Disorders of Craniofacial Development

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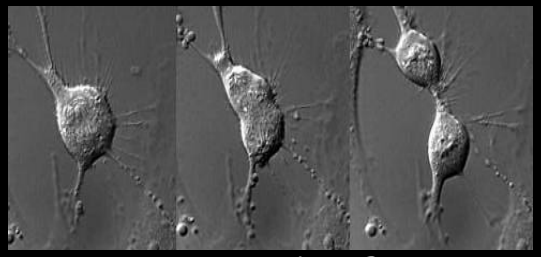
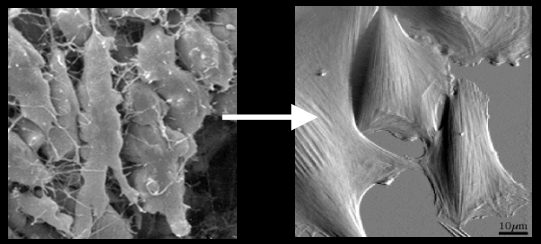
Developmental Biology

How do individual cells form complex anatomical structures in the developing embryo?

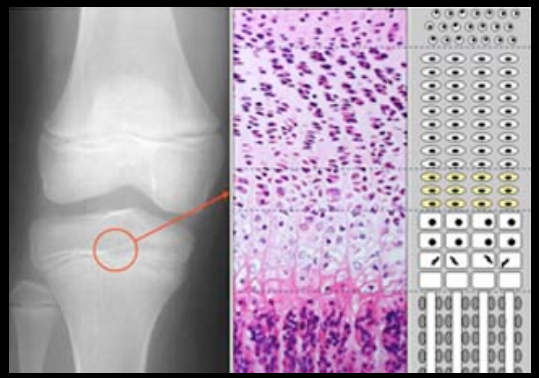
growth: mediates size



differentiation: defines cell type



morphogenesis: establishes shape and function



How do these processes direct formation of the craniofacial skeleton?

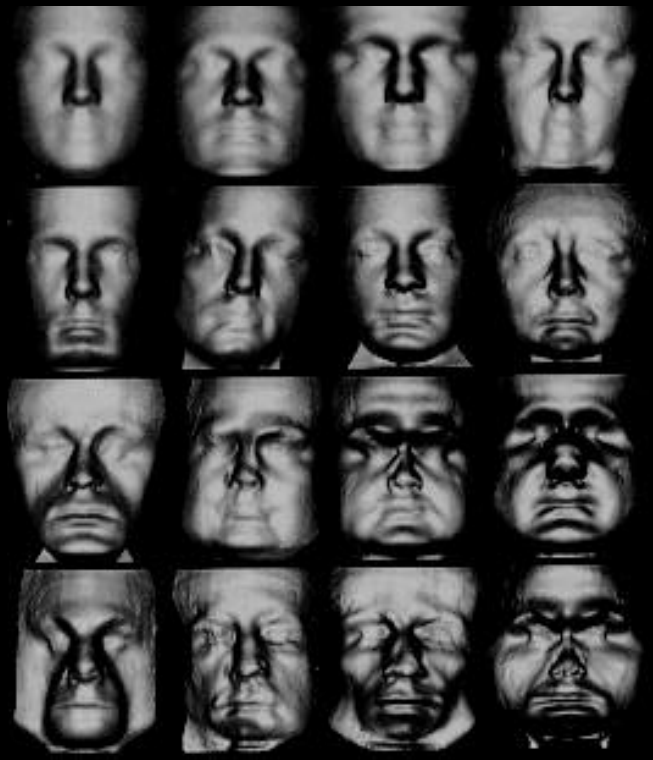
12week Fetus

What does this tell us about craniofacial birth defects?

Morphology:

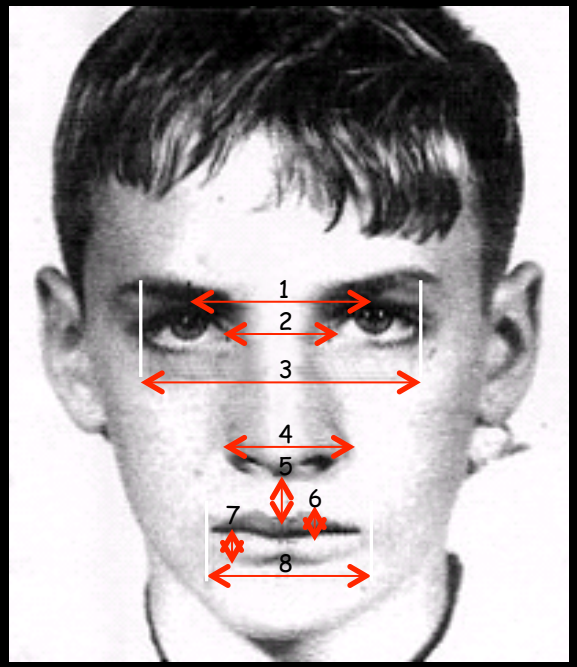
Study of anatomical structure and form

Normal variation is a result of complex interactions between the genome and environment.



What is normal variation?

Anthropometric facial measurements



1. Interpupillary distance
2. Inner canthal distance
3. Outer canthal distance
4. Ineralar distance
5. Philtral length
6. Upper lip thickness
7. Lower lip thickness
8. Intercommisural distance

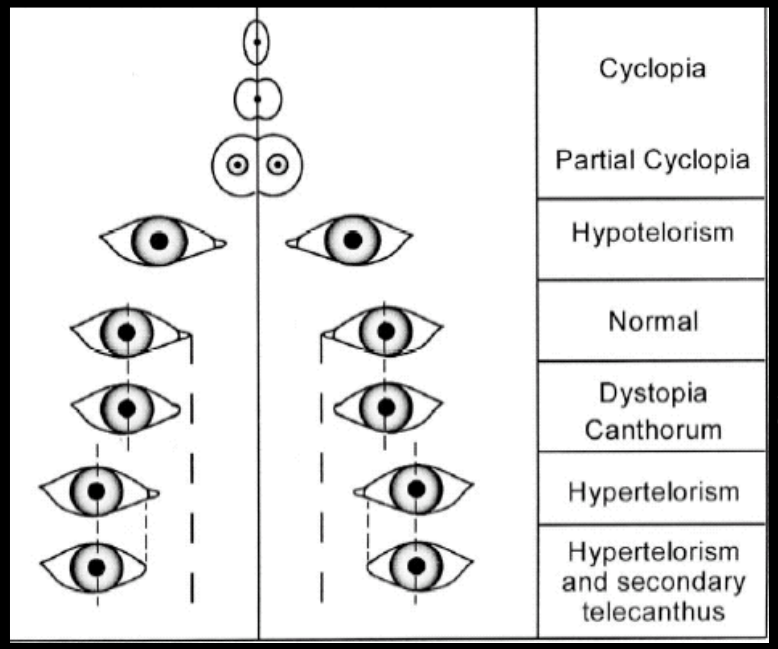
95% are within 2 Standard Deviations of the mean.

Dysmorphology:

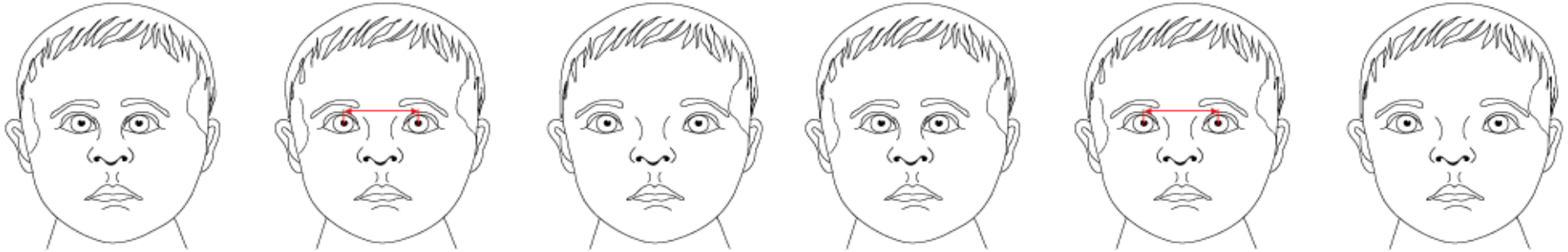
Study of abnormal morphology

A dysmorphic trait measures at least 2 standard deviations outside the normal range

Interpupillary distance



Types of developmental disorders with dysmorphic features:



1. Malformation: poor formation
2. Dysplasia: deregulation
3. Deformation: mechanical forces
4. Disruption: destructive

Syndrome vs. Sequence

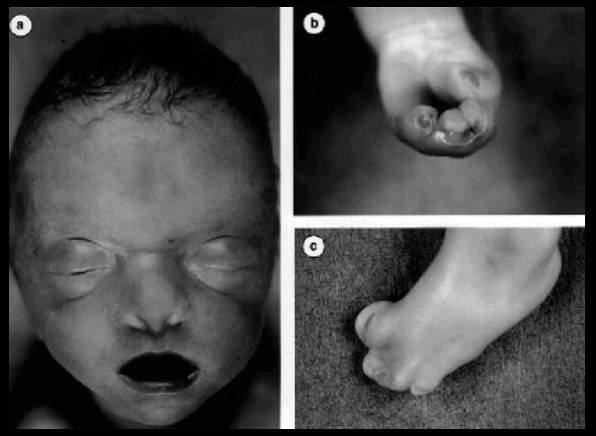
Syndrome:

A well defined constellation of anomalies that occur together in a predictable fashion.

Found usually with malformations and dysplasias.

Due to a single underlying etiology (e.g. gene, chromosome, teratogen).

Example: Apert syndrome.



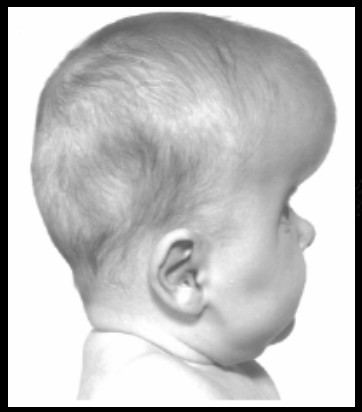
Syndrome vs. Sequence

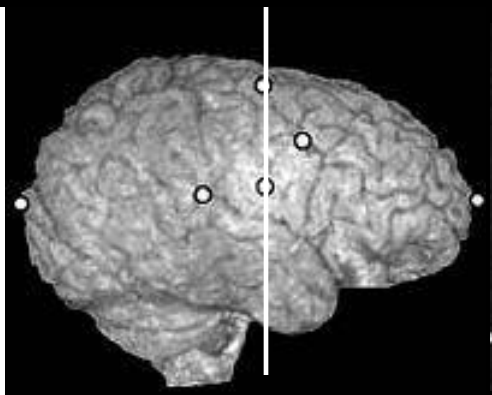
Sequence:

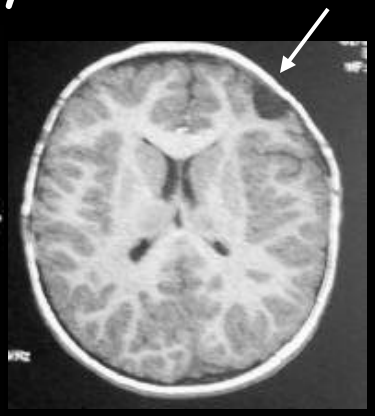
Pattern of anomalies that stems from a single initial anomaly which alters development of surrounding or related tissues.

Found with all types of dysmorphology.

Example: non-syndromic craniosynostosis.







Malformation

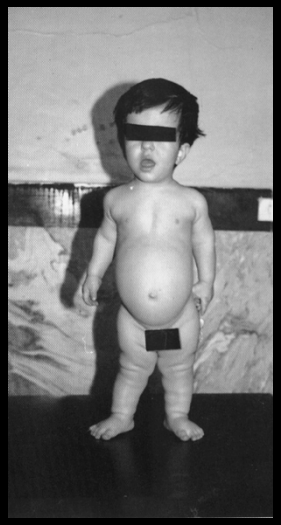
- Morphological defects resulting from intrinsically abnormal developmental processes, often beginning in 1st trimester.

- Due to underlying genetic, epigenetic, or environmental factors.

- Examples: cleft lip or palate, craniosynostosis, Treacher Collins syndrome.

Dysplasia

- Abnormal organization of cells into a particular tissue type (bone, cartilage).
- Distinction between malformation and dysplasia is not absolute.
- Example of Dysplasia: Frontonasal dysplasia and Achondroplasia.



Deformation

- Abnormal growth and form caused by an abnormal but non-disruptive mechanical forces.
- Targets growth sites of previously normal tissue during fetal period (sutures).
- Often temporary.
- Example: positional plagiocephaly.

Disruption

- Defect resulting from a breakdown of an originally normal developmental process.
- Growth is arrested by a factor of a mechanical, vascular, or infectious origin.
- Example: hemifacial microsomia.

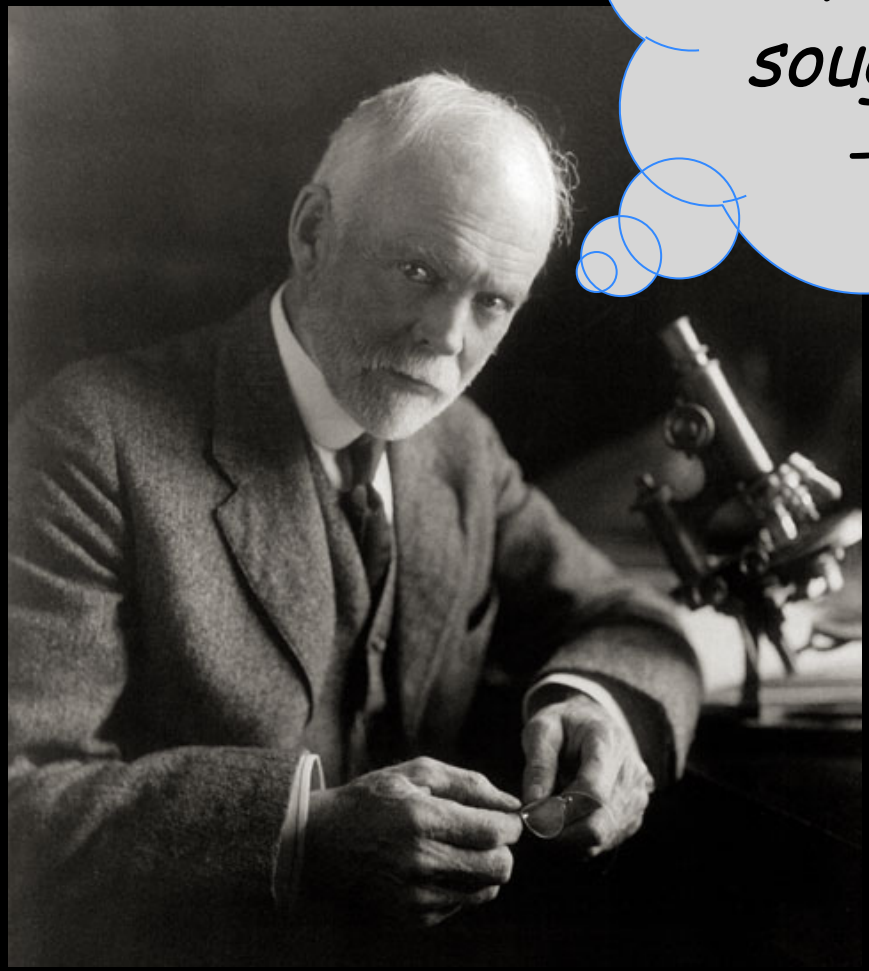
Features of the types of dysmorphology

Features	Malformation	Deformation	Disruption	Dysplasia
Time of occurrence	embryonic	fetal	embryonic	embryonic
Level of disturbance	organ	region	area	region/area
Perinatal mortality	+	-	+	+
Relative recurrence rate	high	low	extremely low	high
Frequency in newborns	2-3%	1-2%	1-2%	1-2%
Spontaneous correction	-	+	-	-
Surgical correction	+	+/-	+	+

How do we uncover the etiology of human craniofacial malformations and dysplasias?

12week Fetus

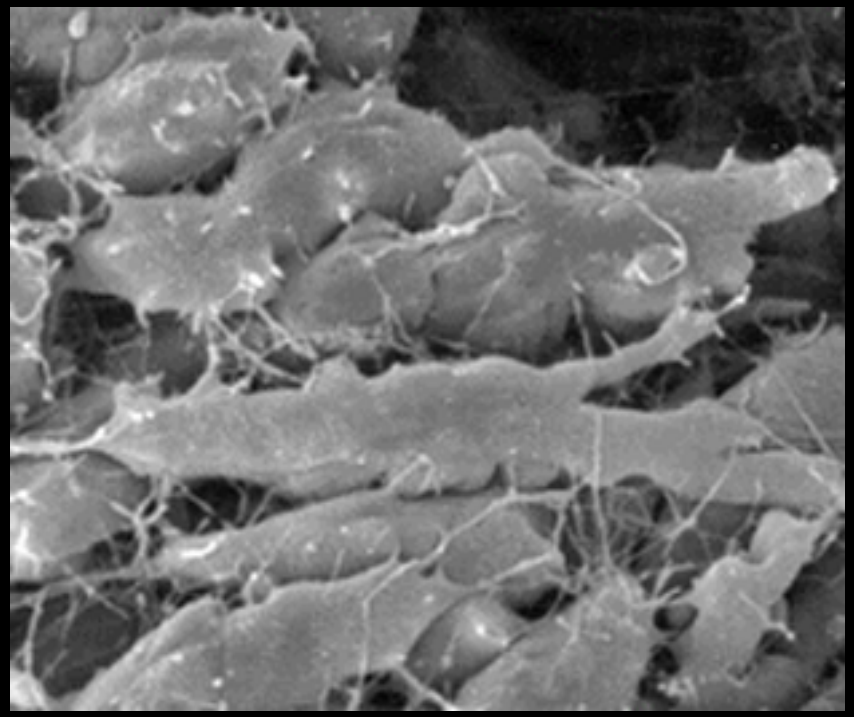
craniofacial skeleton is the foundation for facial form and function



The key to every biological problem must finally be sought in the cell.
-E.B. Wilson

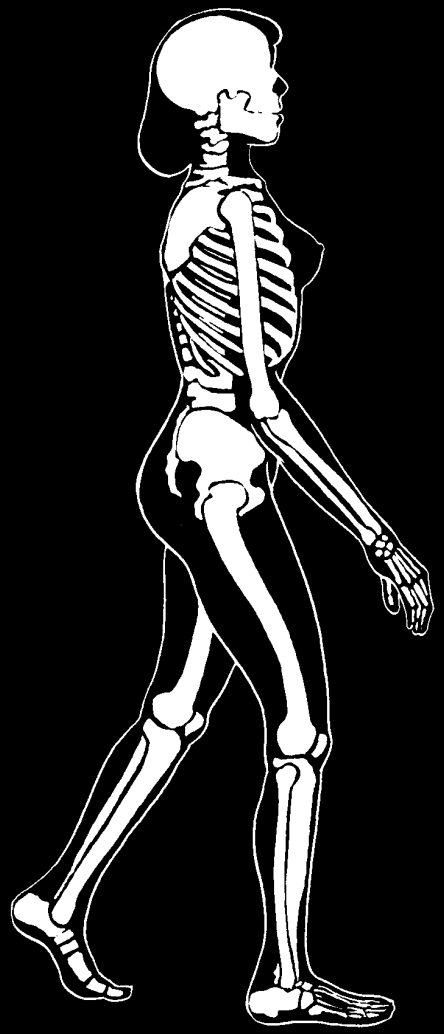
Skeletal Development

Mesenchyme:
precursors of bone and cartilage

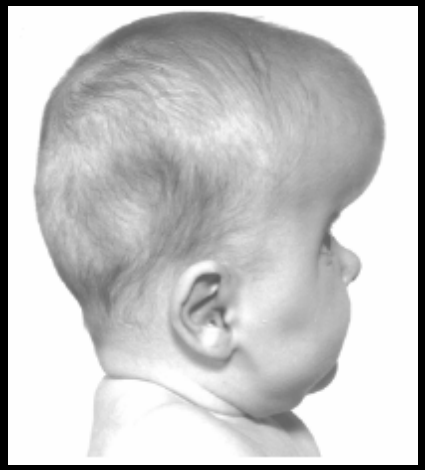
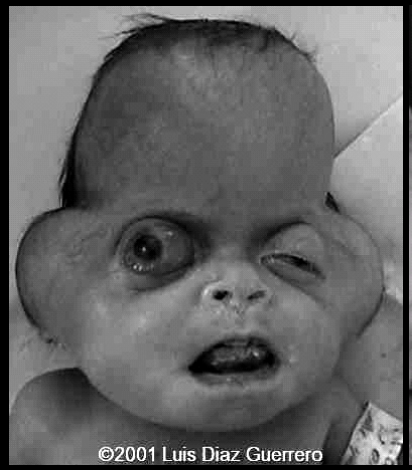


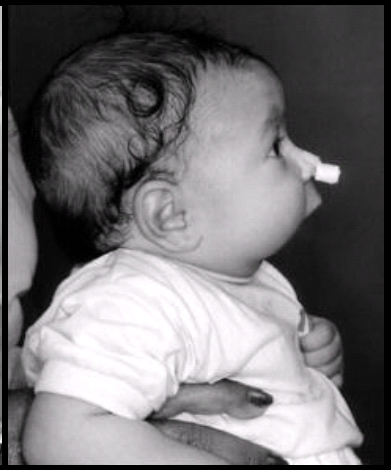
Bone formation

size
shape
orientation
integration



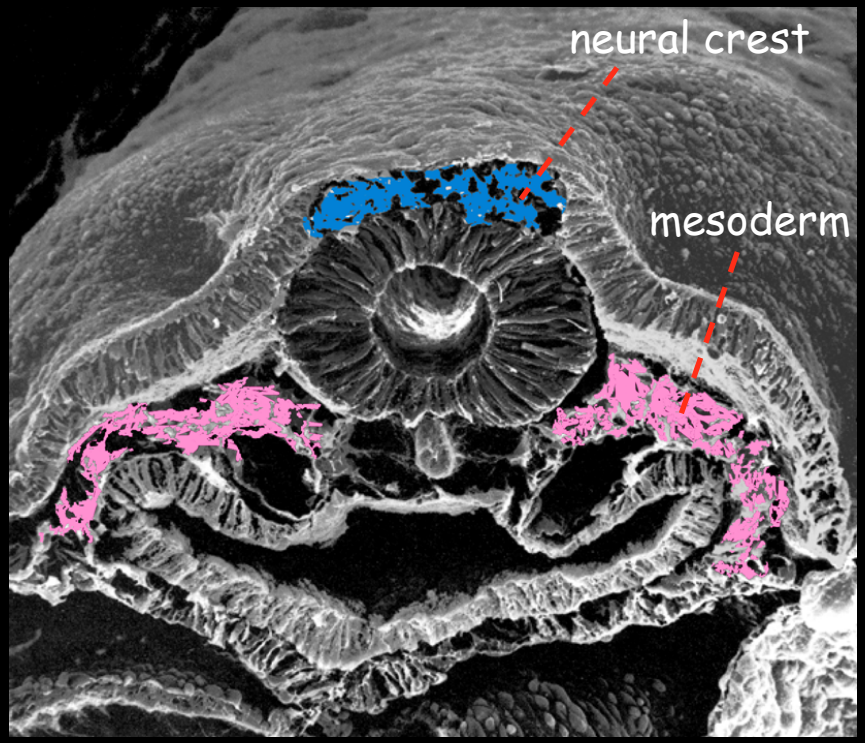
Disruptions in skeletal formation lead to developmental anomalies

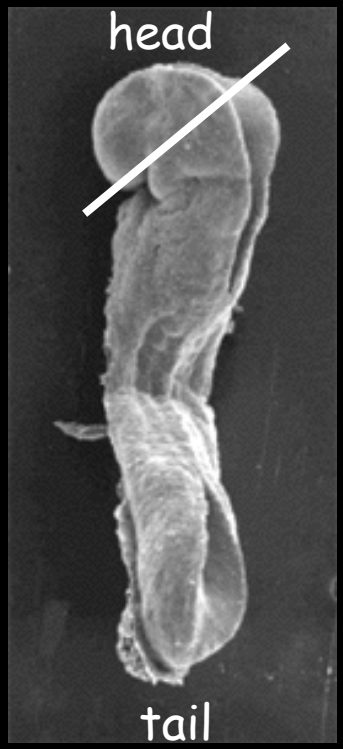


Understanding the steps that govern craniofacial development will reveal the cause of these anomalies

Mesenchyme derived from mesoderm and neural crest form the skeleton

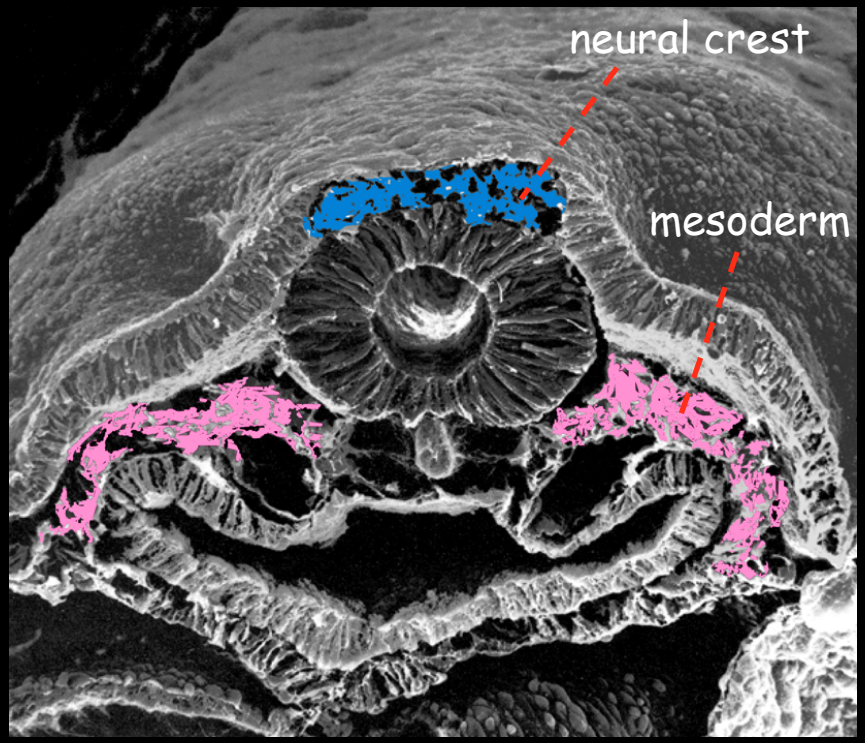


Modified from Larsen, 1993



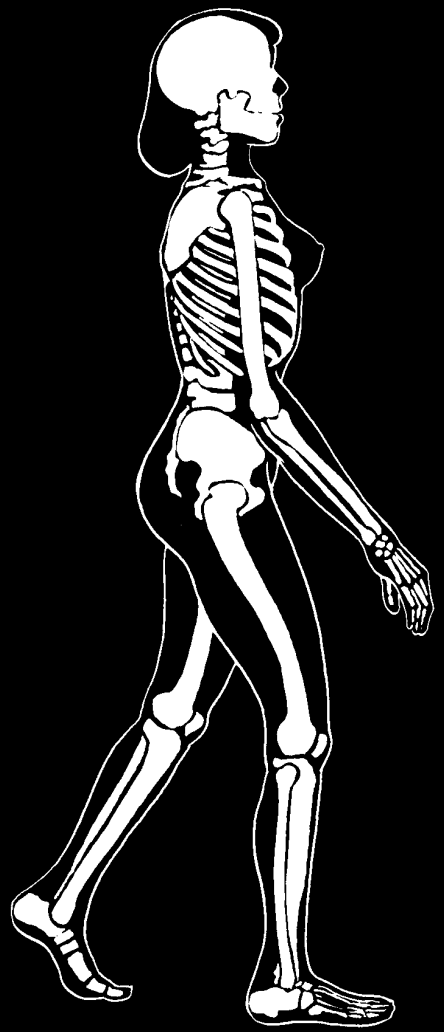
Day 22

Mesenchyme derived from mesoderm and neural crest form the skeleton

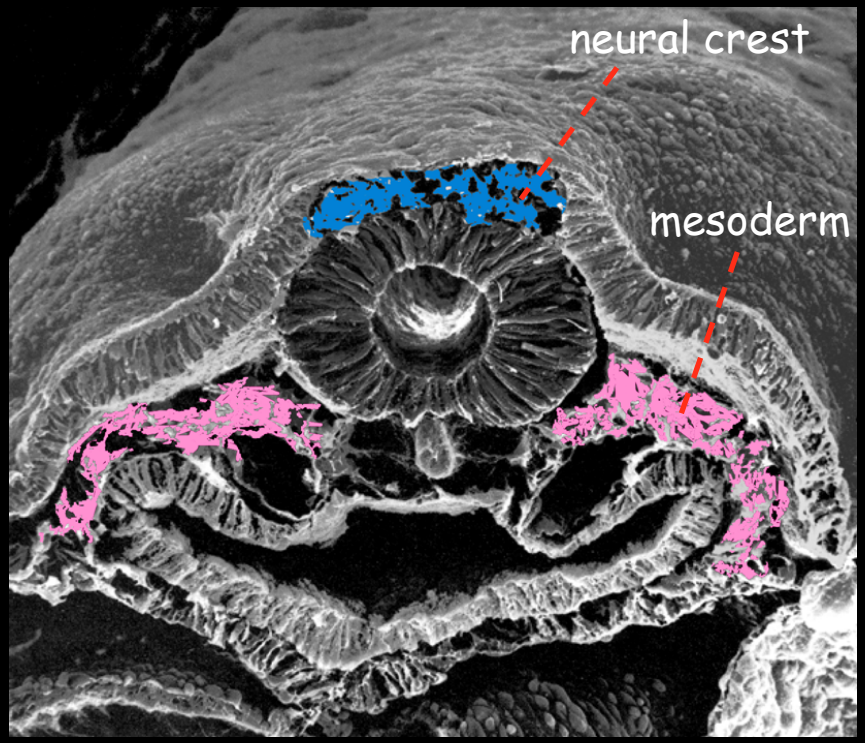


Modified from Larsen, 1993

Bone formation

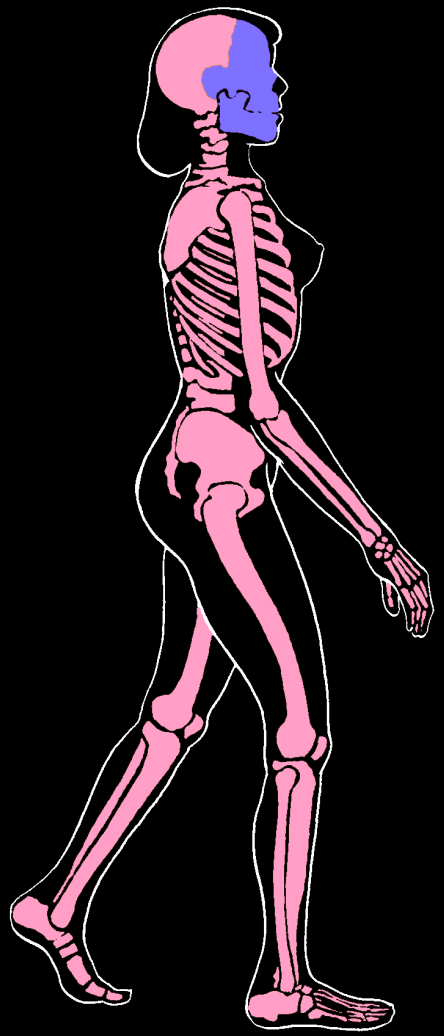


Mesenchyme derived from mesoderm and neural crest form the skeleton

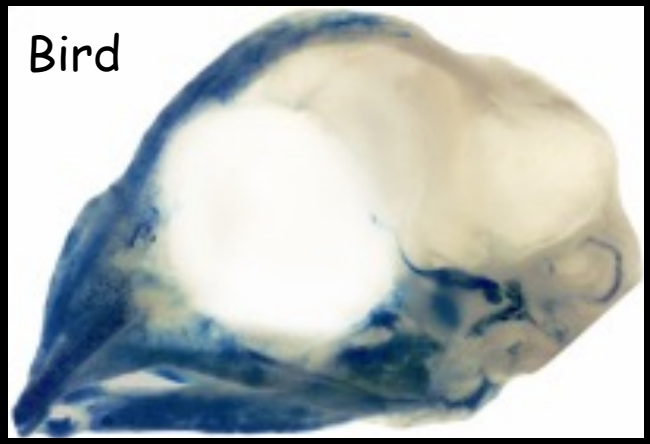


Modified from Larsen, 1993

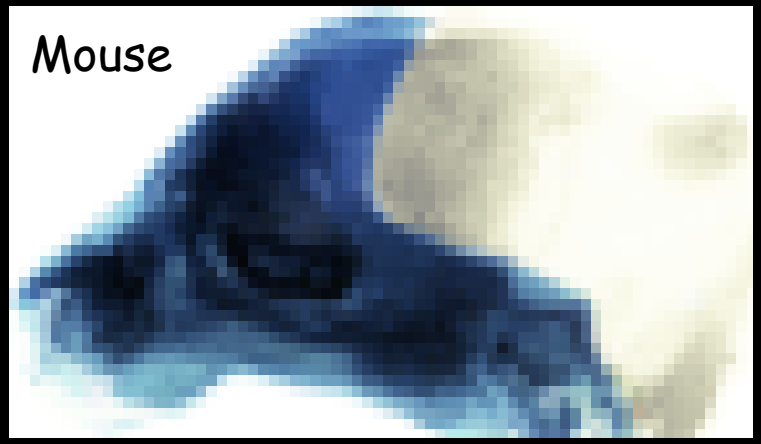
Bone formation



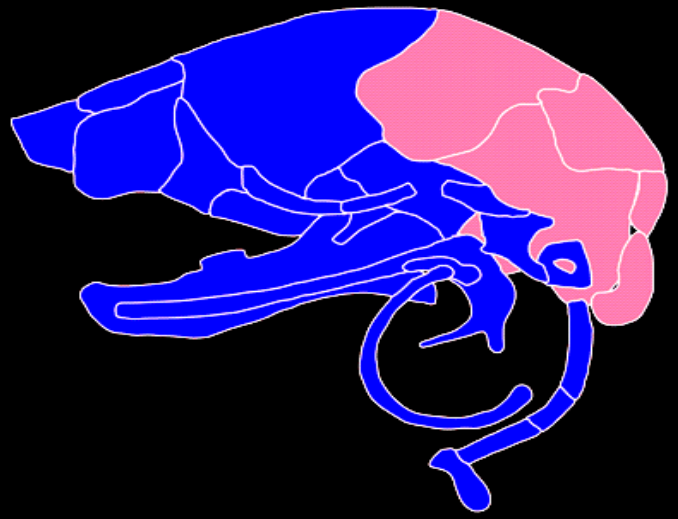
Skull contains both neural crest and mesoderm derived bone



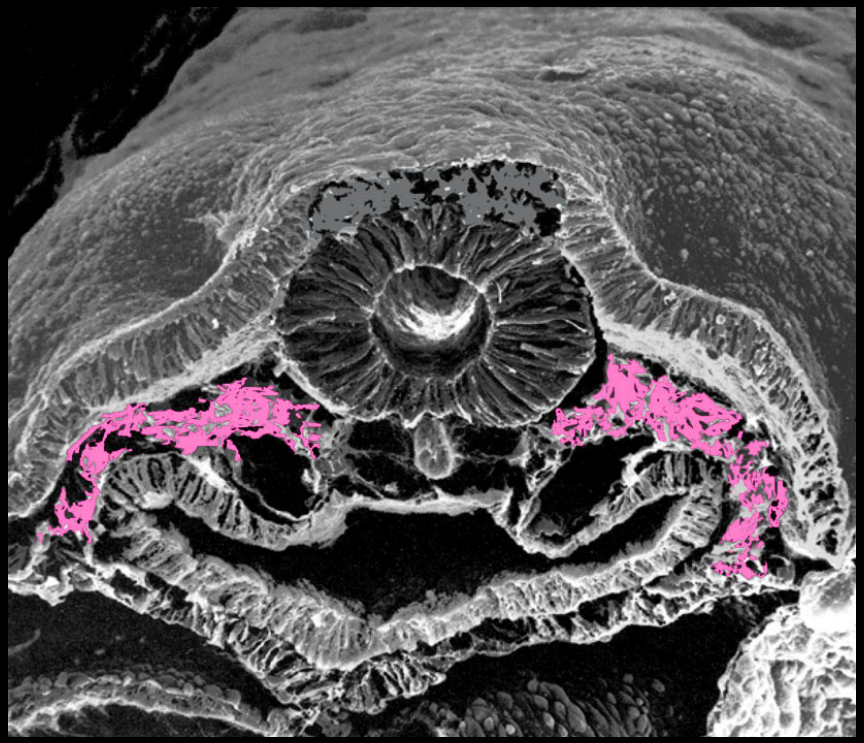
chick retrovirus (*SNV-lacZ*)
Evans and Noden, 2006

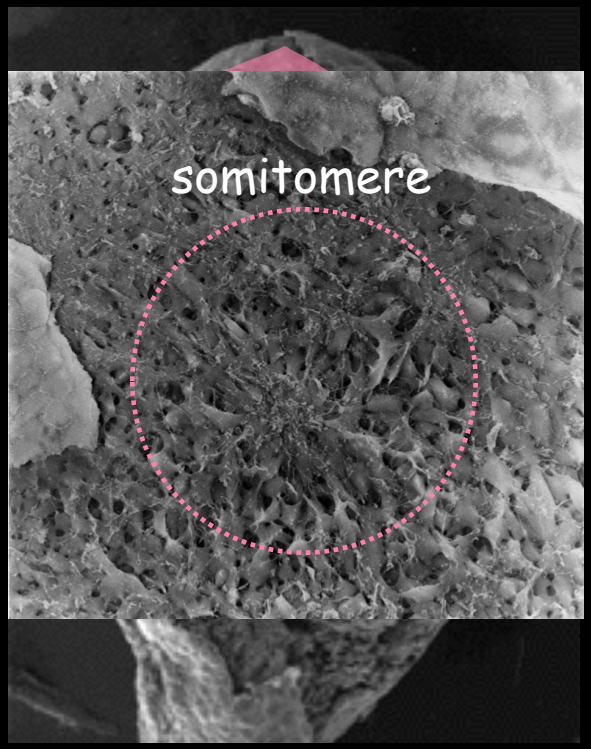


transgenic mouse (*Wnt1-Cre/R26R*)
Jiang *et al.* 2002

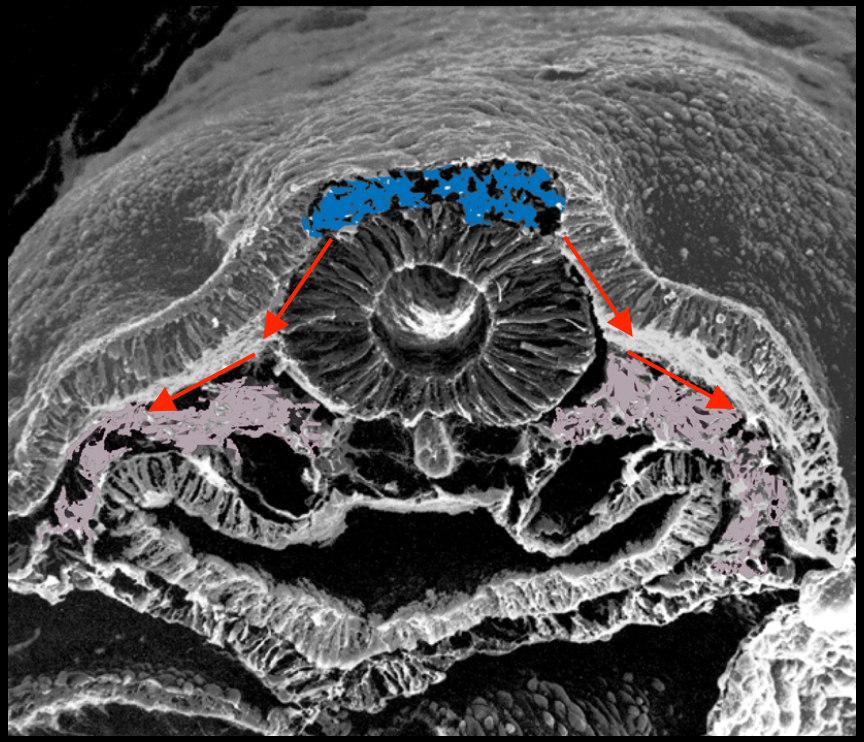


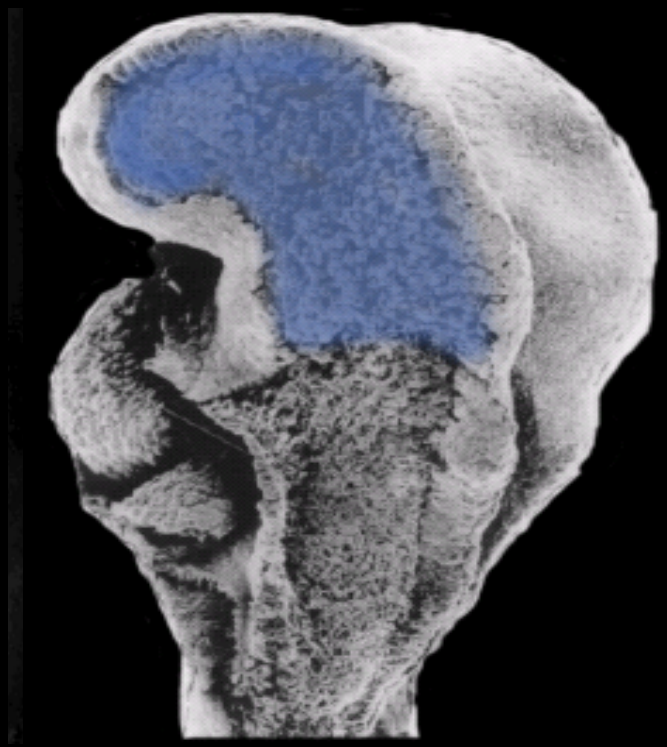
Paraxial mesoderm forms the caudal skull vault





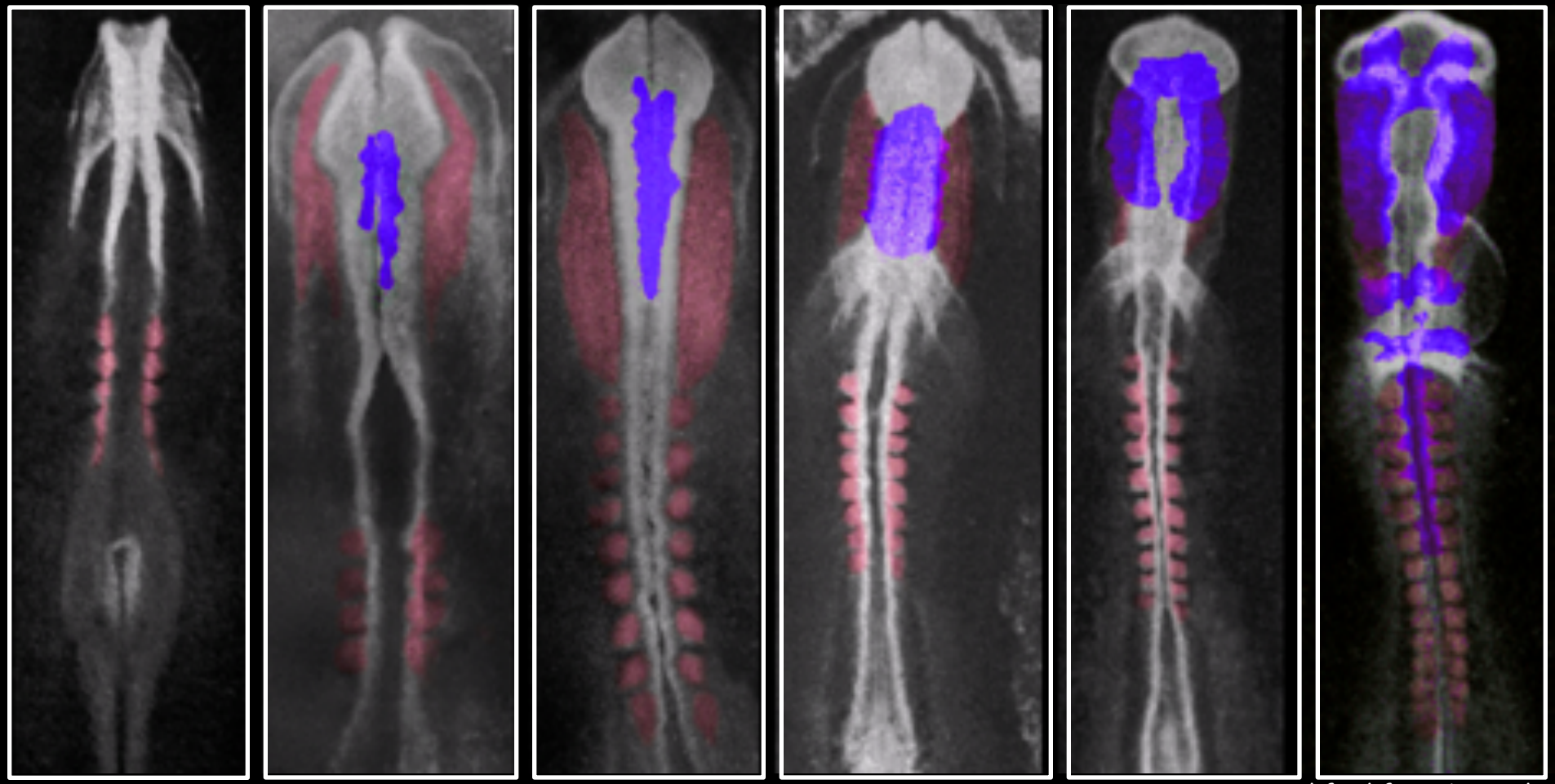
Neural crest cells form rostral skull vault and facial bones





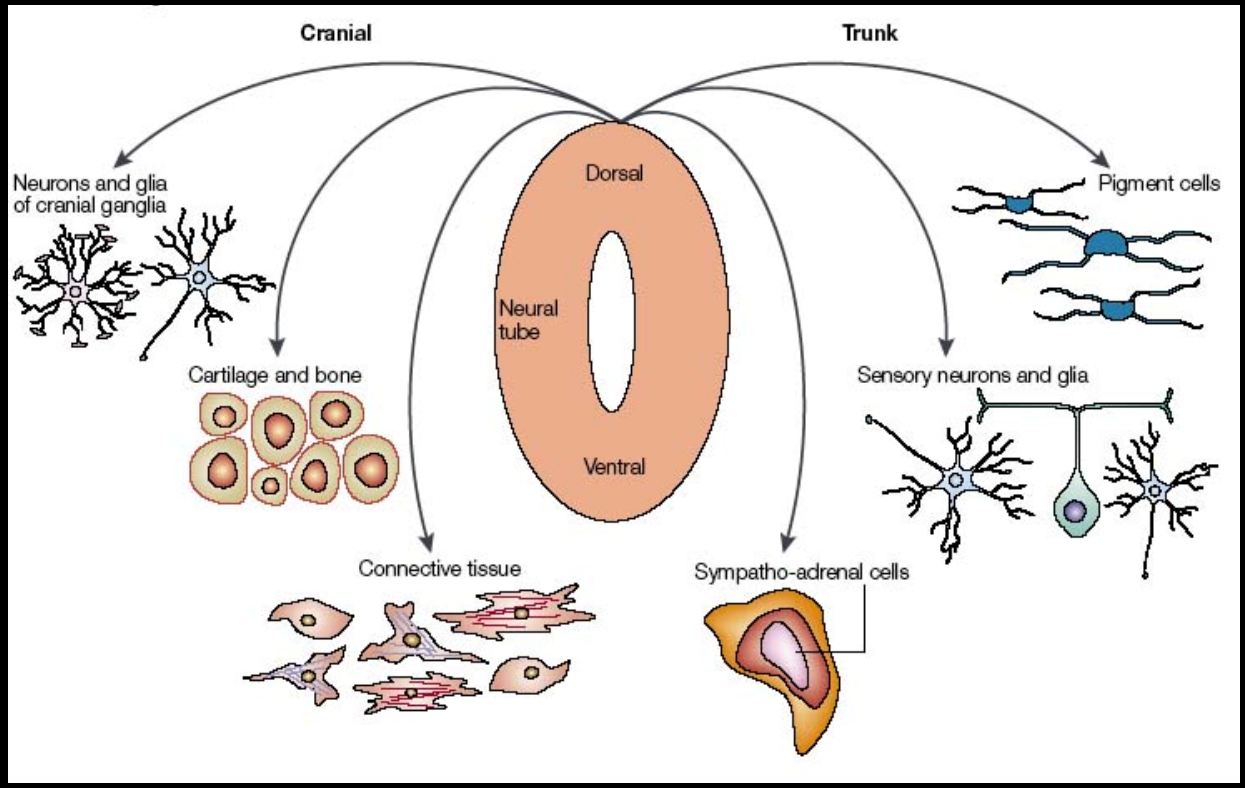
Day 22

Neural crest cells migrate during distinct embryonic stages



Modified from D. Noden

Neural Crest Cell Derivatives



Knecht and Bronner-Fraser, 2002

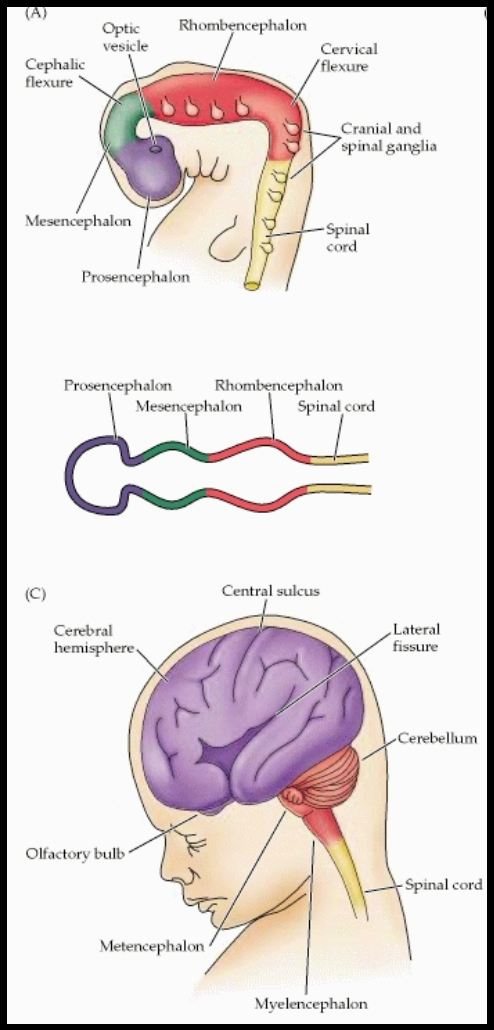
Cranial neural crest cells (CNCC) form bone and cartilage

Origins of the Cranial NCC:

Regions of the developing brain

1. Forebrain (Prosencephalon):
   - hippocampus,
   - olfactory lobes
   - retina
   - thalamus
2. Midbrain (Mesencephalon):
   - optic lobes
   - tectum
3. Hindbrain (Rhobencephalon):
   - cerebellum
   - medulla

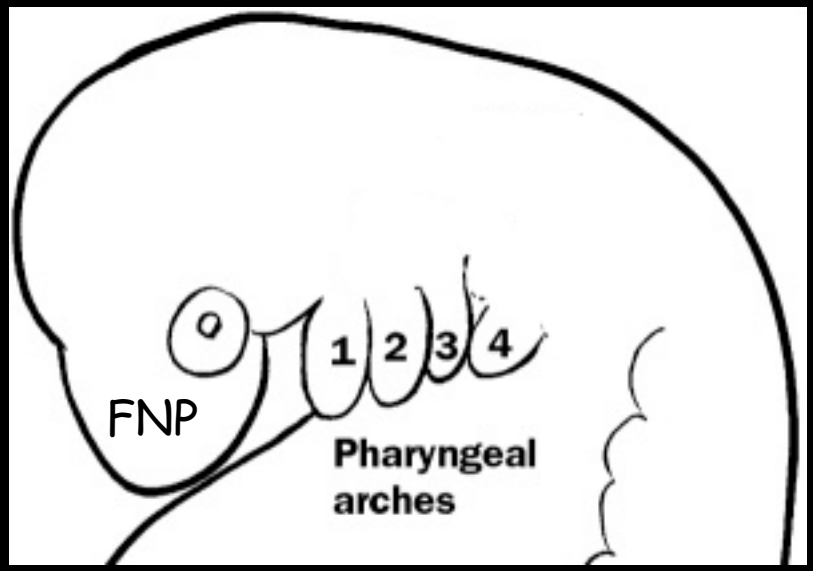
CNCC arising from each region contributes to distinct structures in the head and neck

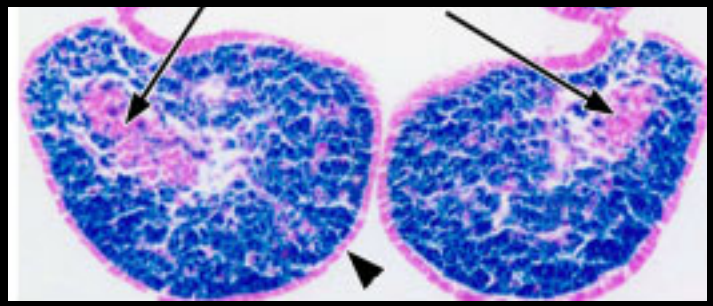


Neuroscience. 2nd edition

Destination of the CNCC:

Frontonasal process and pharyngeal arches

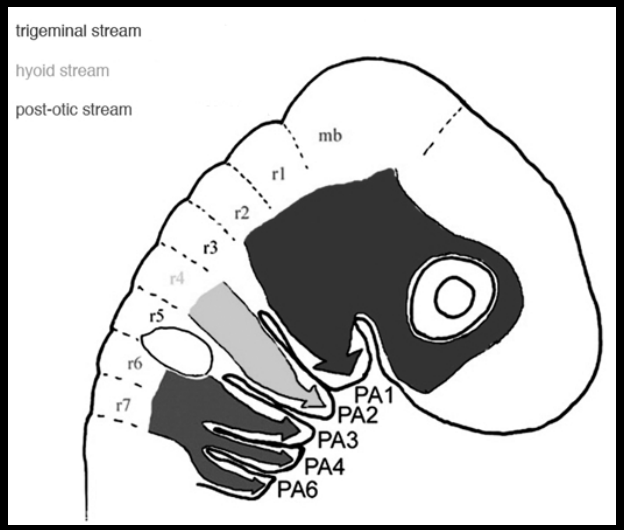


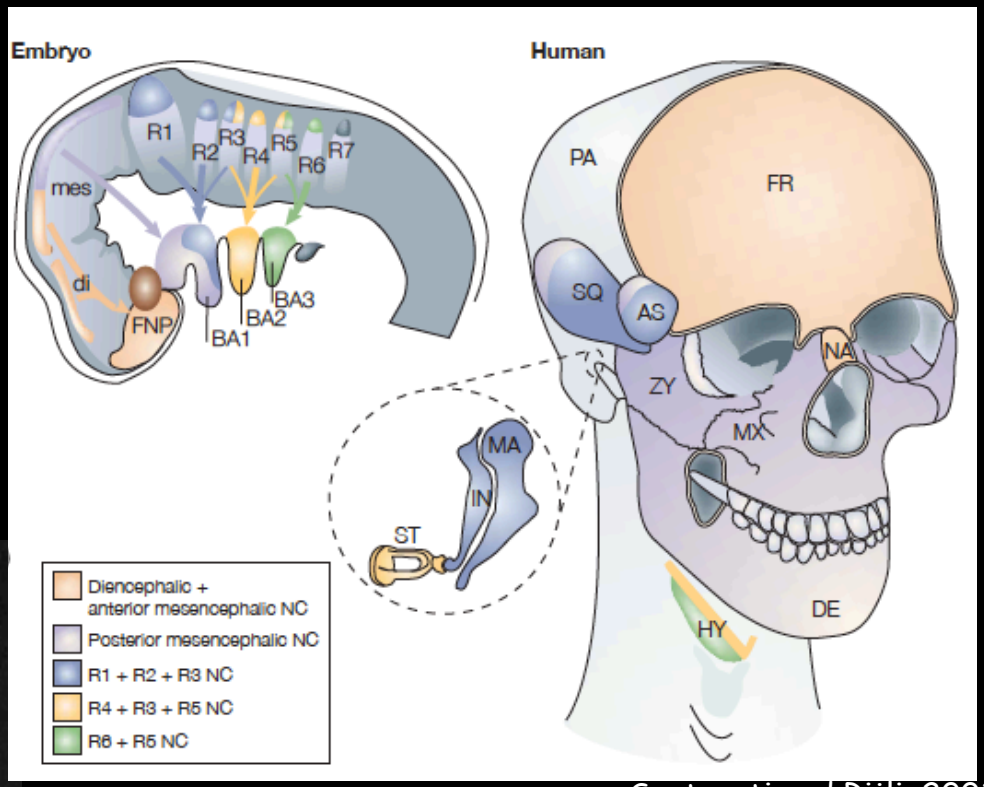


Tissue contribution:
Epithelium
Paraxial mesoderm
CNCC (blue)

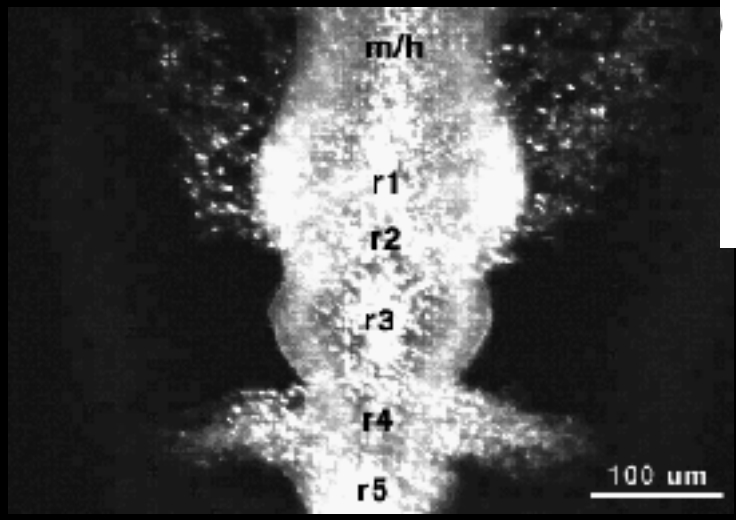
Migration pattern of CNCC:

Distinct streams of CNCC from the developing brain





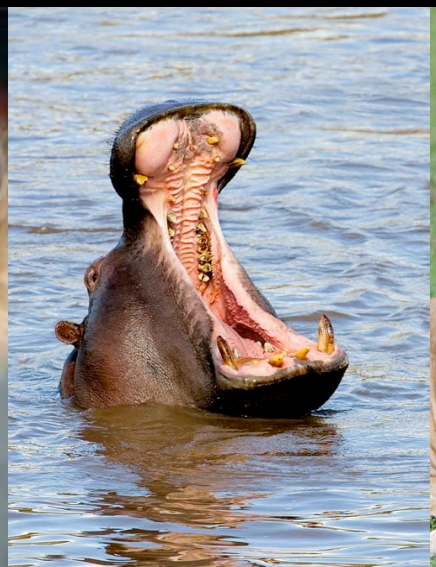
Santagati and Rijli, 2003



Trigeminal: jaw/facial bones, frontal and nasal bones, middle ear bones
Hyoid: hyoid, middle ear bone (stapes)
Post-otic: thymus, parathyroid, and thyroid

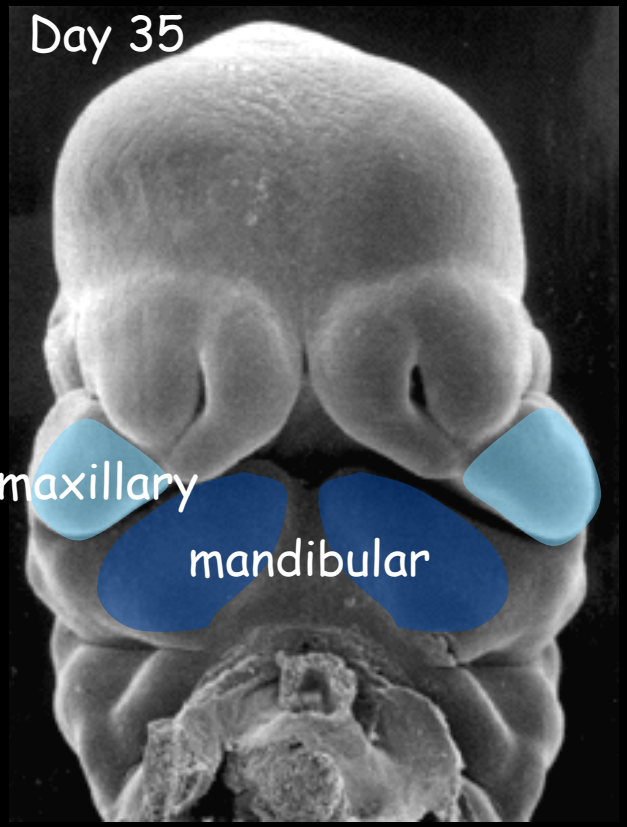


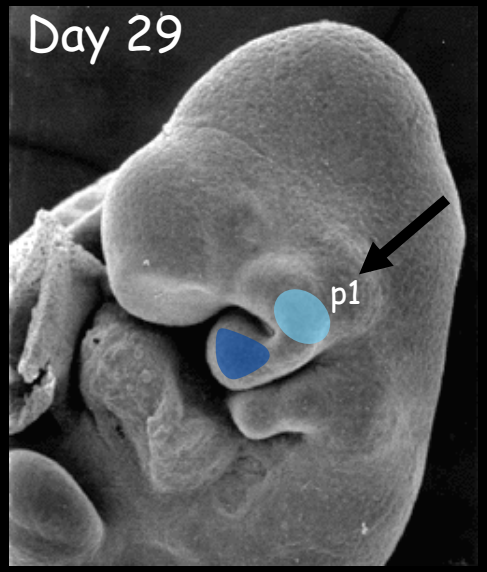
Jaw Bone Development

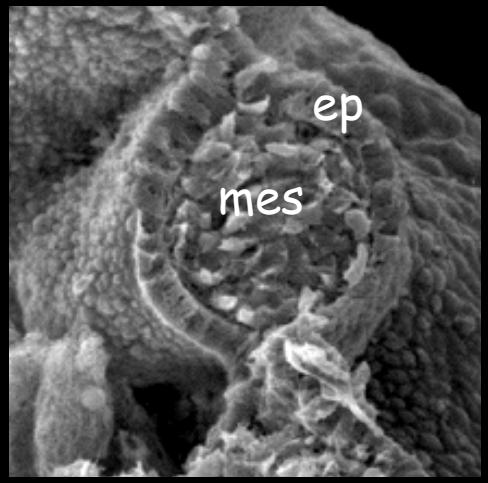



Jaw Bone Development

1. CNCC from the midbrain and hindbrain migrate into 1st pharyngeal arch and communicate with overlying epithelium



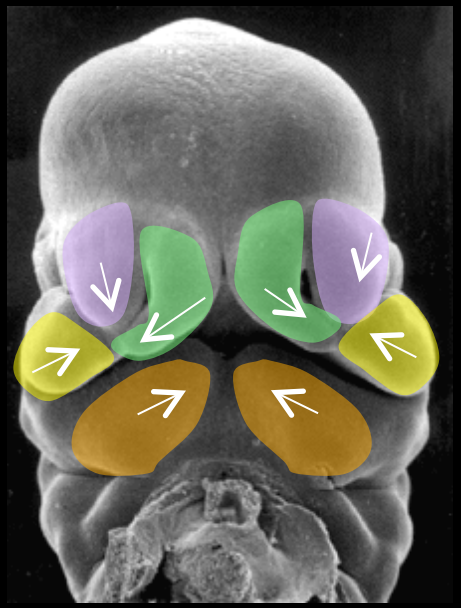


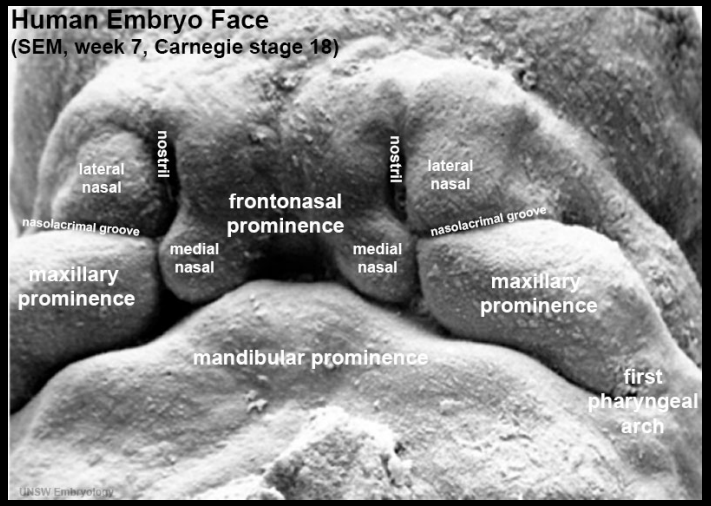


Tissue interactions between the CNCC and epithelium initiate bone formation

Jaw Bone Development

2. Morphogenic movements of facial processes to form the upper and lower jaw





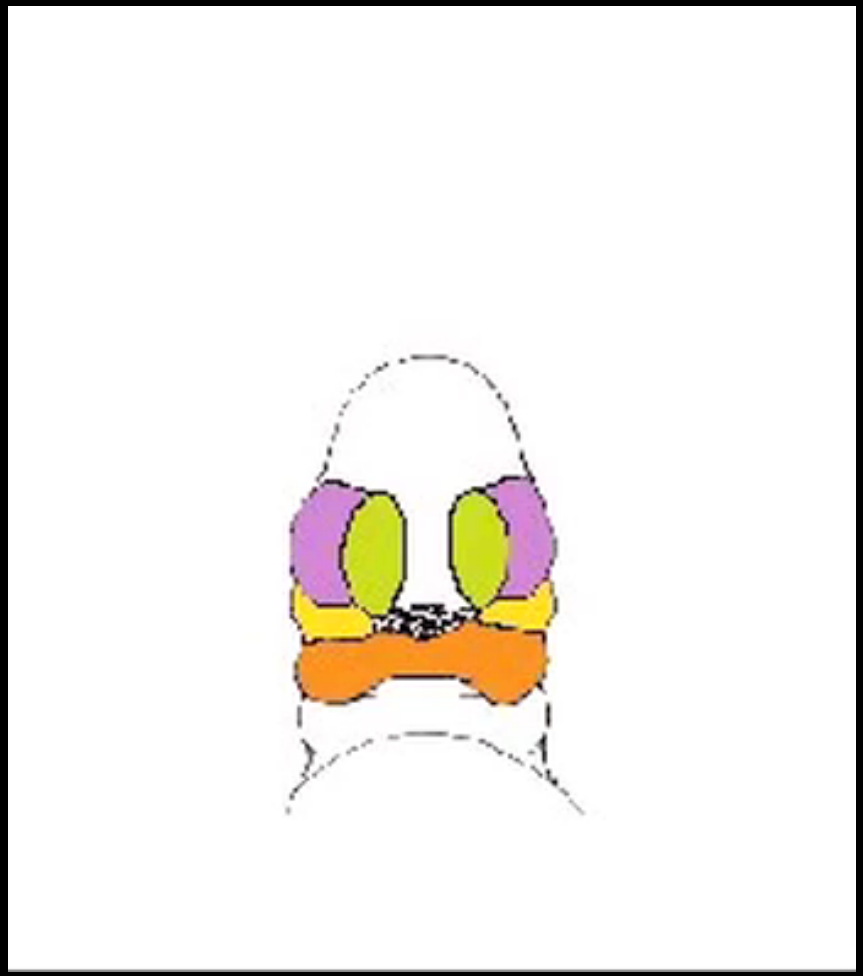
Bilateral converging facial processes:

1. Lateral nasal
2. Medial nasal
3. Maxillary
4. Mandibular

Complete by Week 6

Jaw Bone Development

2. Morphogenic movements of facial processes to form the upper and lower jaw




BBC one