Neural Crest Development

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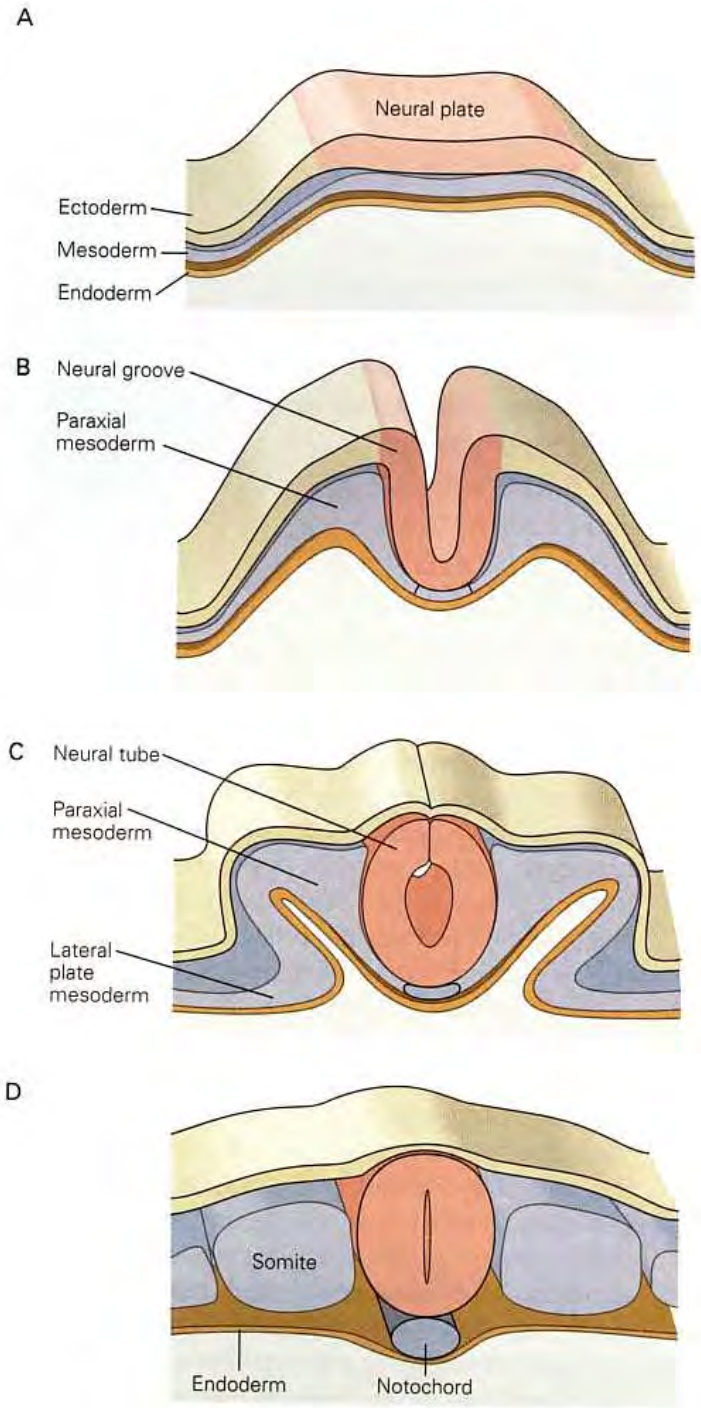
Lecture plan

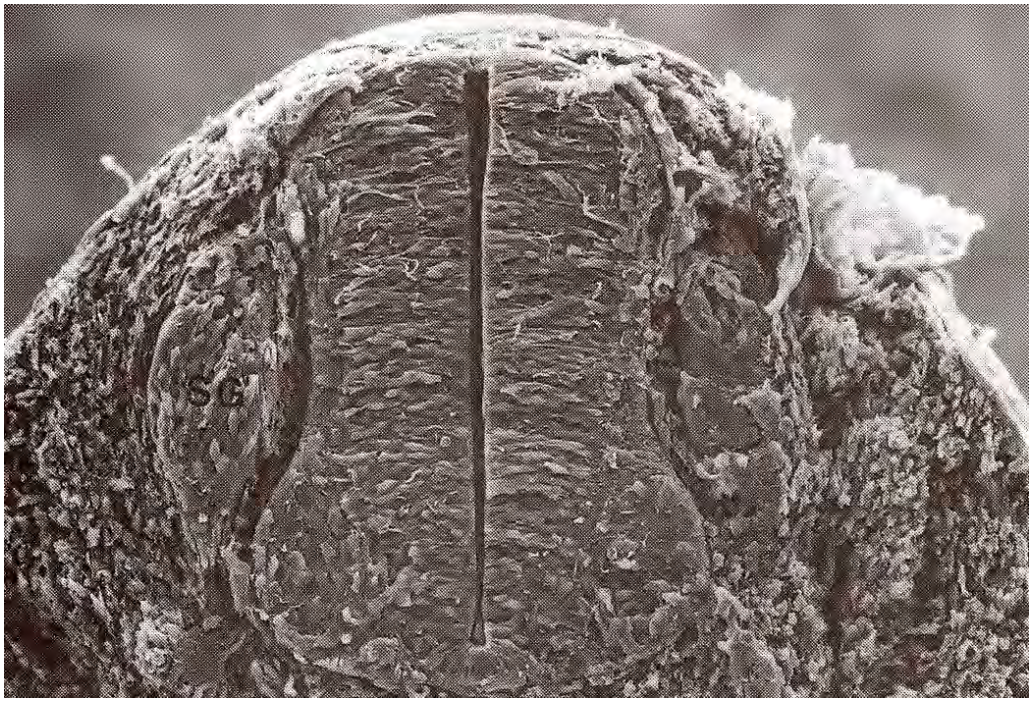
- What is the neural crest?
- Where does neural crest come from?
- Derivatives of the neural crest
- Migration of different types of neural crest
- Molecular biology of neural crest
- Congenital anomalies due to defects in neural crest migration

What is the neural crest?

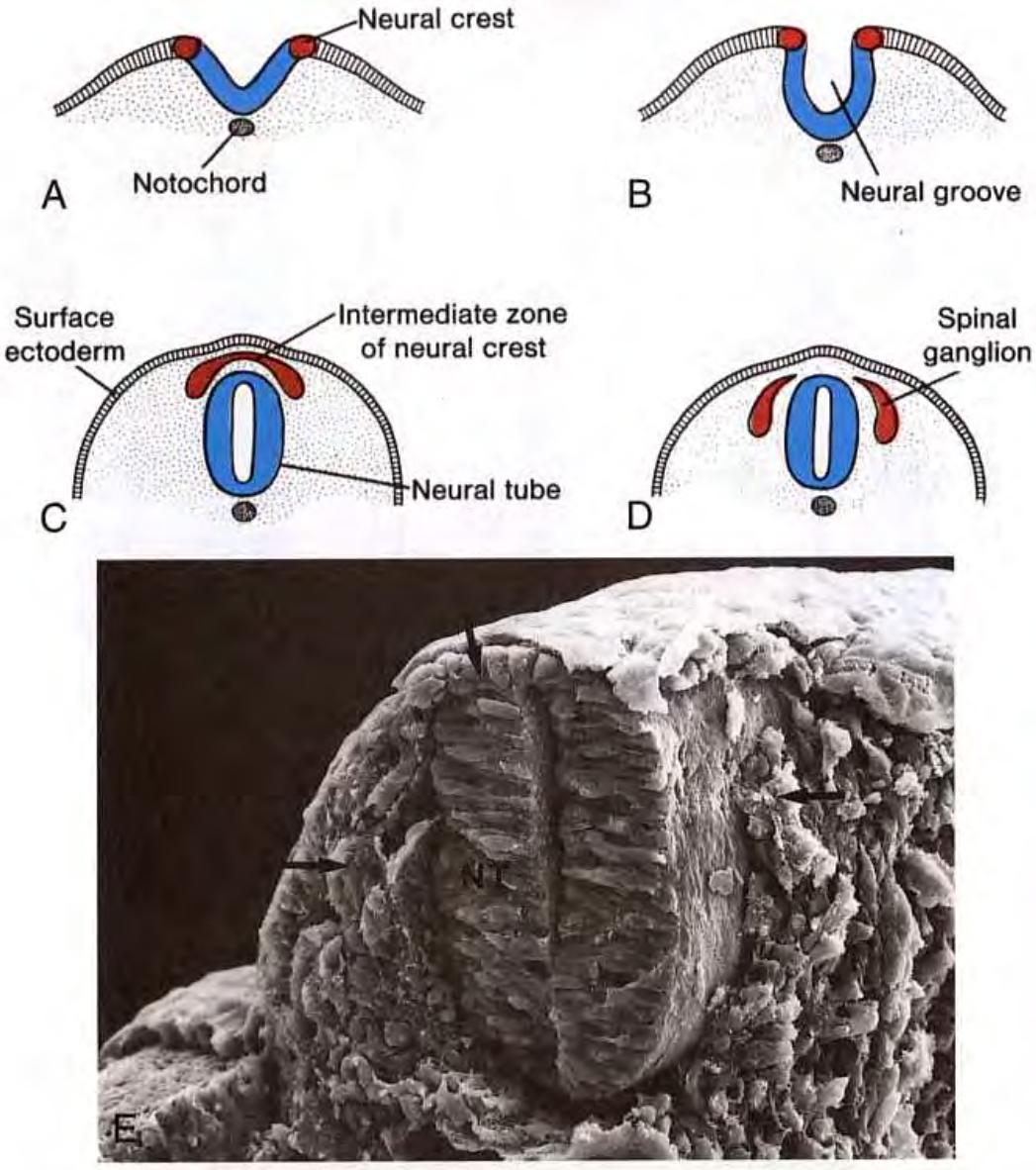
- A transient, migratory embryonic cell population with multipotent capabilities (may become many different cell types).
- It is unique to vertebrates.
- Disordered neural crest development underlies many significant developmental anomalies in mammals (neurocristopathies).



The neural tube gives rise to the brain and spinal cord



The neural crest



As the name implies, the neural crest are a group of cells that develop at the ridge (crest) of the folding neural tube.

Neural crest origins

- The earliest neural crest arise in the midbrain region (trigeminal neural crest)
- Other neural crest arise from the rim of the neural fold in a cranial-to-caudal sequence at or shortly after neural fold fusion to form the neural tube
- Neural crest migration is a very early event (21 to 35 days of development)

Derivatives of the neural crest

Connective tissue and bones of the face and skull
Cranial nerve ganglia (see Table 19.2)
C cells of the thyroid gland
Conotruncal septum in the heart
Odontoblasts
Dermis in face and neck
Spinal (dorsal root) ganglia
Sympathetic chain and preaortic ganglia
Parasympathetic ganglia of the gastrointestinal tract
Adrenal medulla
Schwann cells
Glial cells
Arachnoid and pia mater (leptomeninges)
Melanocytes

Many neural crest derivatives are neural (red rectangles), but not all:

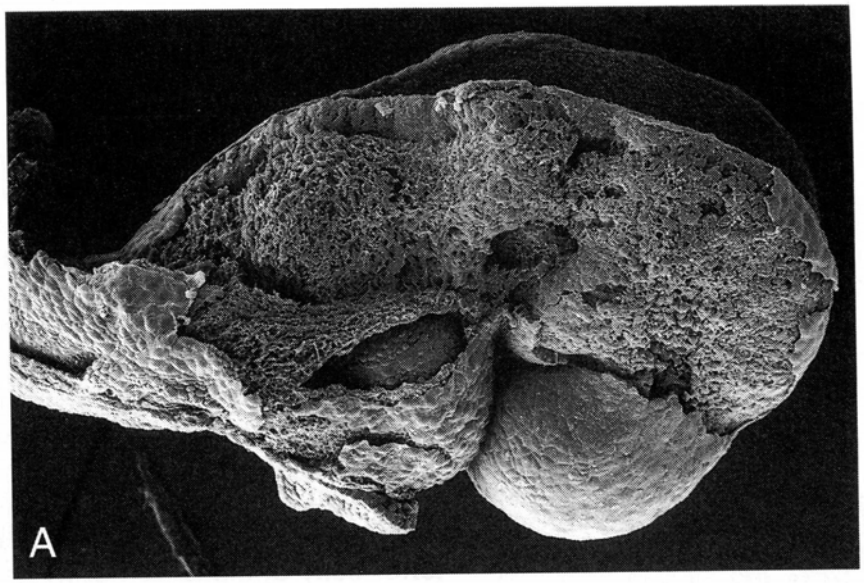
Derivatives of the neural crest include nerve cells, pigment cells and connective tissue elements.

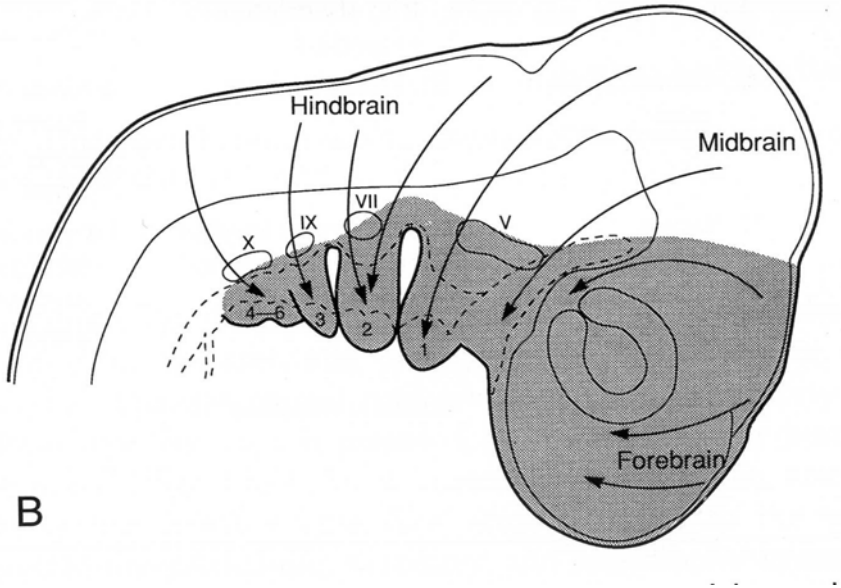
Cranial neural crest migration 1

Cranial neural crest migrates from the region of the brain into the adjacent pharyngeal arches.

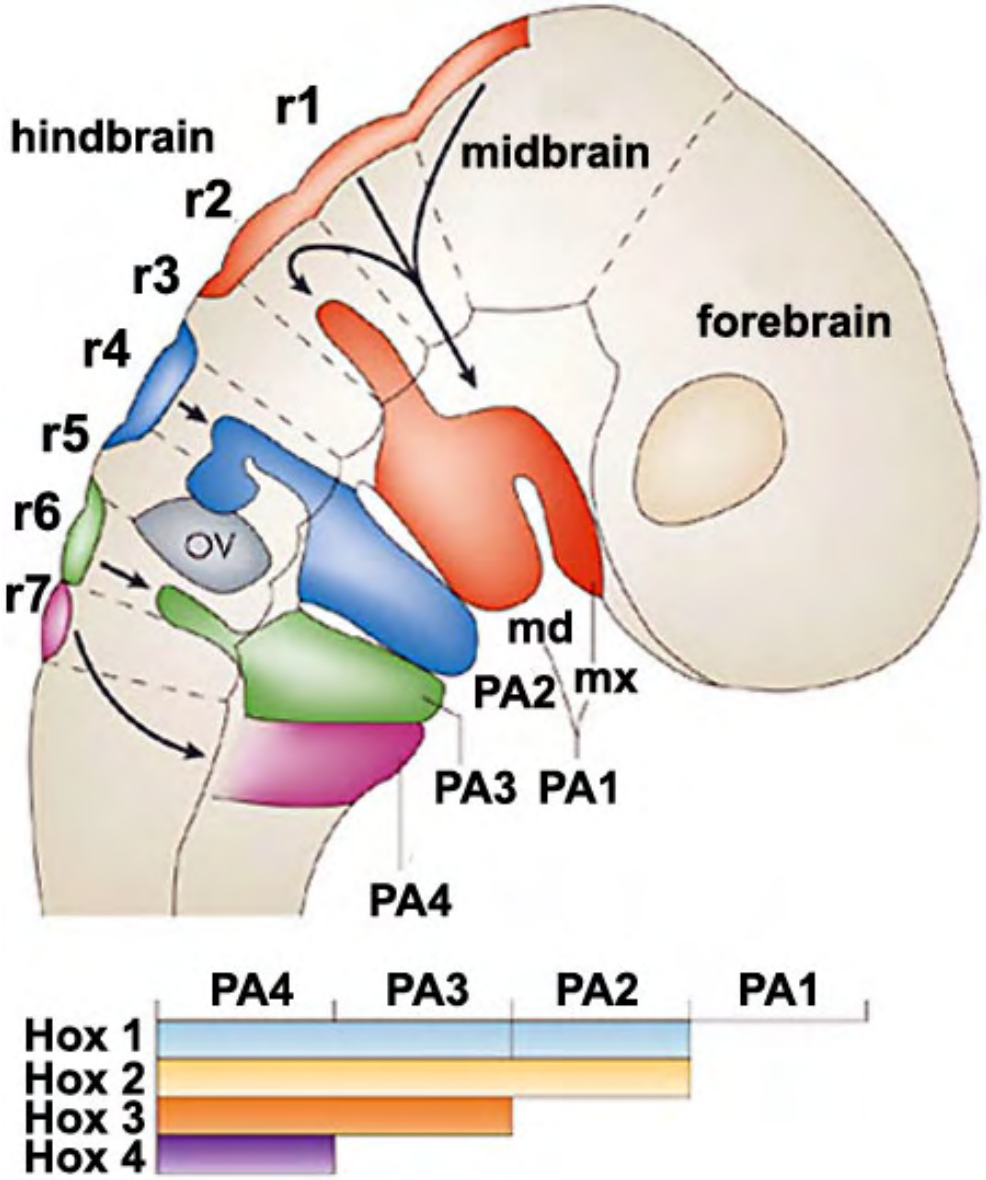
Cranial neural crest contributes to:

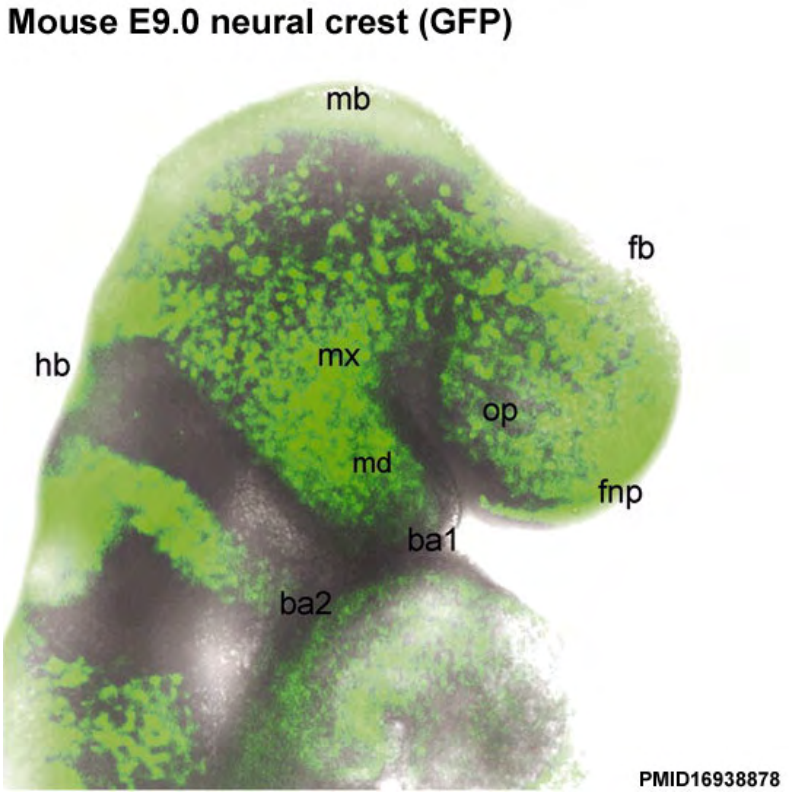
- Cranial sensory and autonomic ganglia
- Pharyngeal arch skeletal structures
- Exocrine and endocrine glandular stroma
- Meninges
- Dermis
- Dentin (of teeth)
- Cartilage and bone





Cranial neural crest migration 2



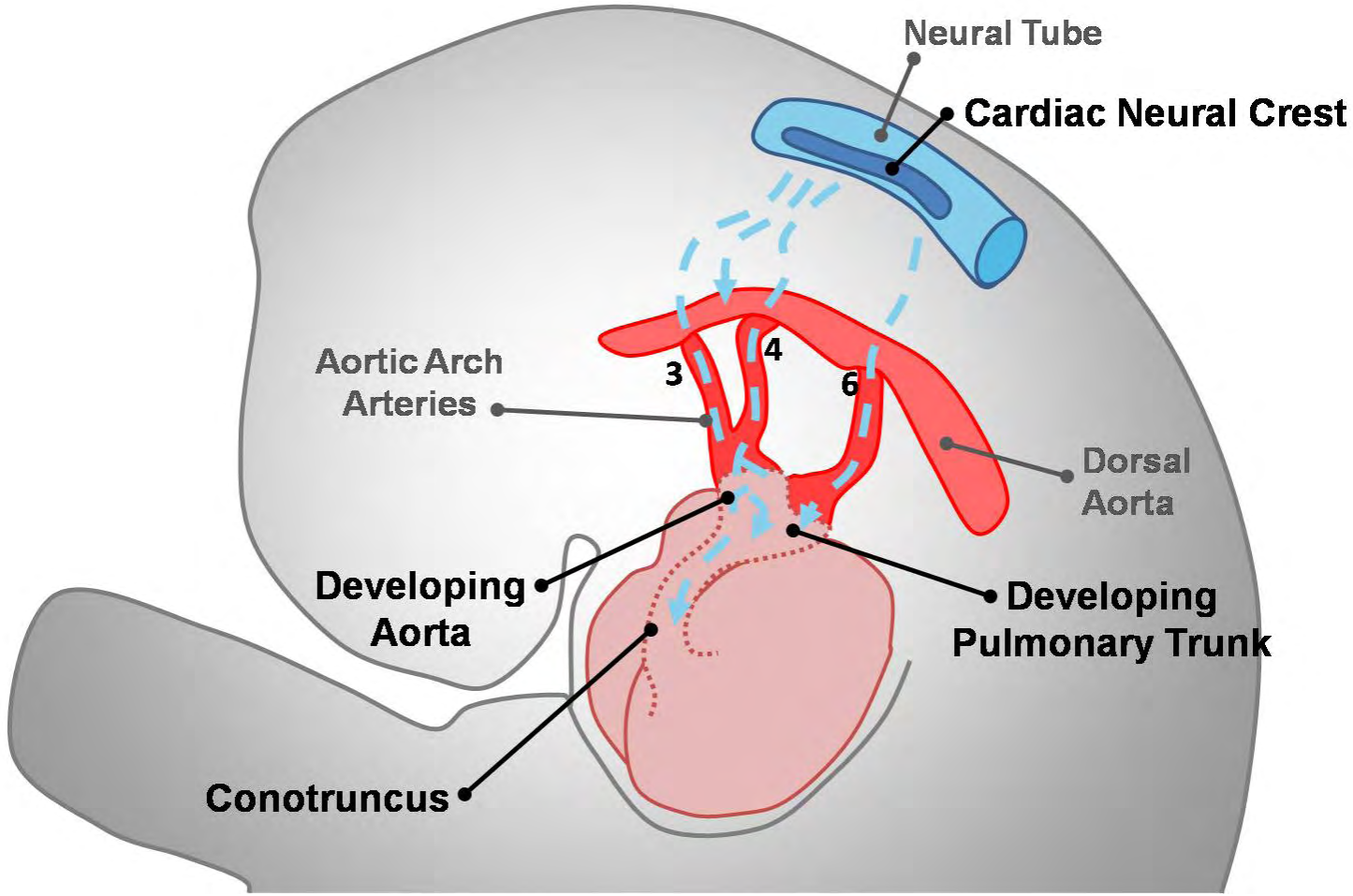


Postcranial neural crest migration

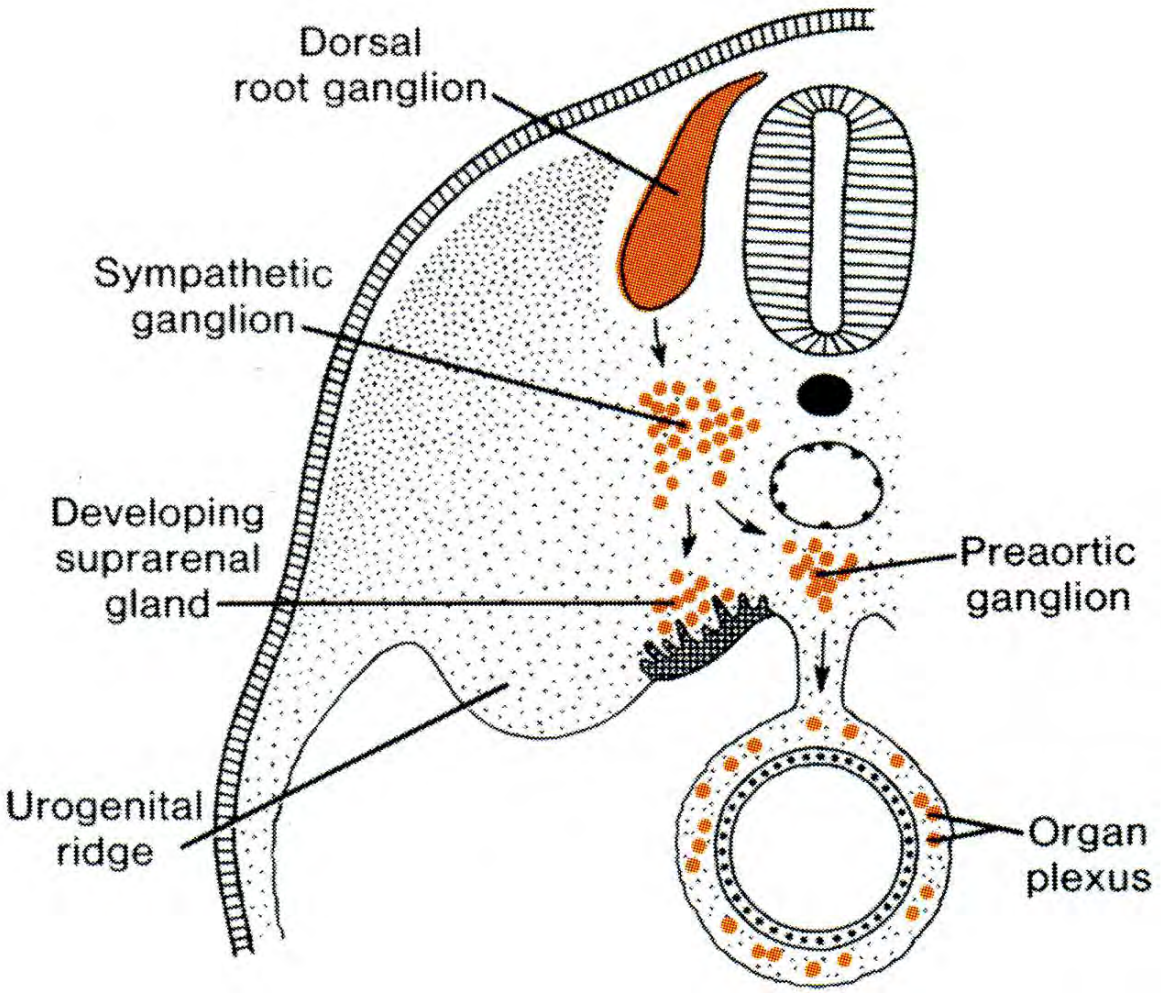
- Contribution to cardiovascular structures (e.g. aortopulmonary septum, endocardial cushions)
- Dorsal root (sensory) ganglia
- Autonomic ganglia (sympathetic trunk, prevertebral ganglia, parasympathetic ganglia)
- Adrenal medulla (actually modified postganglionic sympathetic neurons)
- Enteric nervous system (neurons in gut wall)
- Pia and arachnoid around spinal cord
- Melanocytes throughout skin of body
- Schwann cells of peripheral nerve

Cardiovascular neural crest

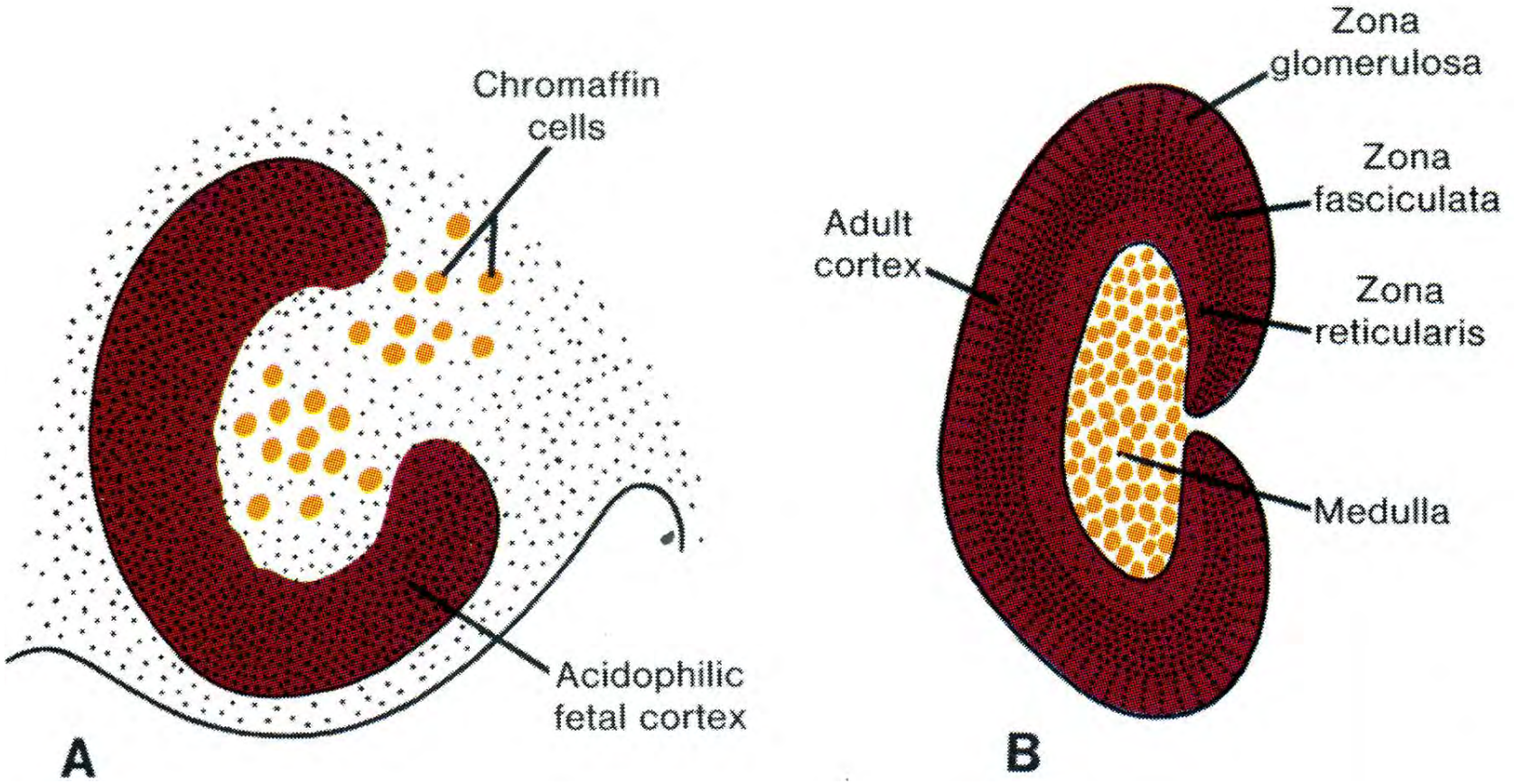
Embryo – Week 5: Migration of the Cardiac Neural Crest



Development of autonomic ganglia



Development of adrenal medulla



Chromaffin cells are of neural crest origin (modified sympathetic postganglionic cells)

Molecular biology of neural crest

Neural crest cells are a population of multipotent, migratory cells

- How do embryonic cells become defined as neural crest (as opposed to epithelial or central nervous cells)?
- How is neural crest migration controlled?
- What interactions occur between the neural crest and the substrate they migrate over?

Neural crest induction

- Not understood with certainty, but may involve BMP, Wnt and Fgf.
- BMP antagonists diffusing from the ectoderm generate a gradient of BMP activity. The neural crest lineage forms from intermediate levels of BMP signaling required for the development of the neural plate (low BMP) and epidermis (high BMP).
- Fgf from the paraxial mesoderm has been suggested as a neural crest induction agent.

Neural crest border specification

- Signalling events that establish the neural plate border.
- Molecules expressed at the neural plate border.
- May include Zic factors, Pax3/7, Dlx5, Msx1/2 which may mediate the influence of Wnts, BMPs, and Fgfs (see above).

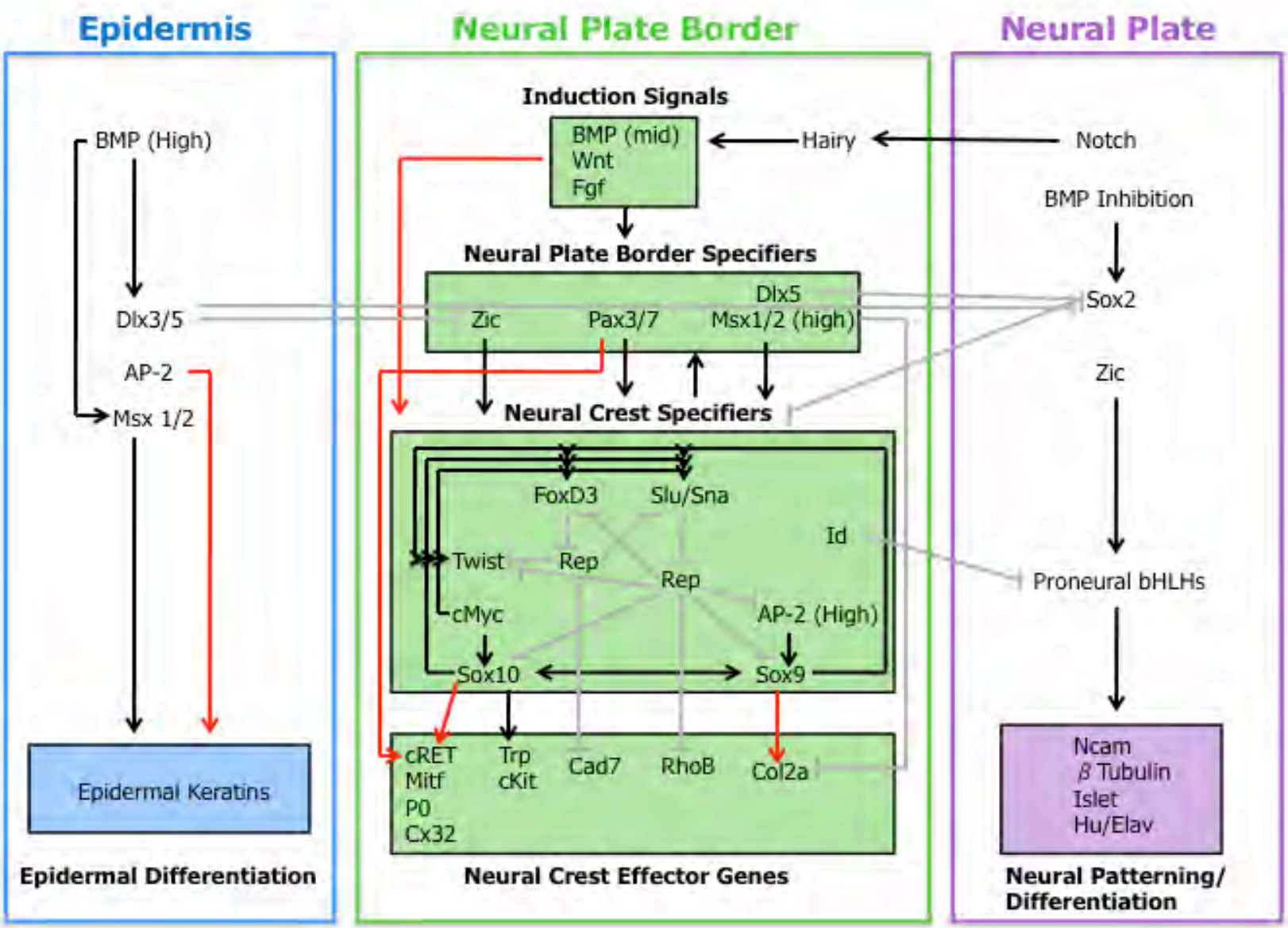
Neural crest specifiers

- Activated in emergent neural crest
- Factors including Slug/Snail, FoxD3, Sox10, Sox9, AP-2 and c-Myc

Neural crest effector genes

- Confer migration and multipotency.
- Two neural crest effectors, Rho GTPases and cadherins, are active in delamination (separation from site of origin) by regulation of neural crest cell shape and adhesiveness.
- Sox9 and Sox10 regulate neural crest differentiation by activating cell-specific effector molecules such as Mitf, P0, Cx32, Trp and cKit.

How Wikipedia summarises it!



Neural crest and birth defects

- Craniofacial abnormalities (Treacher Collins syndrome, Robin sequence, DiGeorge sequence, hemifacial microsomia)
- Cardiac abnormalities (persistent truncus arteriosus, tetralogy of Fallot, transposition of the great vessels)
- Hirschsprung's disease

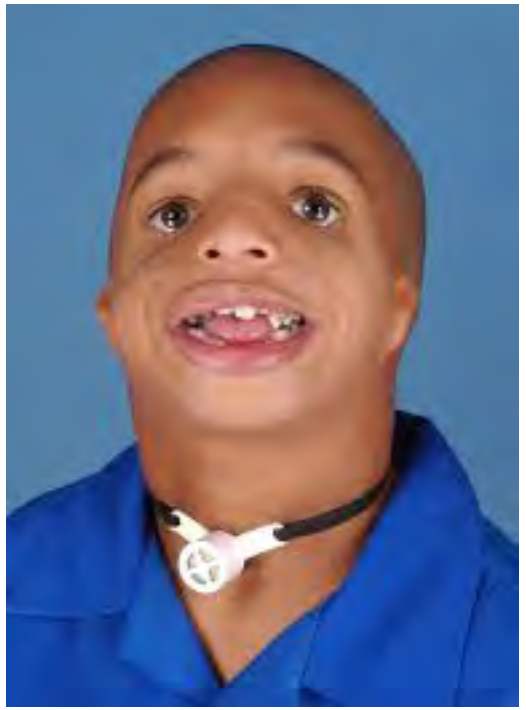
Note that craniofacial and cardiovascular neural crest related defects often occur together.

Neural crest cells are vulnerable

- Neural crest cells are highly vulnerable to a number of teratogens, e.g.
  - Ethanol
  - Retinoic acid (isotretinoin)
- This may be due to low levels of superoxide dismutase and catalase in neural crest cells. These scavenge free radicals produce by exposure to teratogens.

Treacher Collins Syndrome

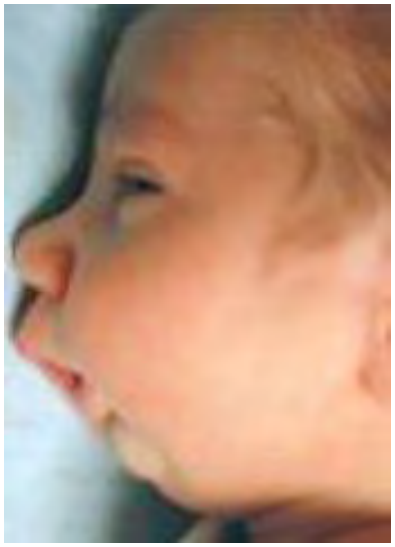
- Also known as mandibulofacial dysostosis
- Affects 1st pharyngeal arch structures
- Autosomal dominant with 60% arising as new mutations. May be induced in animals by retinoic acid exposure
  - Underdevelopment of the zygoma
  - Mandibular hypoplasia
  - Down-slanting palpebral fissure
  - Lower eyelid colobomas
  - Malformed external ears



Robin sequence (Pierre Robin syndrome)

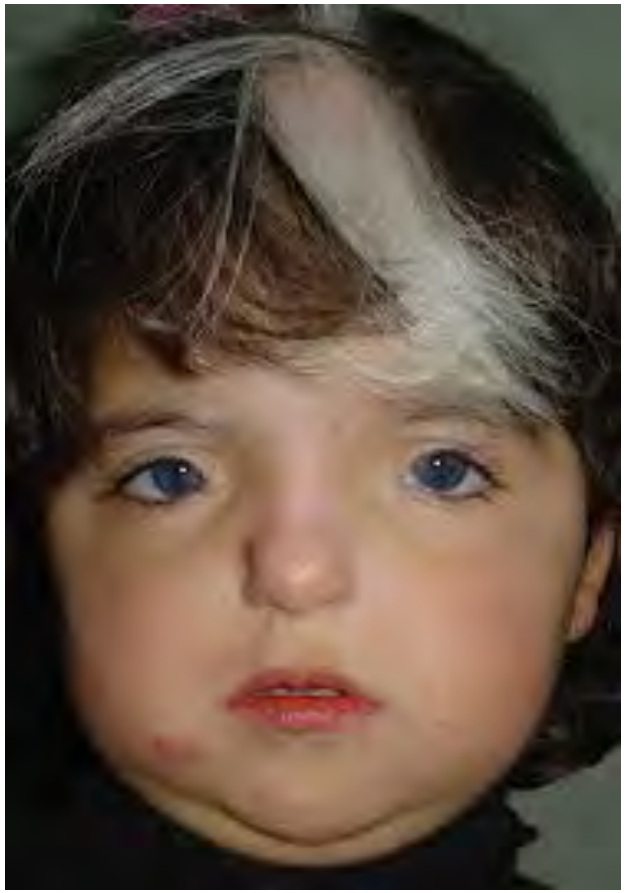
- Involves 1st arch structures (but mainly mandible)
- 1/8500 live births
- Features:
  - Micrognathia
  - Cleft palate
  - Glossoptosis (posteriorly place tongue)

Note that cleft palate may be secondary to the mandible and tongue affecting palate development



Di George sequence
(third and fourth pharyngeal pouch syndrome)

- Occurs sporadically and may be due to teratogens, e.g. retinoids
- The complete syndrome has a poor prognosis due to immune system defects and hypocalcaemia
- Features:
  - Hypoplasia or absence of thymus (neural crest provide the stroma)
  - Hypoplasia or absence of parathyroid glands
  - Cardiovascular defects (persistent truncus arteriosus, interrupted aortic arch)
  - Abnormal external ears
  - Micrognathia
  - Widely spaced eyes (hypertelorism)



Hemifacial microsomia
(oculoauriculovertebral spectrum, Goldenhar syndrome)

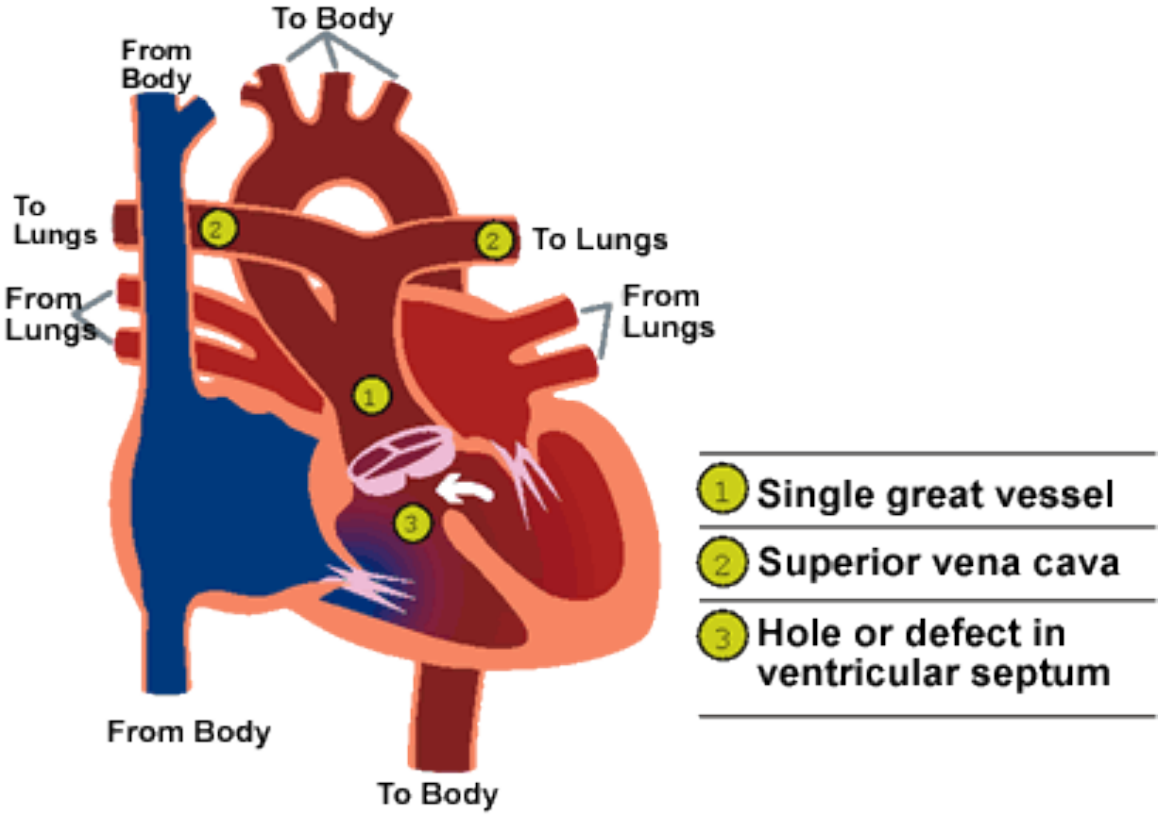
- 1/6500 live births
- Features are often asymmetrical
  - Small and flat maxillary, temporal and zygomatic bones
  - Anotia/microtia
  - Tumours in eyeball
  - Fused and hemivertebrae; spina bifida

May also have cardiac defects

Neural crest related cardiovascular defects 1

Persistent truncus arteriosus

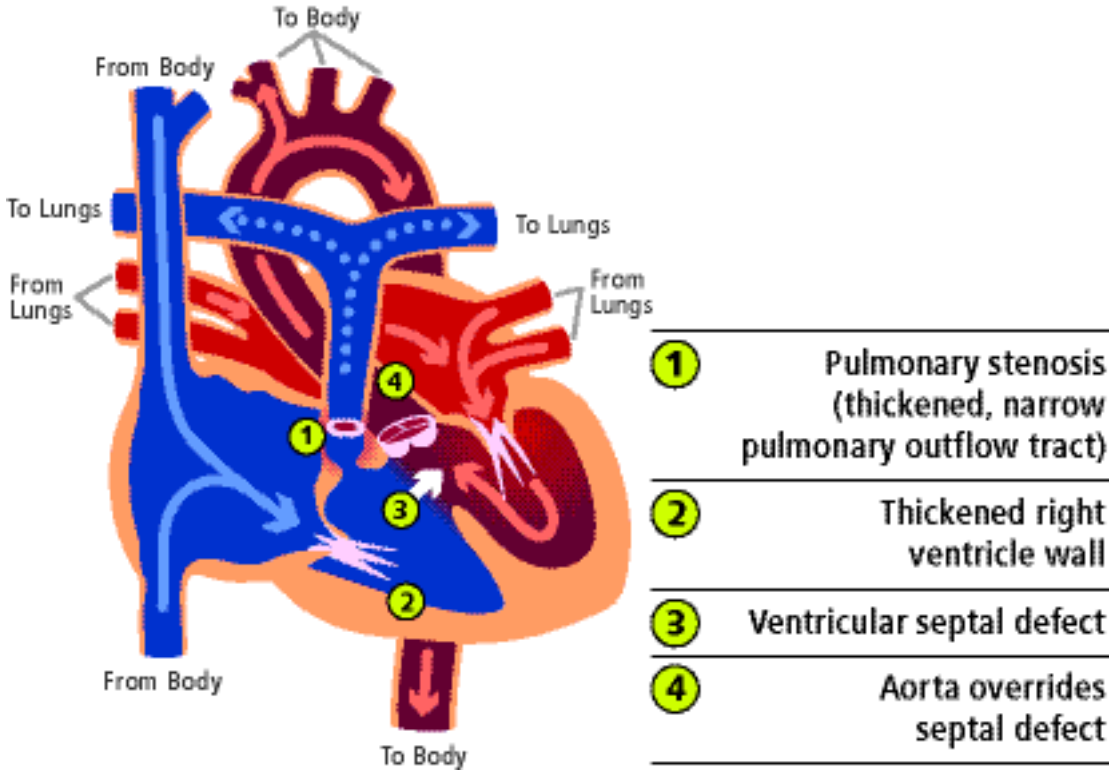
- 0.8/10,000 live births
- The neural crest directly contributes to the aortopulmonary septum
- May be sporadic or associated with Chromosome 22q deletion



Neural crest related cardiovascular defects 2

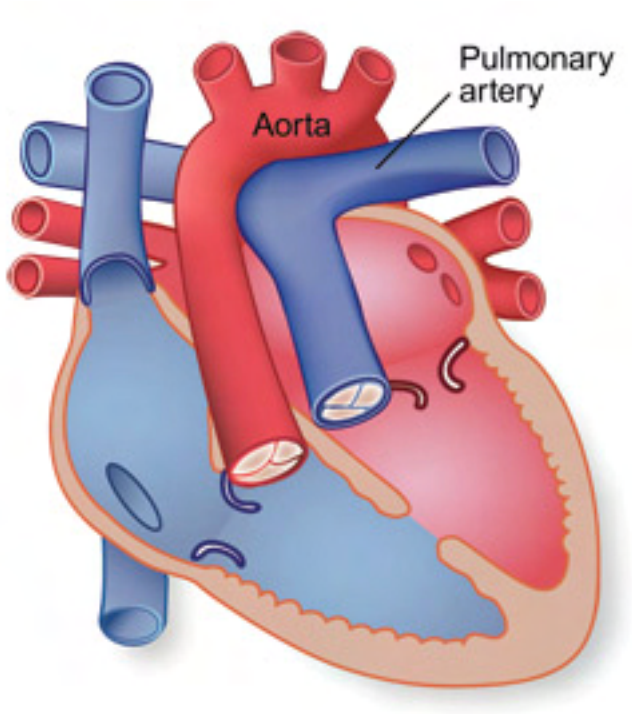
Tetralogy of Fallot

- 9.6/10,000 live births
- cyanotic heart disease
- probably involves unequal growth of the aortopulmonary septum (which may be due to problems with neural crest migration)
- May involve problems with genes: *VEGF, JAG1*



Neural crest related cardiovascular defects 3

- 4.8/10,000 live births
- Transposition of the great vessels
- True transposition (dextro-transposition) is a type of cyanotic heart disease
- May be associated with maternal diabetes mellitus



Hirschsprung's disease (aganglionic megacolon)

- Ganglia of the gut wall are of neural crest origin
- Mainly involves the rectum and caudal sigmoid colon (80%), but may extend to transverse or ascending colon. Involves entire colon in only 3% of cases
- Caused by mutations in *RET*, a gene for the tyrosine kinase receptor involved in neural crest migration