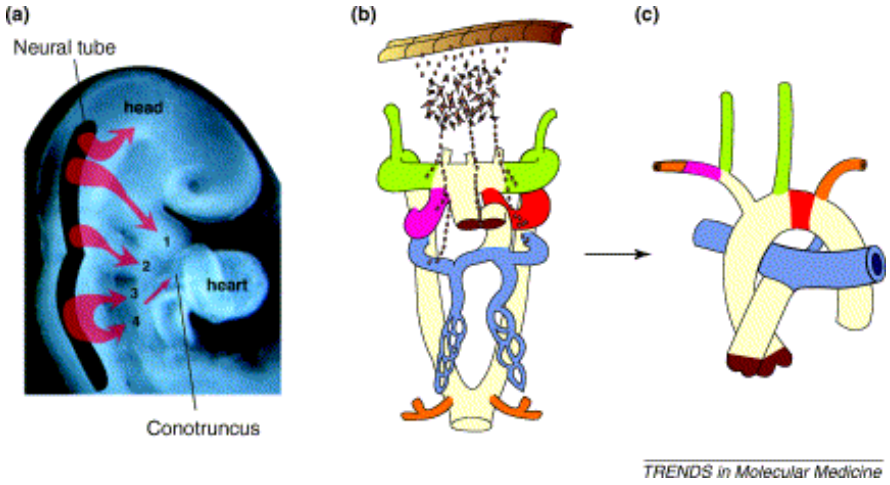


Mice with deletions of 22q11 and mutatins of Tbx1 have aortic arch abnormalities



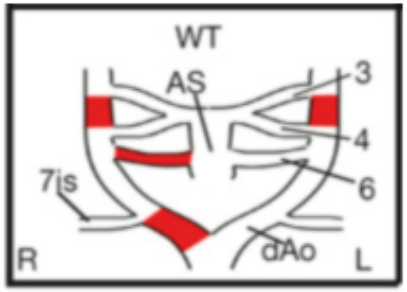
DiGeorge or 22q11 Syndrom



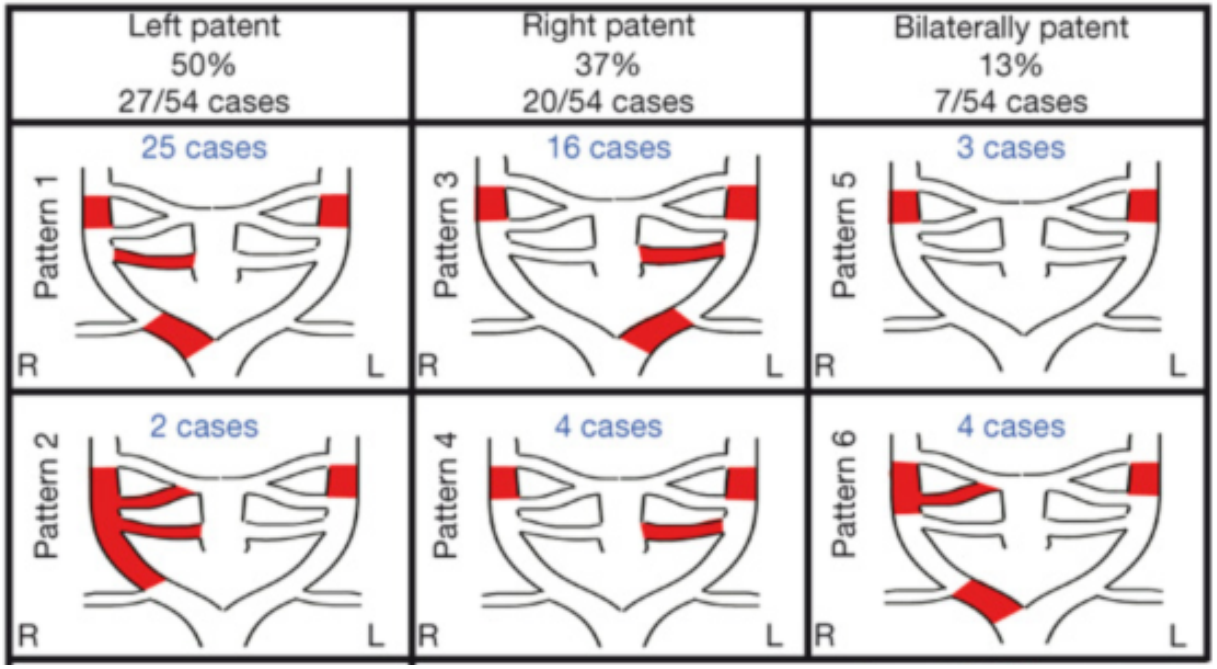


Blood Flow as an epigenetic factor

WT



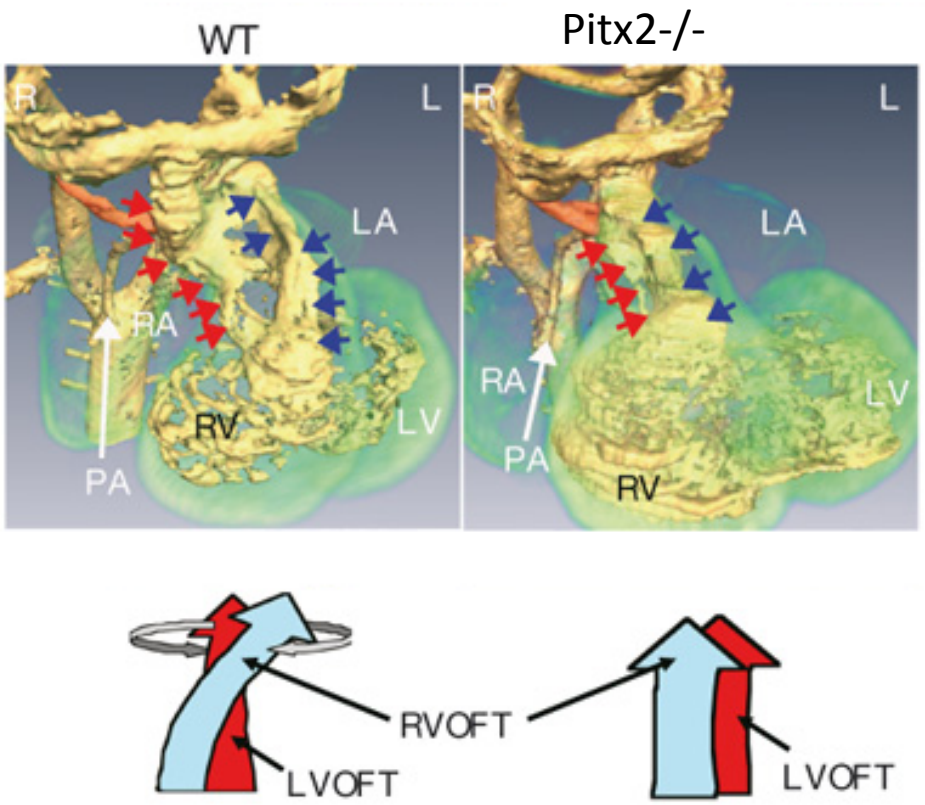
Pitx2$^{-/-}$



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

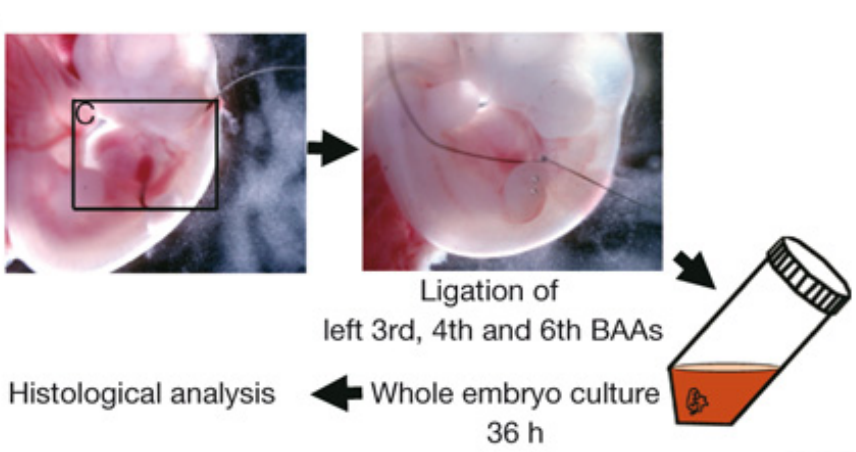
Yashiro, et al. (2007) *Nature* ***450, 285-288***

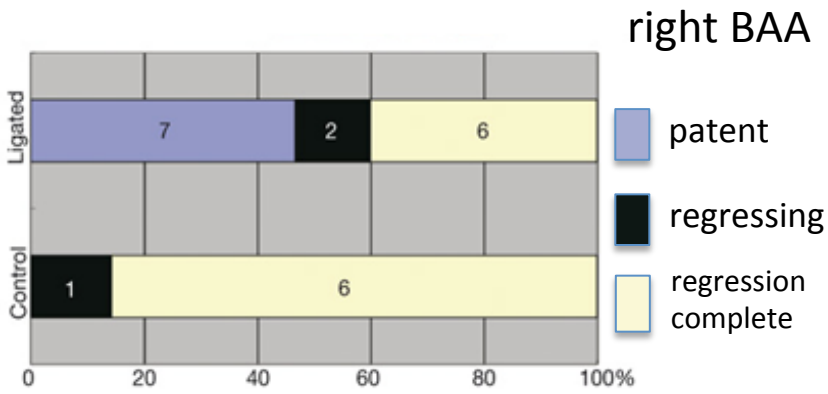
Pitx2 induces asymmetric aortic arch remodelling through an flow-dependent mechanism

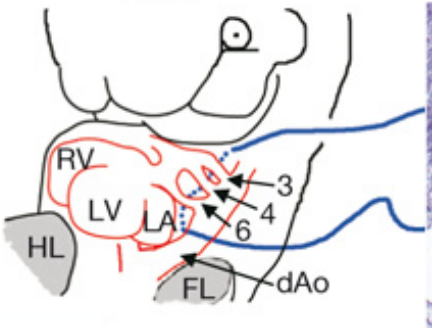


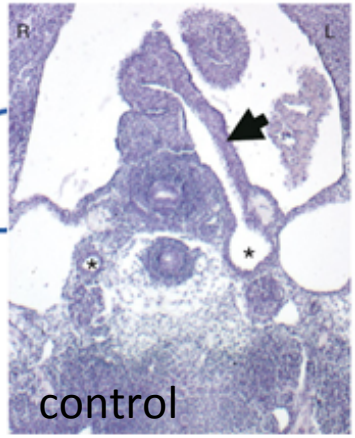
Yashiro, et al. (2007) *Nature* ***450, 285-288***

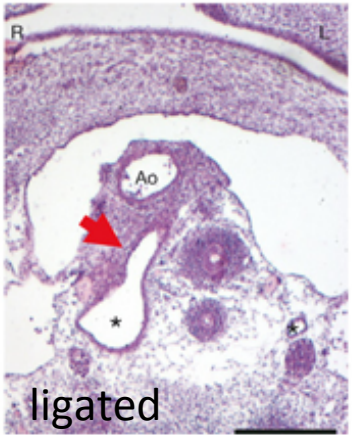
Manipulation of flow reverses aortic arch pattern











Epigenetic factors

hemodynamic flow
affects valve morphogenesis modulates aortic arch patterning

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

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.

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