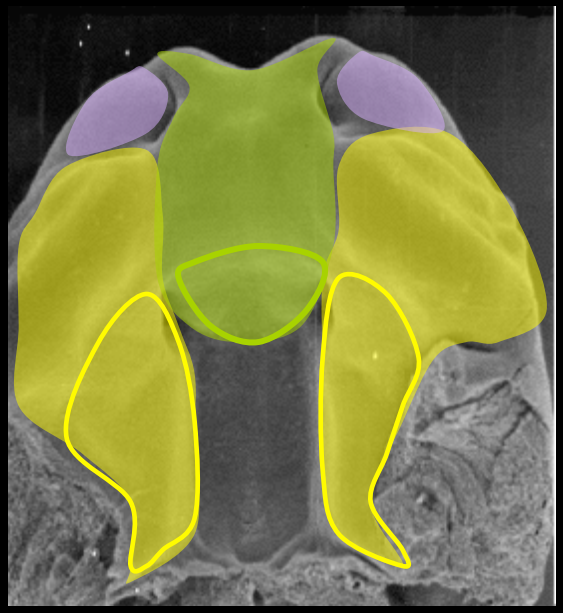
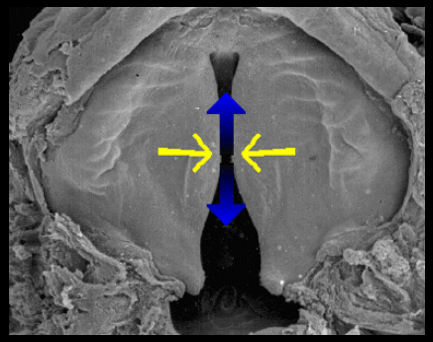
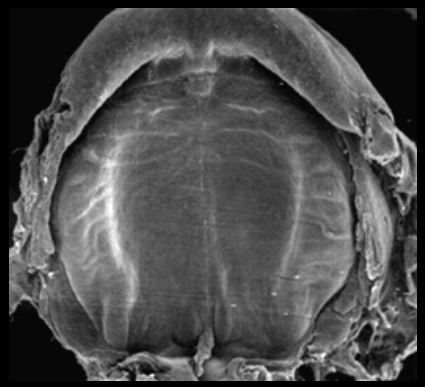
Jaw Bone Development

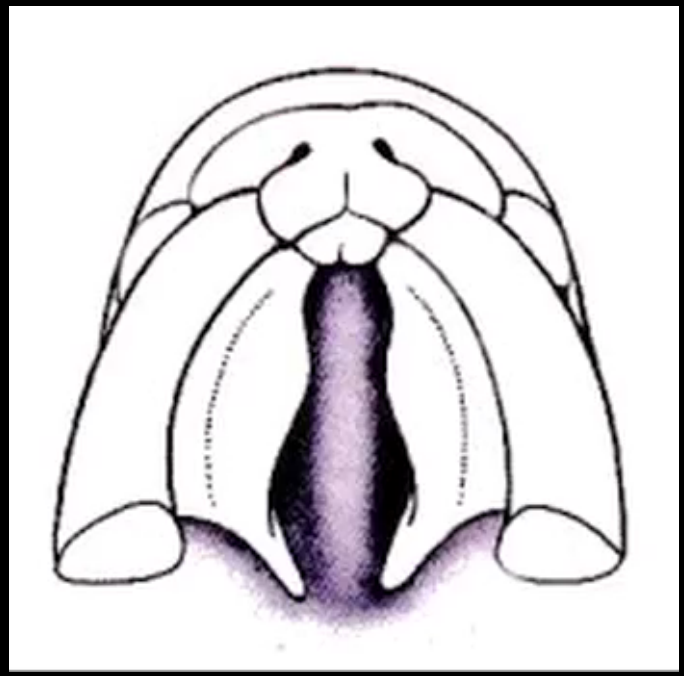
2. Morphogenic movements of facial processes to form the upper and lower jaw



Medial nasal: Primary palate
Maxillary: Secondary palate

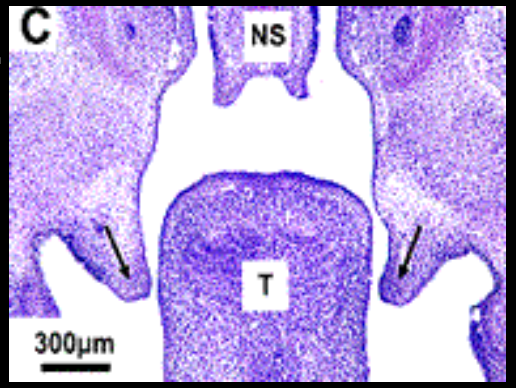


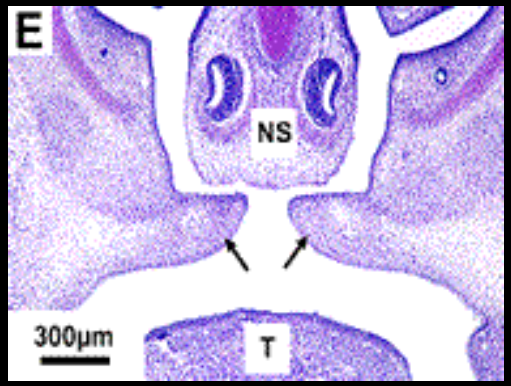


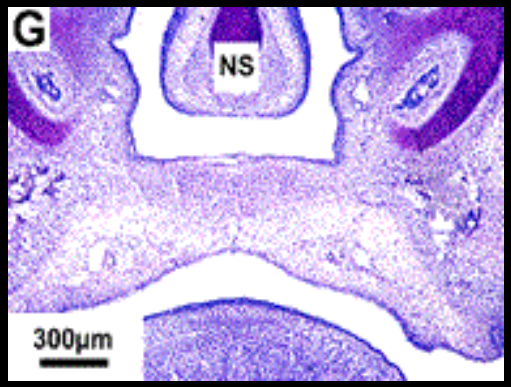


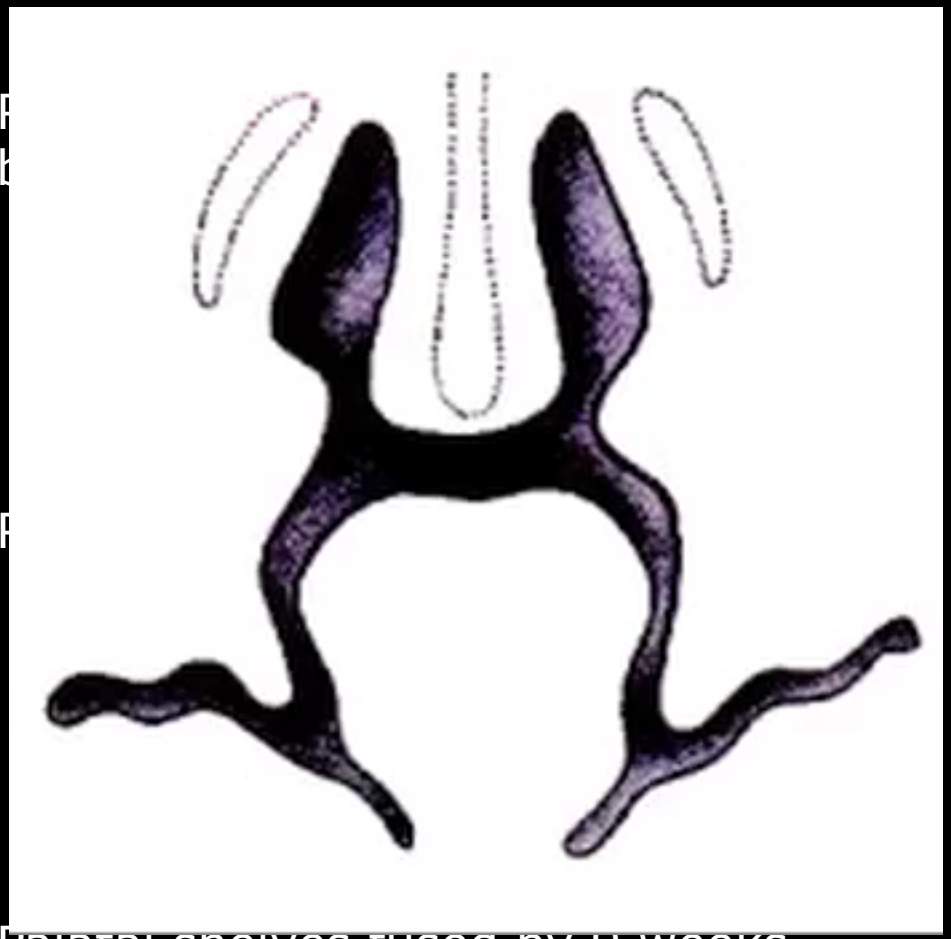
Begins at Week 7

Histological View of Palate Fusion

1. 

2. 

3. 



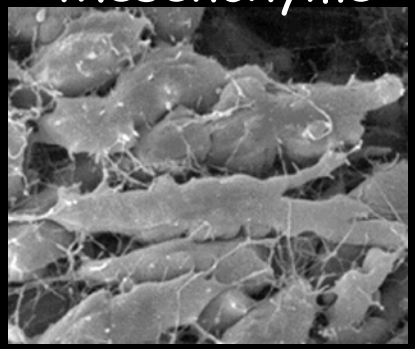
Palatal shelves fused by 9 weeks

Jaw Bone Development

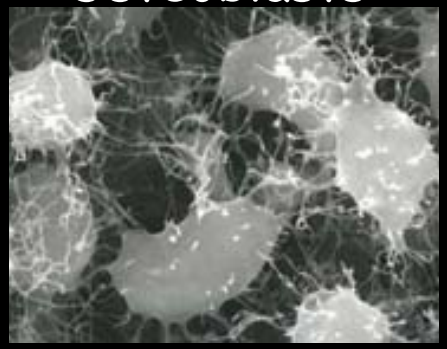
3. Condensation and differentiation of CNCC

Intramembranous Ossification

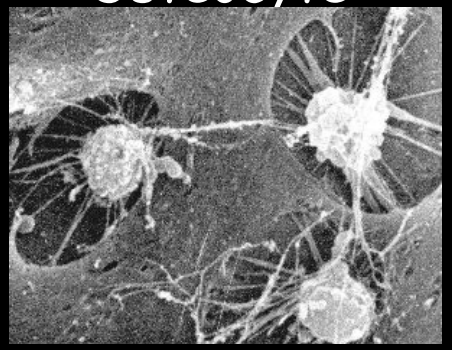
Mesenchyme



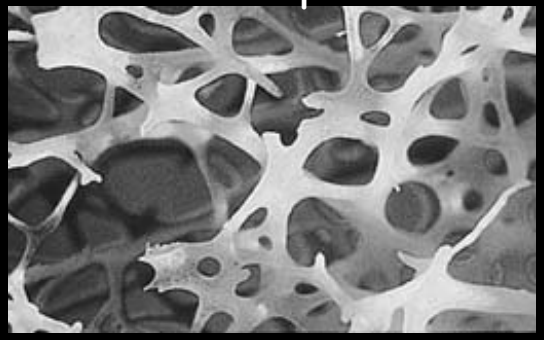
Osteoblasts



Osteocyte

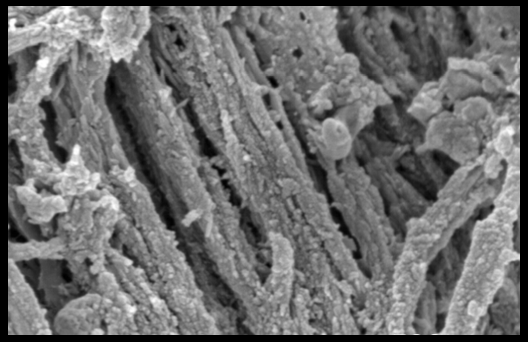


Matrix deposition



Calcium

Mineralizatrion





Skull Vault Development



Skull Vault Development

1. CNCC from the forebrain populate the presumptive frontal bones through two waves of migration

1. Into the FNP
2. Into the cerebral hemispheres

Neural crest
Mesoderm

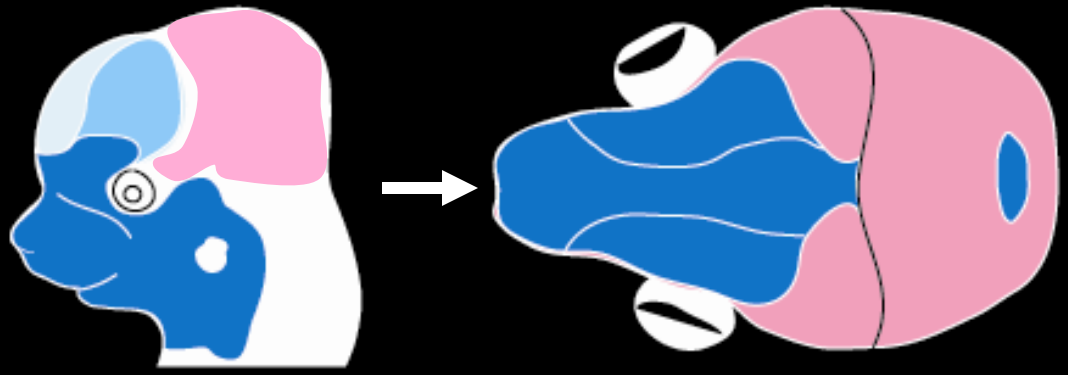
Skull Vault Development

2. Condensation and differentiation of mesenchyme

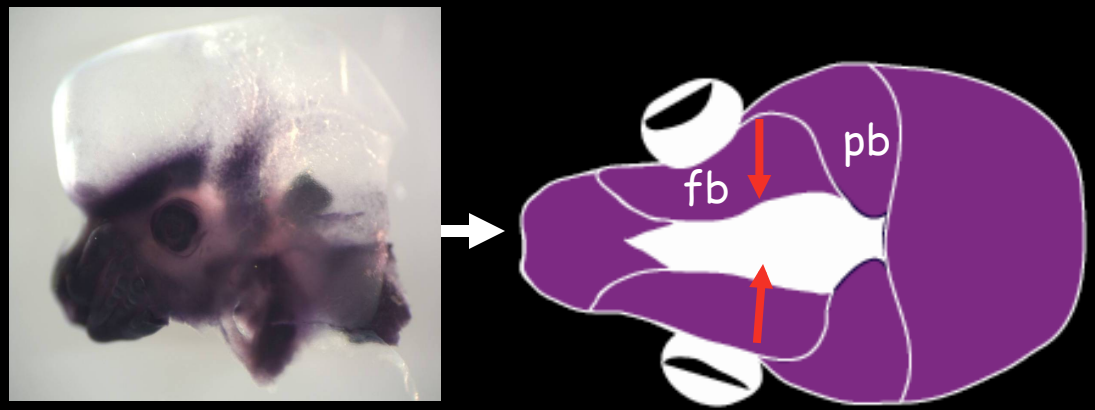
E12.5/7 weeks

E16.5/3.5 months

Osteogenic Mesenchyme



Osteoblast Differentiation



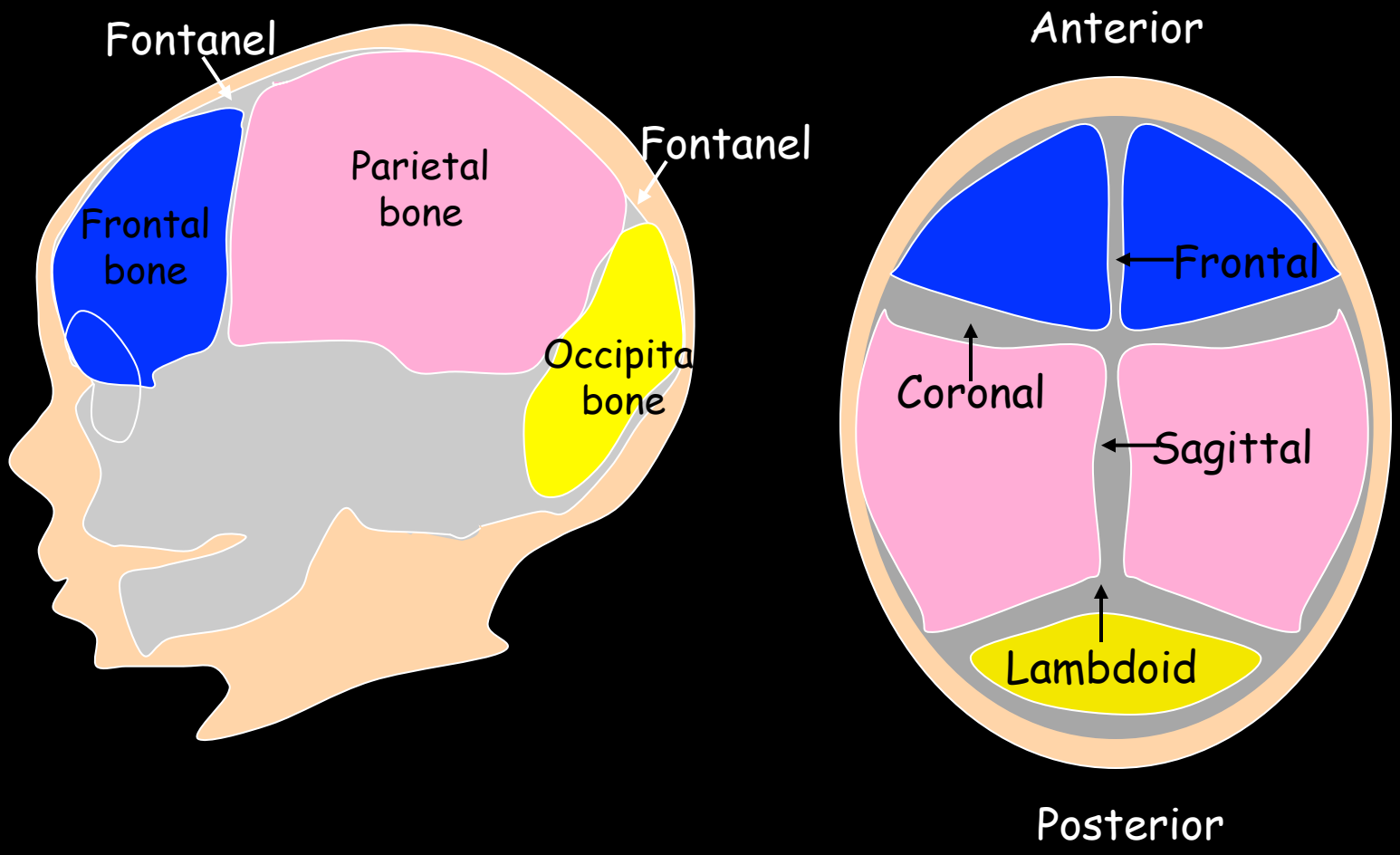
Neural crest

Mesoderm

Alkaline phosphatase (early marker for bone)

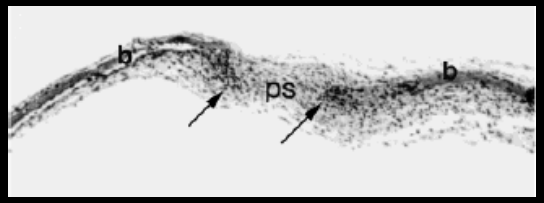
Skull Vault Development

3. Appositional growth of bone plates at the suture

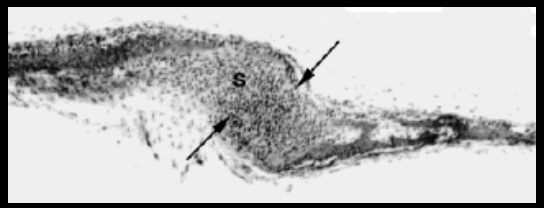


Suture development:

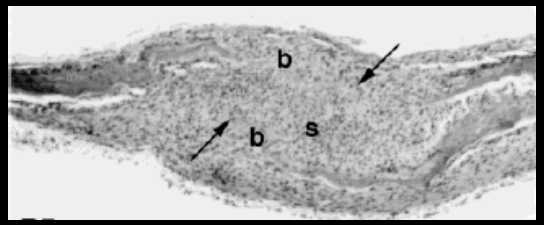
Approximation of bones (b) to form the presumptive suture (ps)



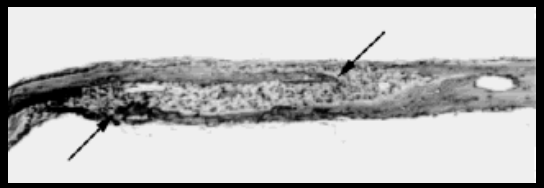
Overlap of bones to form the suture (s).

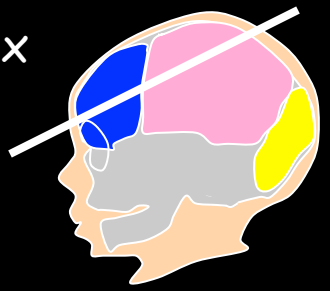


Separation of bones by undifferentiated mesenchyme

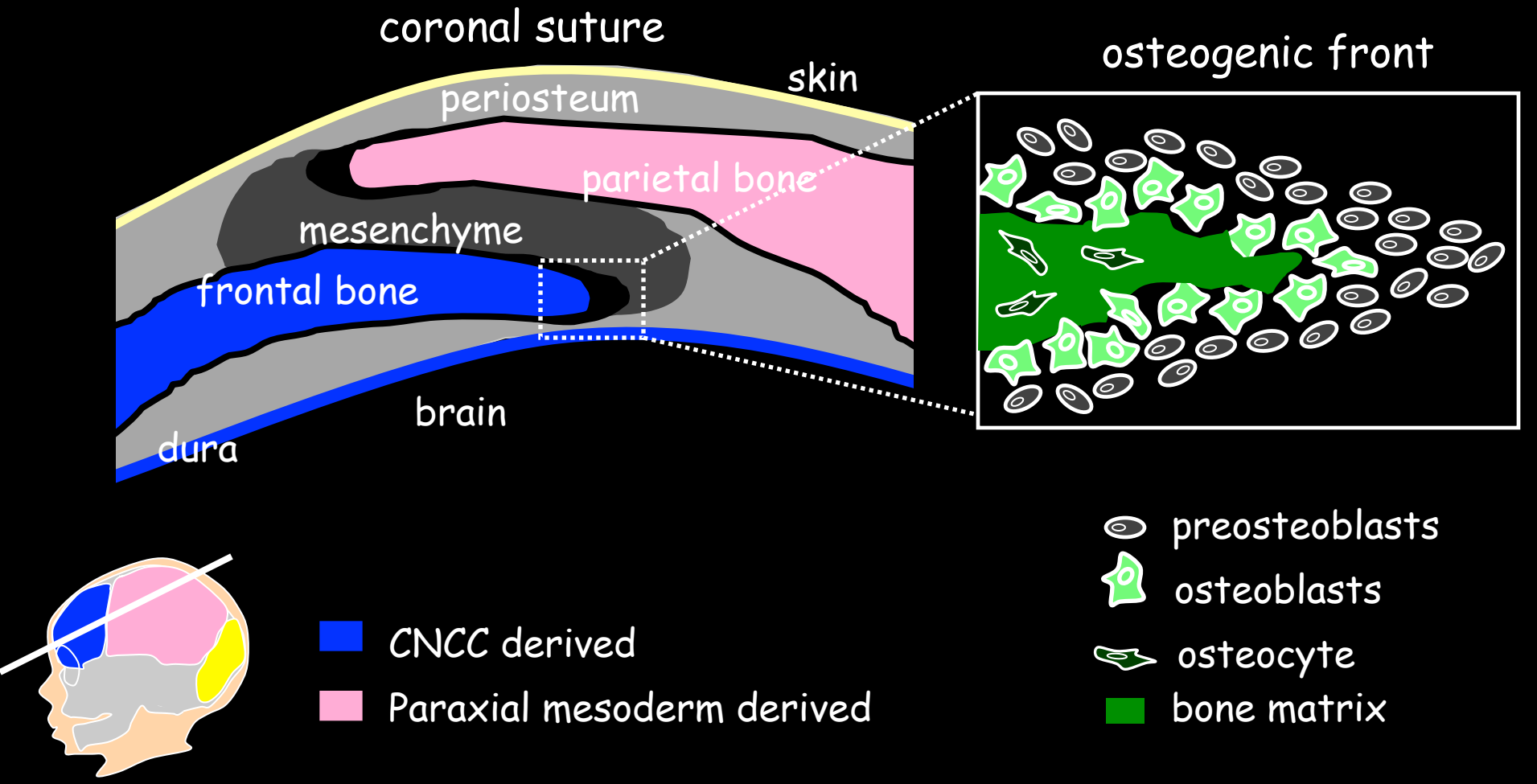


Fusion of bones by remodeling suture matrix





Sutures regulate growth by organizing intramembranous ossification



Craniofacial Malformations

- Morphological defects
  - Craniosynostosis
  - Frontonasal Dysplasia
  - Cleidocranial dysplasia
  - Treacher Collins
  - Orofacial Clefts

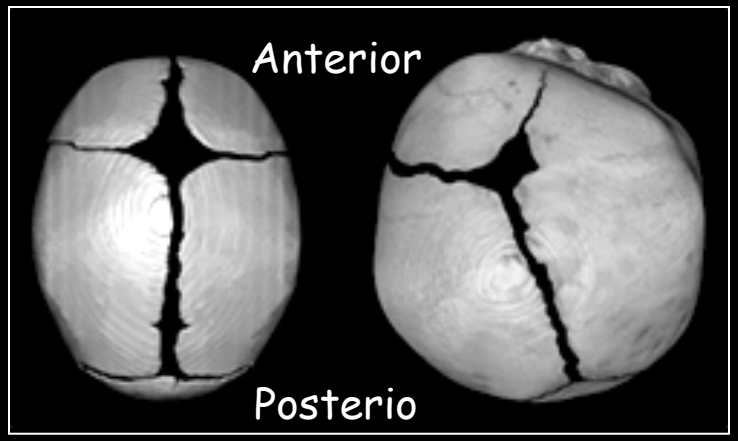
- Genetic causes for these malformations

Craniosynostosis

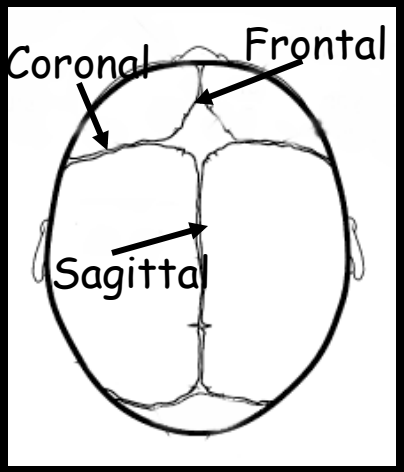
- Premature closure of one or more cranial sutures before brain growth is complete

- Abnormally shaped skull, impaired brain growth, mental retardation, seizures, and/or blindness

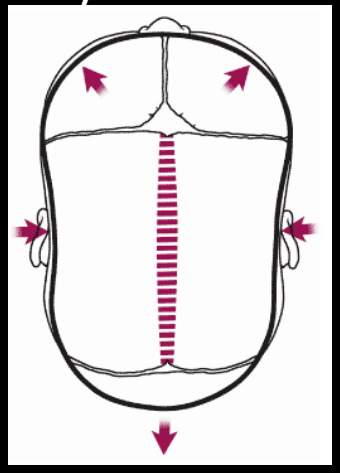
- Occurs 1/2500 live births.



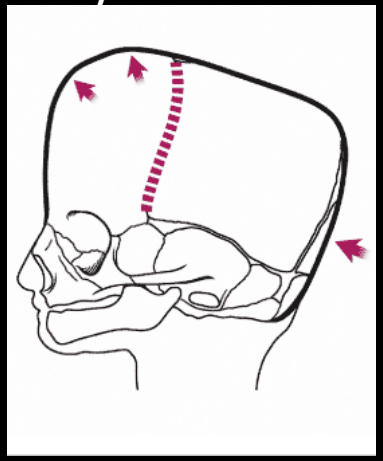
Calvarial shape is characteristic for each type of sutural synostosis

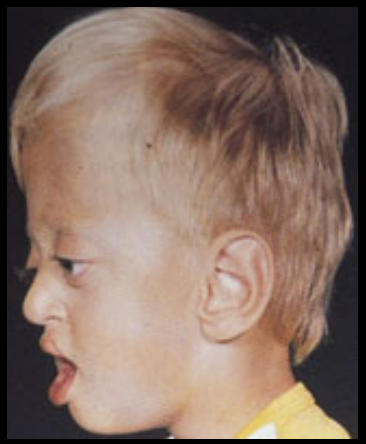


Sagittal synostosis

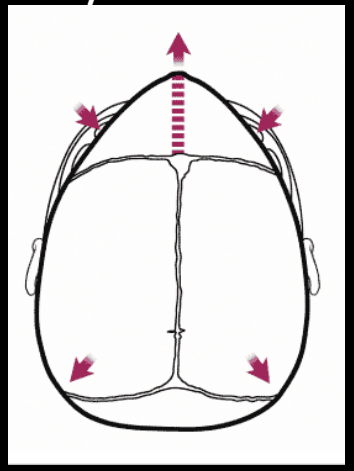


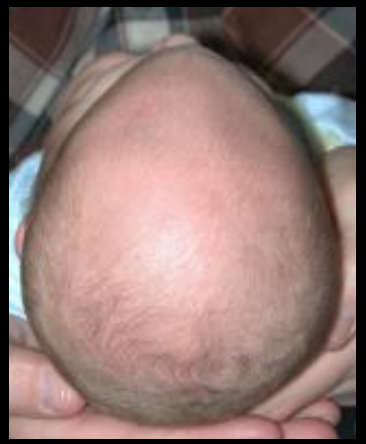
Coronal synostosis





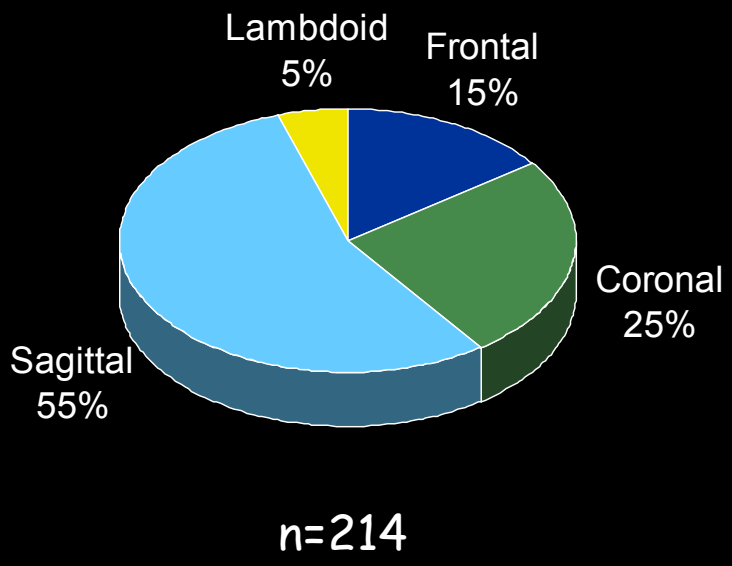
Frontal synostosis

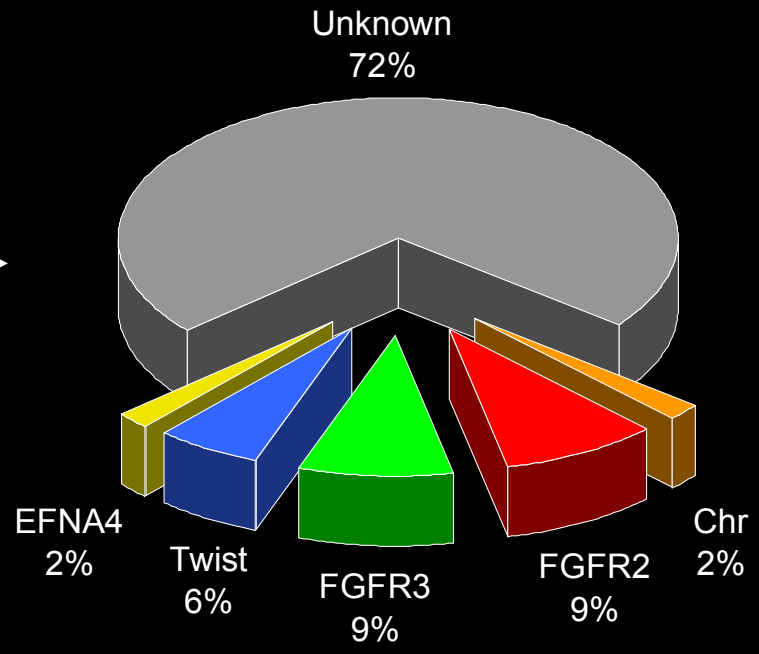




Kabbani and Raghuveer, 2004

Genetic epidemiology of craniosynostosis

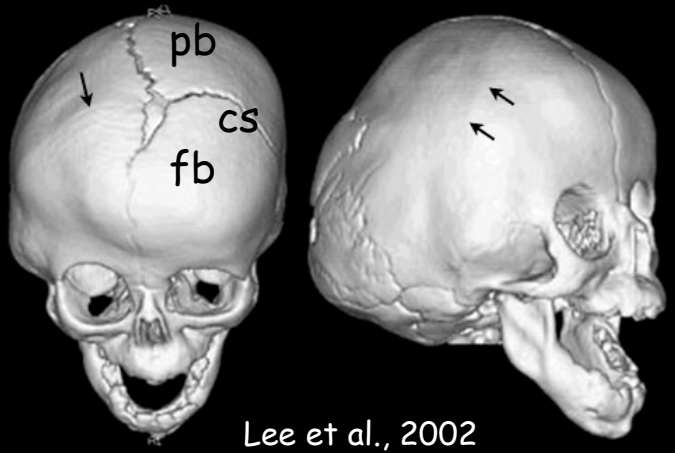




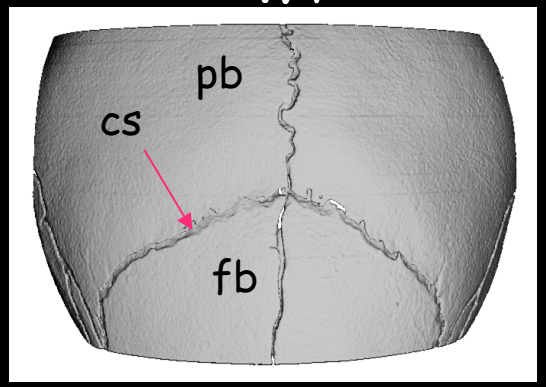
Wilkie and Morriss-Kay, 2005

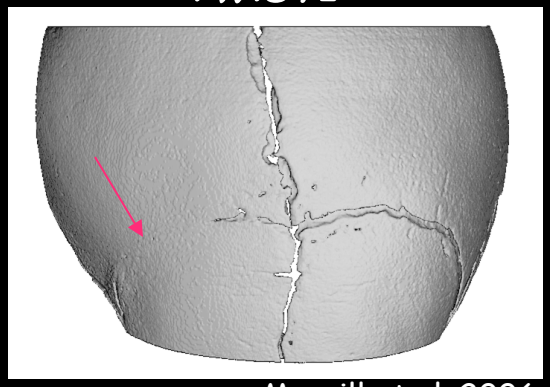
TWIST

- Basic helix-loop-helix transcription factor expressed by CNCC
- Named after *Drosophila* mutant: a twisted larva caused by gastrulation defects and a lack of mesoderm
- *TWIST1* loss of function (LOF) mutations cause Saethre-Chotzen syndrome which includes craniosynostosis



Lee et al., 2002



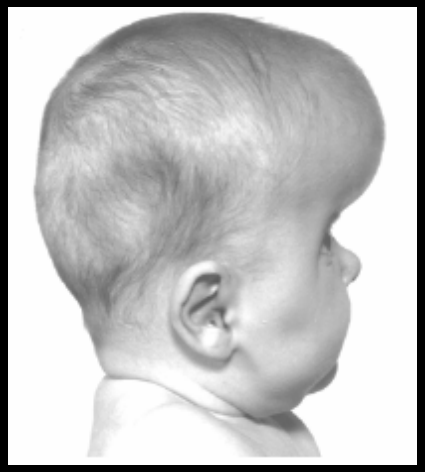


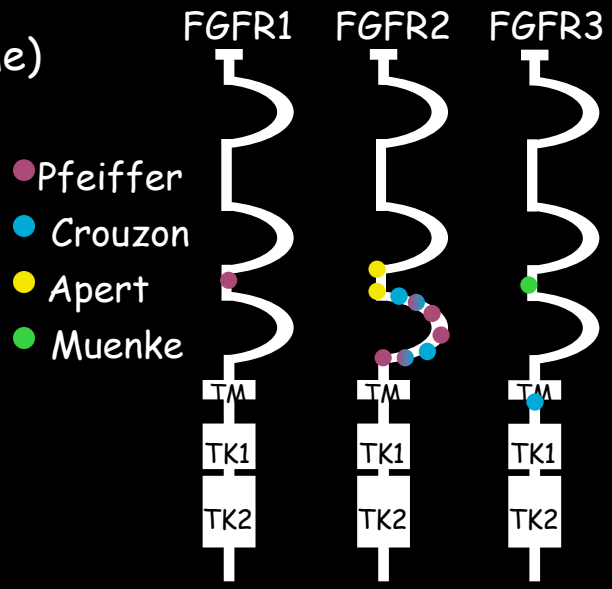
Merrill et al.,2006

FGFR's

- Tyrosine Kinase receptors activated by the secreted ligand, Fibroblast Growth Factor
- Role in skeletogenesis of long bones and calvarial sutures
- Gain of function (GOF) mutation cause multiple disorders with craniosynostosis.

FGFR2 GOF (Apert syndrome)





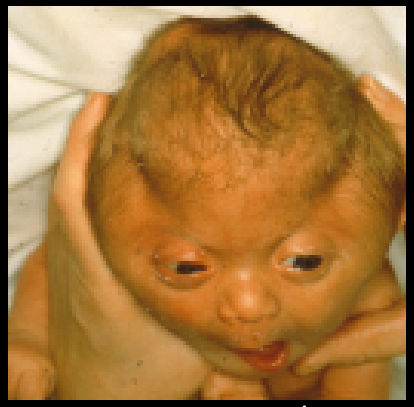
Wt FgfR2 GOF

Wang et al., 2005

MSX2

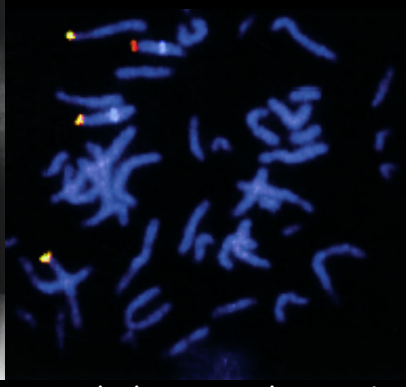
- Homeodomain transcription factor expressed by CNCC
- Directly regulated by Bone Morphogenetic Proteins (BMP)
- Represses osteoblast differentiation
- Increase Msx2 function or dosage causes craniosynostosis

GOF *MSX2*



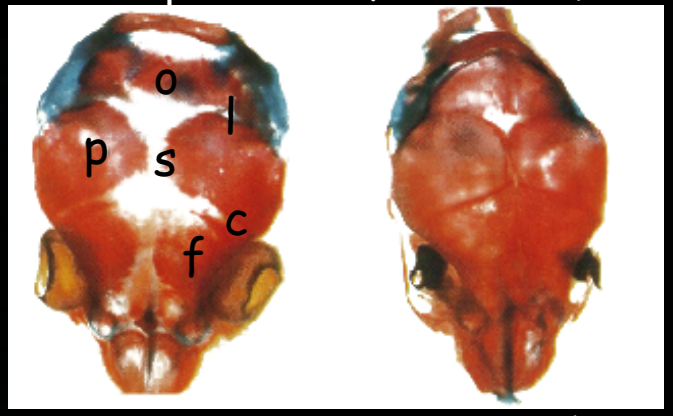
Ma et al., 1996

5p trisomy of *MSX2*



Shiihara et al., 2004

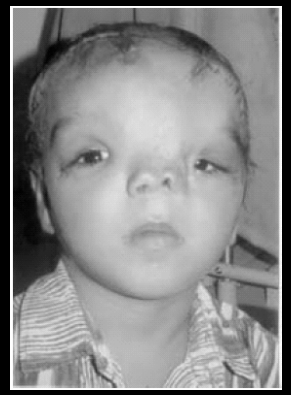
Overexpression of murine *Msx2*



Liu et al., 1995

Frontonasal dysplasia

- Median cleft face syndrome
- Variability: tip of the nose may be missing or nose may separate vertically into two parts
- Ossification defect in frontal bone

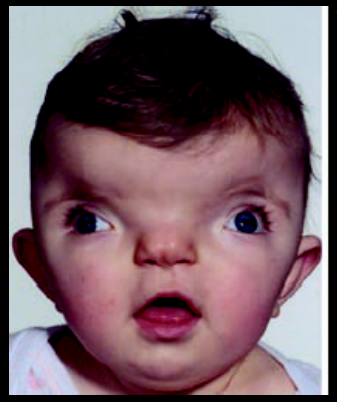


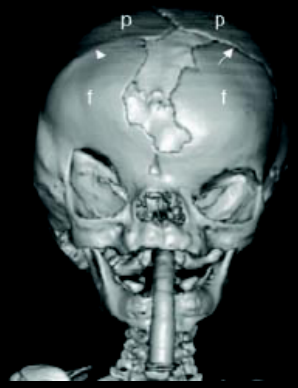
Ephrin B1

- LOF mutations in *Ephrin B1* (*EFNB1*) causes X-linked Craniofrontonasal Dysplasia

- Females have frontonasal dysplasia, craniofacial asymmetry, craniosynostosis, and bifid nasal tip

- Males only mildly affected with hypertelorism: X-inactivation in females causes patches of activity.

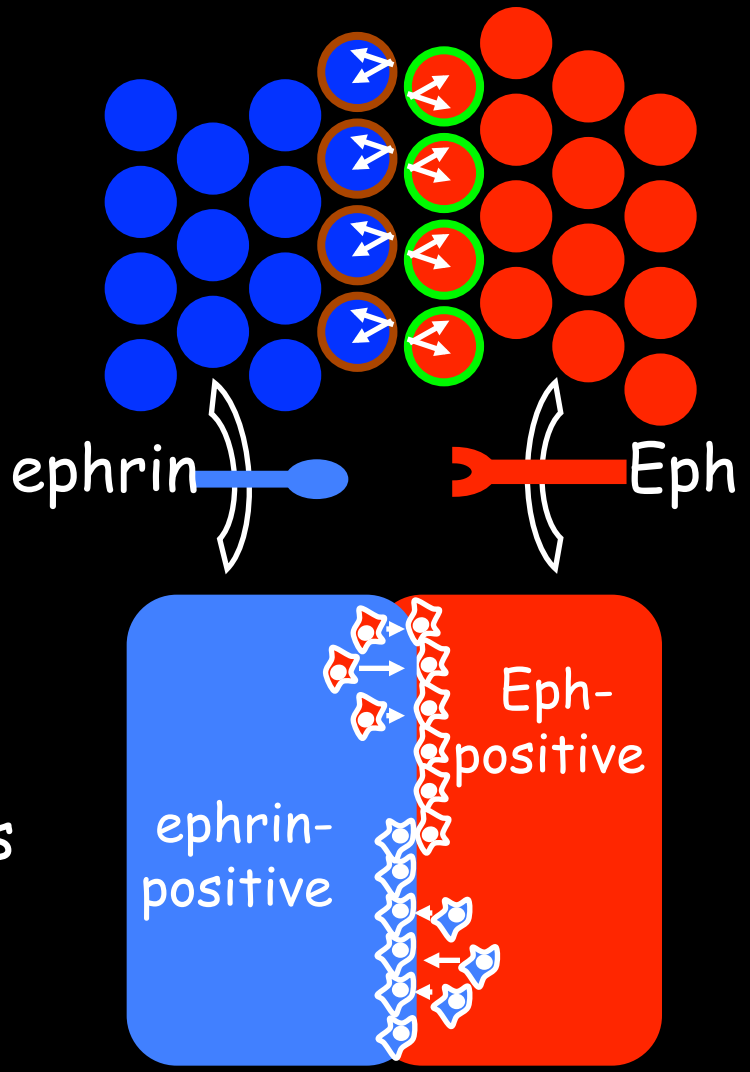




Twigg et al., 2004

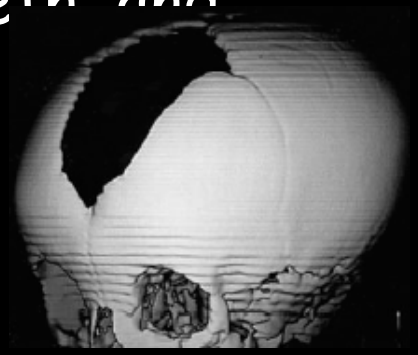
Ephrin

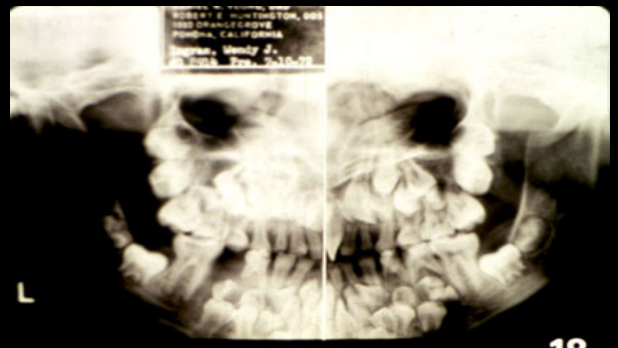
- Regulate cell/cell interactions during patterning (hindbrain segmentation and skeletal formation)
- Binding initiates bi-directional signaling cascade necessary for sorting
- Expressed in complementary patterns to Eph and interactions causes repulsion



Cleidocranial dysplasia

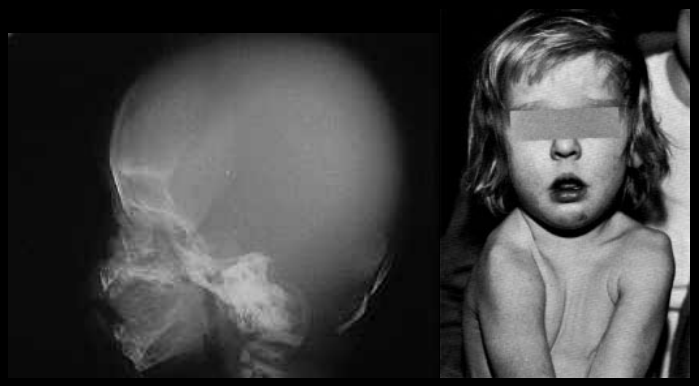
- Delayed ossification of frontal and parietal bones
- Dental anomalies include delayed loss of primary teeth, delayed eruption of permanent teeth, and supernumerary teeth
- Underdeveloped or missing clavicles
- Occurs 1/1,000,000 live births.



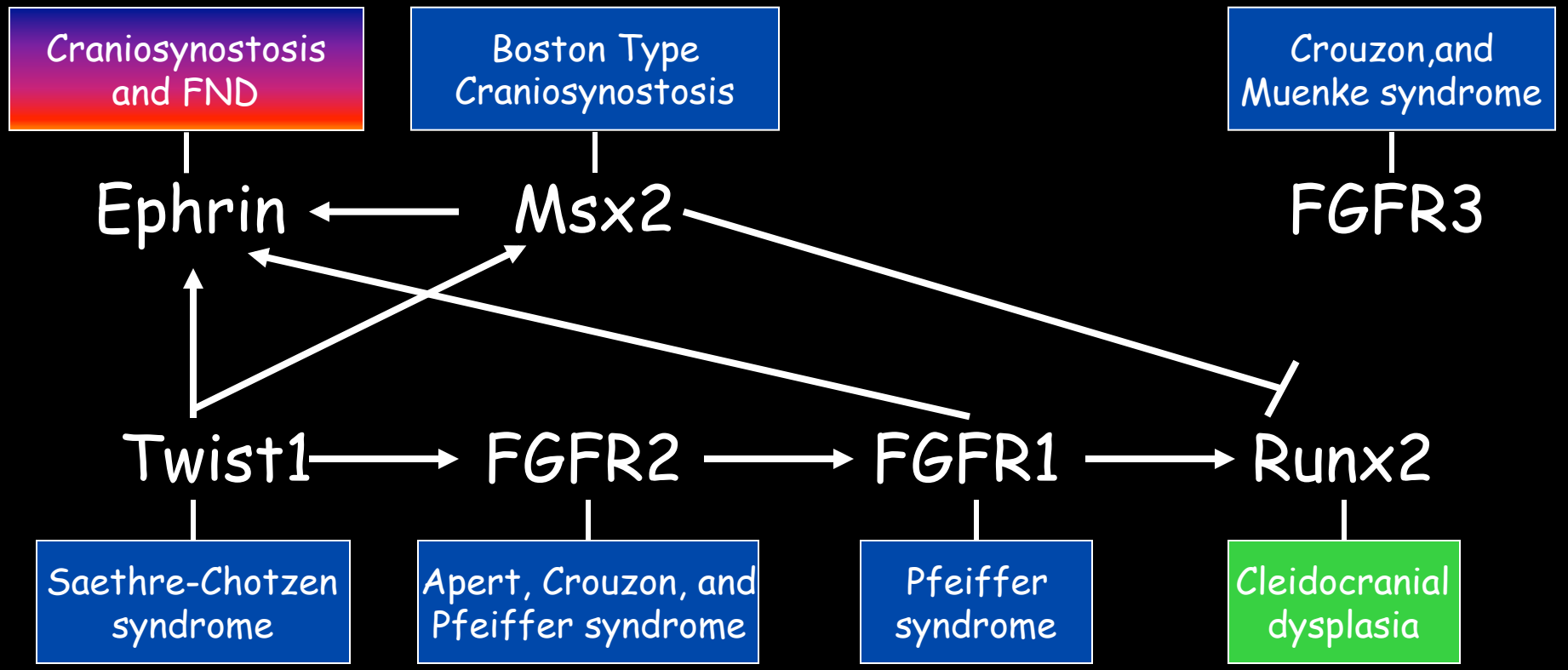


RUNX2

- LOF mutation in this Runt class transcription factor cause CCD
- Transcription regulator of osteoblast differentiation (bone matrix proteins) expressed in CNCC
- Essential for commitment of multipotent mesenchymal cells into osteoblastic lineage

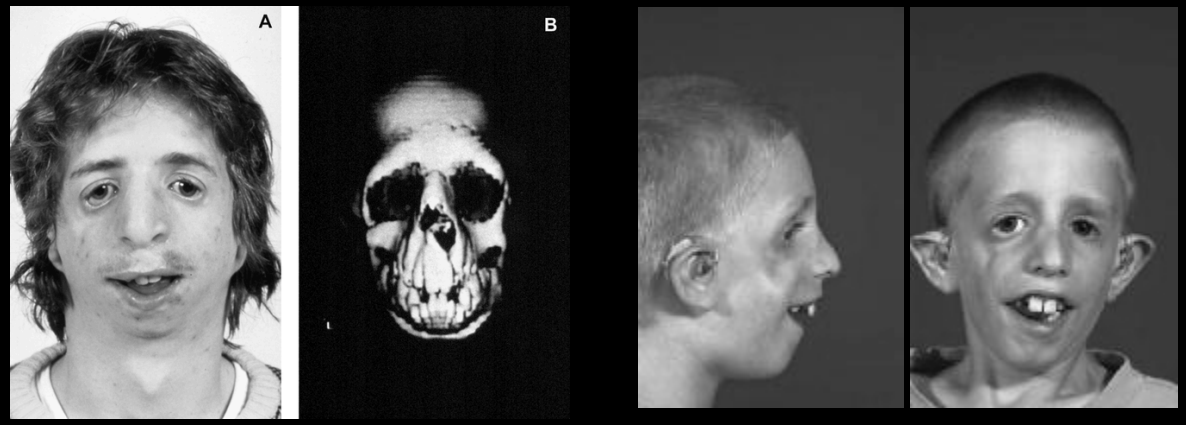


Molecular pathways in skull vault development



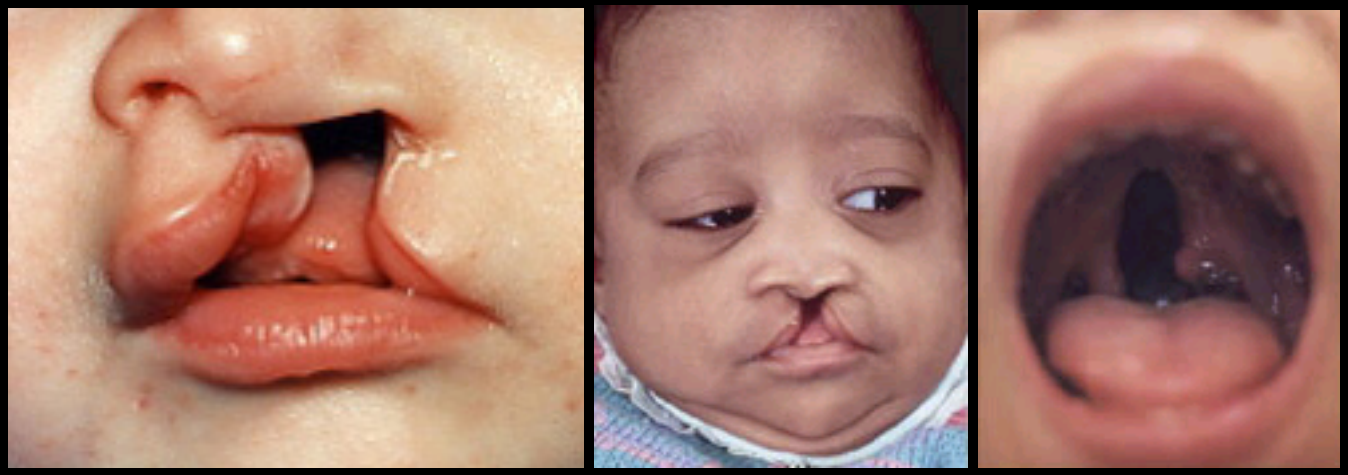
Treacher Collins syndrome

- Single dominant mutation occurs 1/10,000 live births.
- Hypoplasia of the facial bones, cleft palate, and ear defects that result in conductive hearing loss.
- TCOF-1, POLR1C, POLR1D: regulators of ribosome biogenesis required for CNCC generation and proliferation.

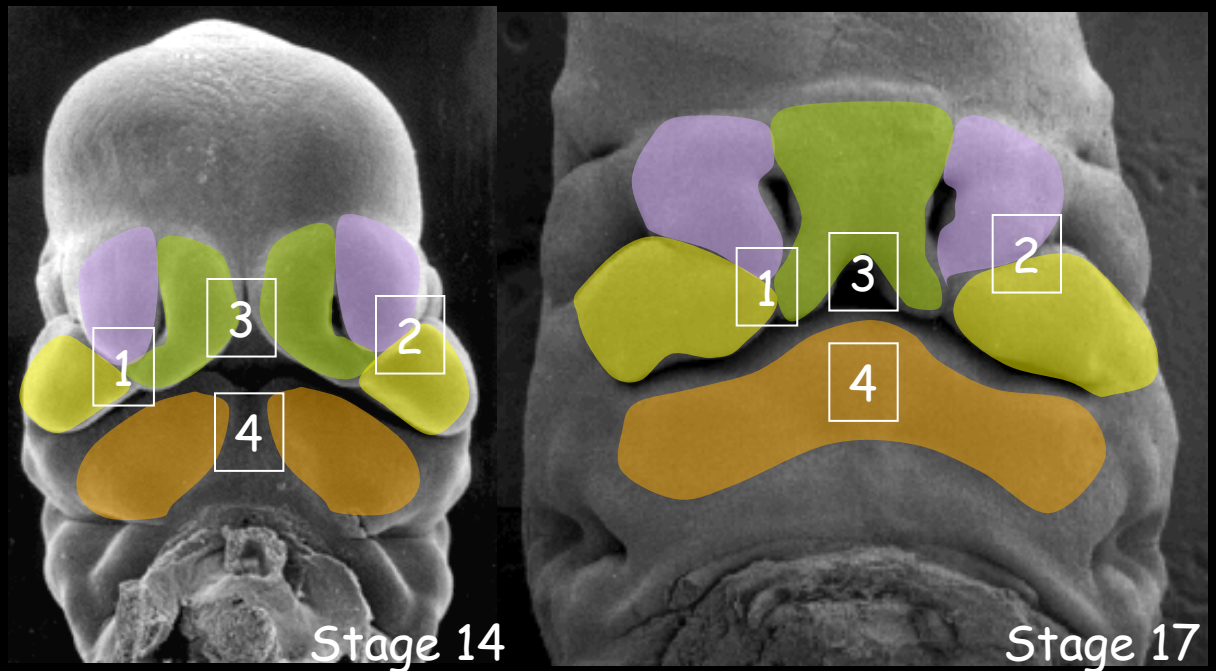


Orofacial Clefts

- Most common birth defect, occurring in 1/750 births
- Multifactor: genes and environment
- Can occur as part of a syndrome or in isolation



Facial Cleft Locations

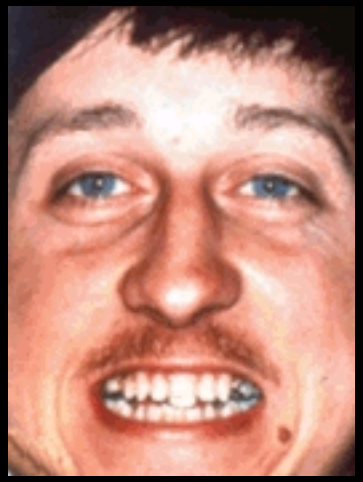
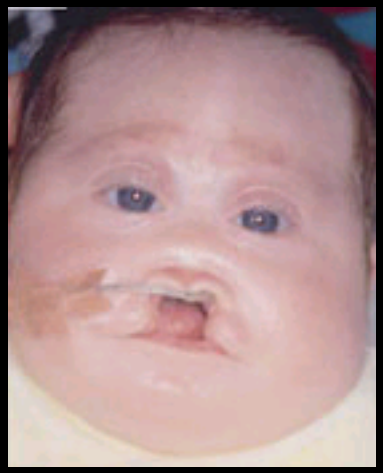
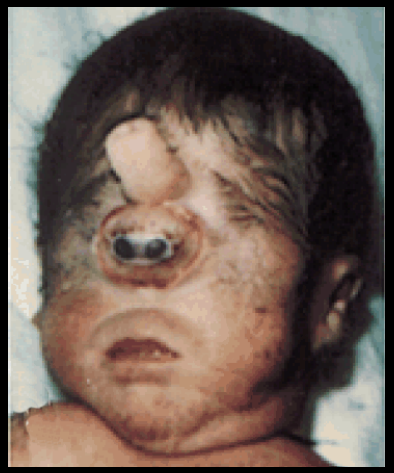


Clefts occur at the lines of union between converging facial processes

1. Unilateral or bilateral cleft lip
2. Unilateral facial cleft
3. Median cleft lip
4. Median mandibular cleft

Sonic Hedgehog (SHH)

- Secreted growth factor expressed in pharyngeal arch epithelium
- LOF mutations cause Holoprosencephaly
- Defects range from mild (only a single central incisor) to moderate (orofacial clefts) to severe (proboscis, cyclopia)

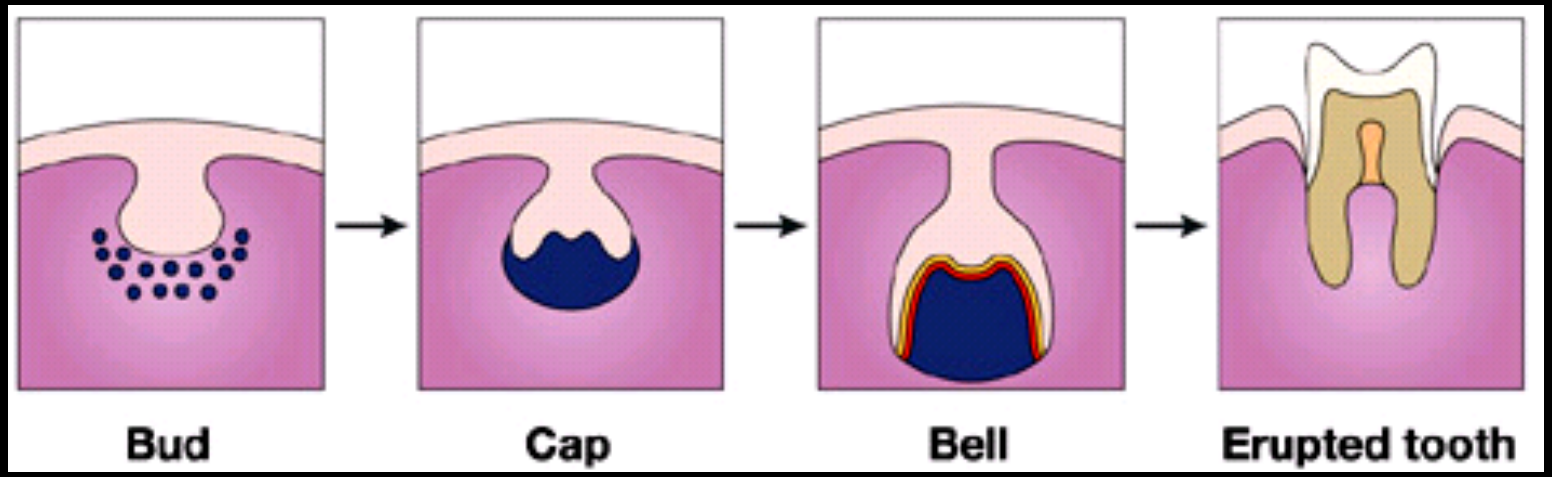




MSX1

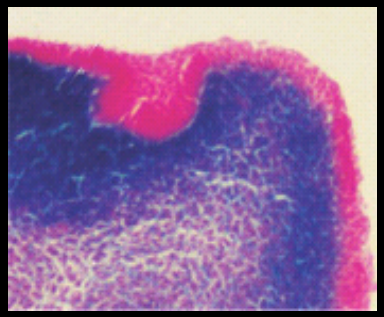
- Homeodomain transcription factor expressed in CNCC closely related to *MSX2*
- Critical for epithelial-mesenchymal interactions during development
- LOF *MSX1* results in nonsyndromic cleft lip, cleft palate, and tooth agenesis

Jumlongras et al., 2001

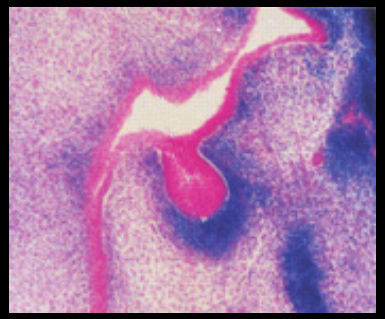
CNCC in tooth development



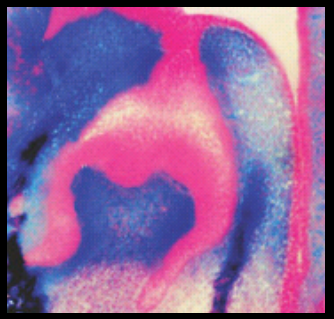
Blue= NCC
Pink=ecto



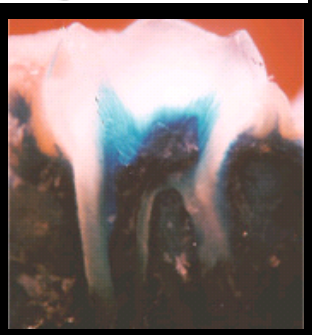
E-M interactions ectodermal thickening



Proliferation and Condensation of CNCC



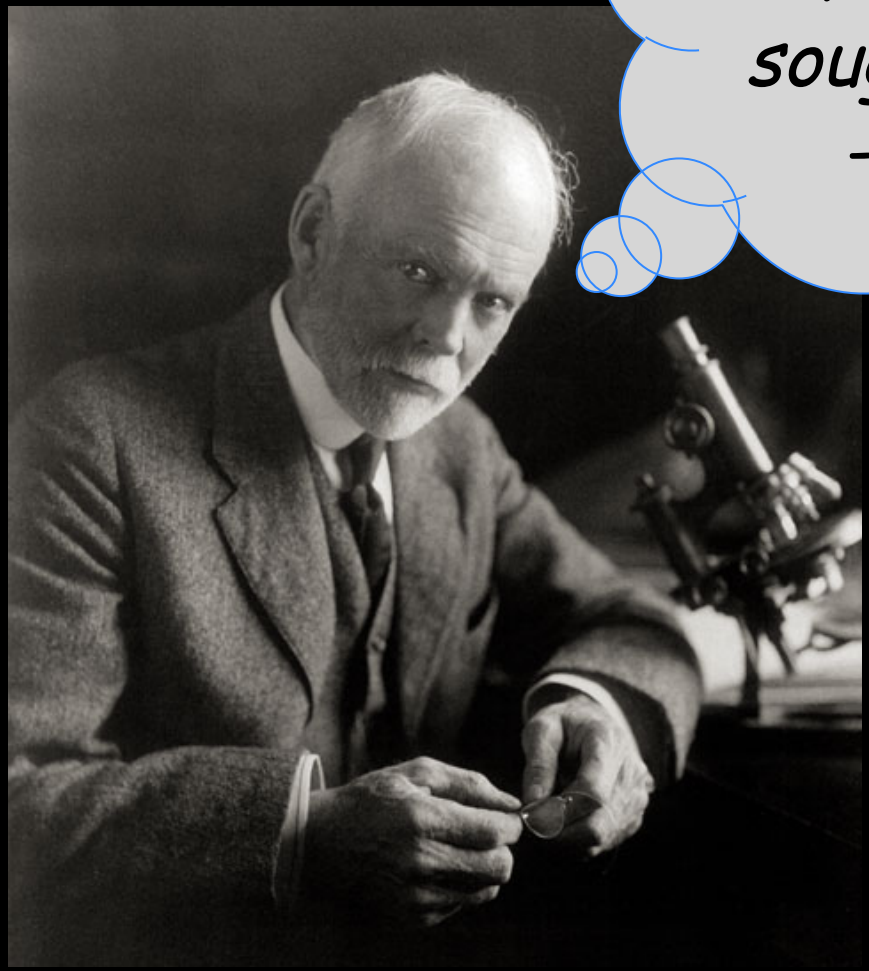
CNCC push up into ectoderm form dental papilla



CNCC differentiate into odontoblasts (pulp) and produce dentin

What are the etiologies of craniofacial disorders?

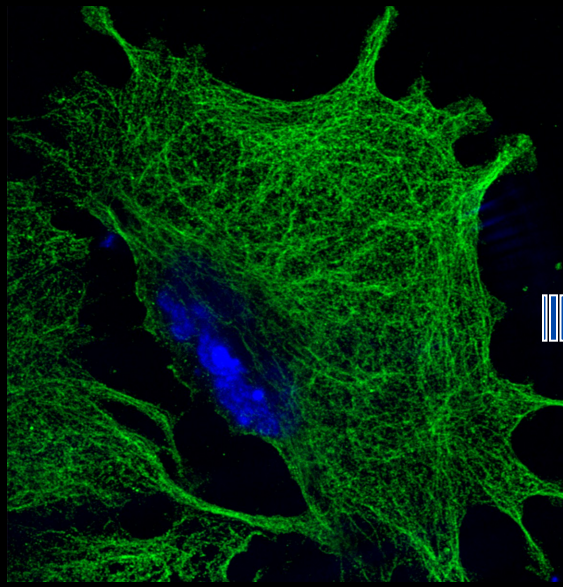
What are the etiologies of craniofacial disorders?



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

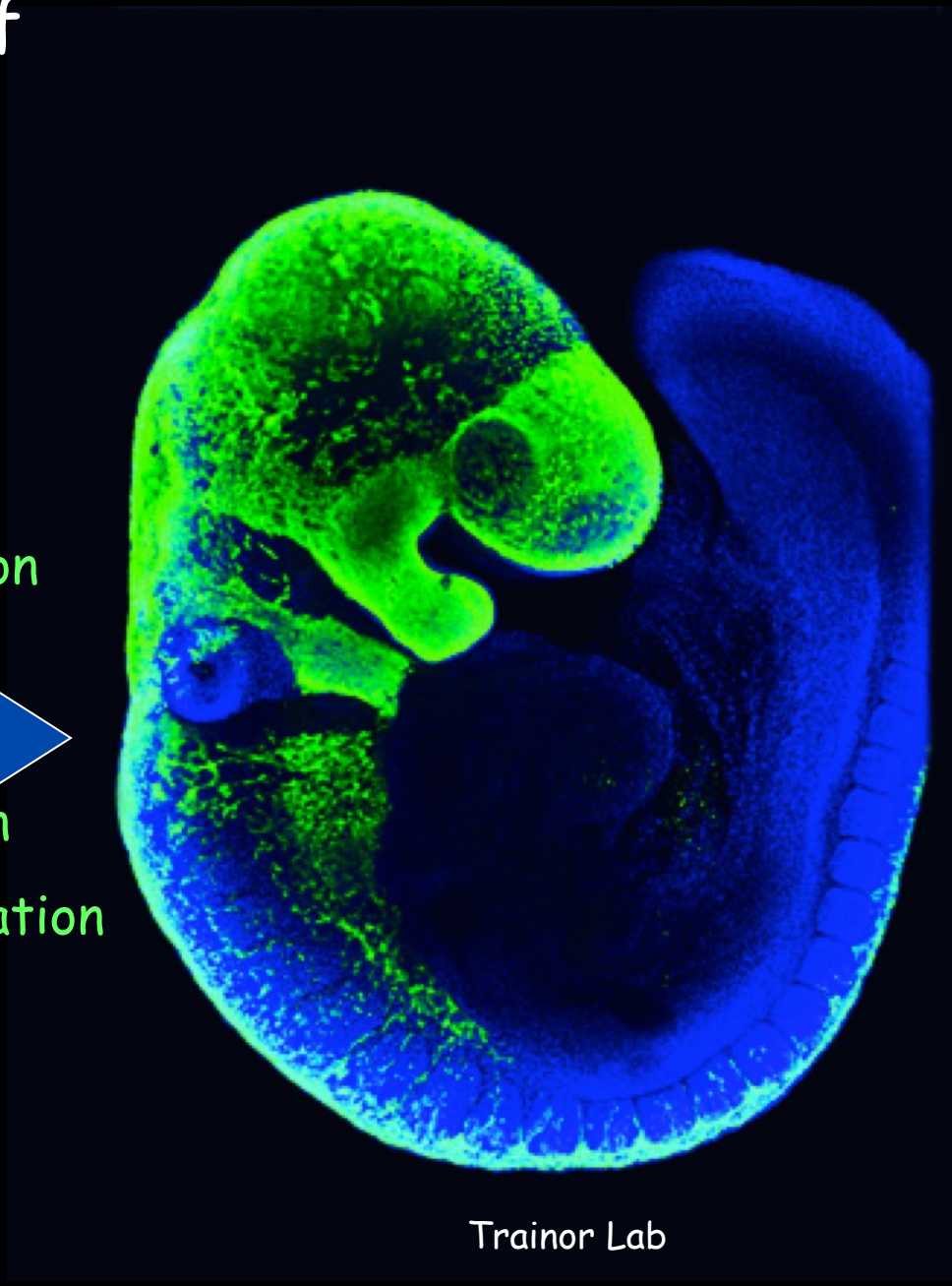
What are the etiologies of craniofacial disorders?

Cranial Neural Crest Cell



Proliferation
Survival

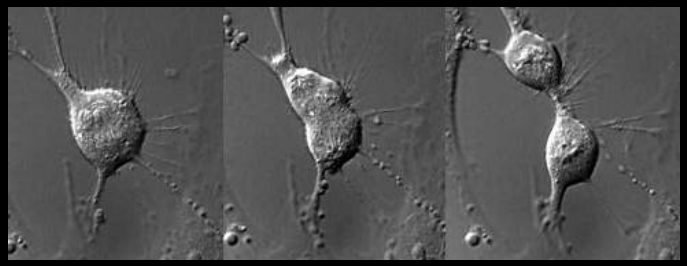
Migration
Differentiation



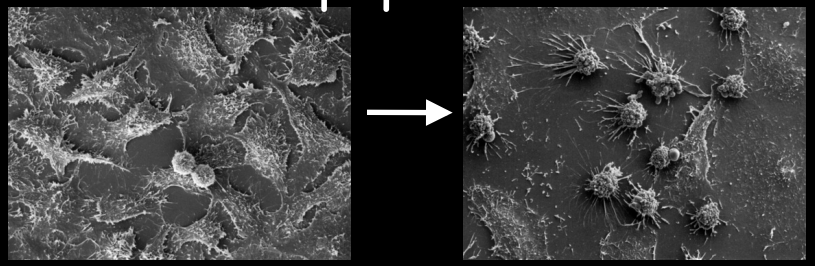
Trainor Lab

CNCC growth in Treacher Collins Syndrome

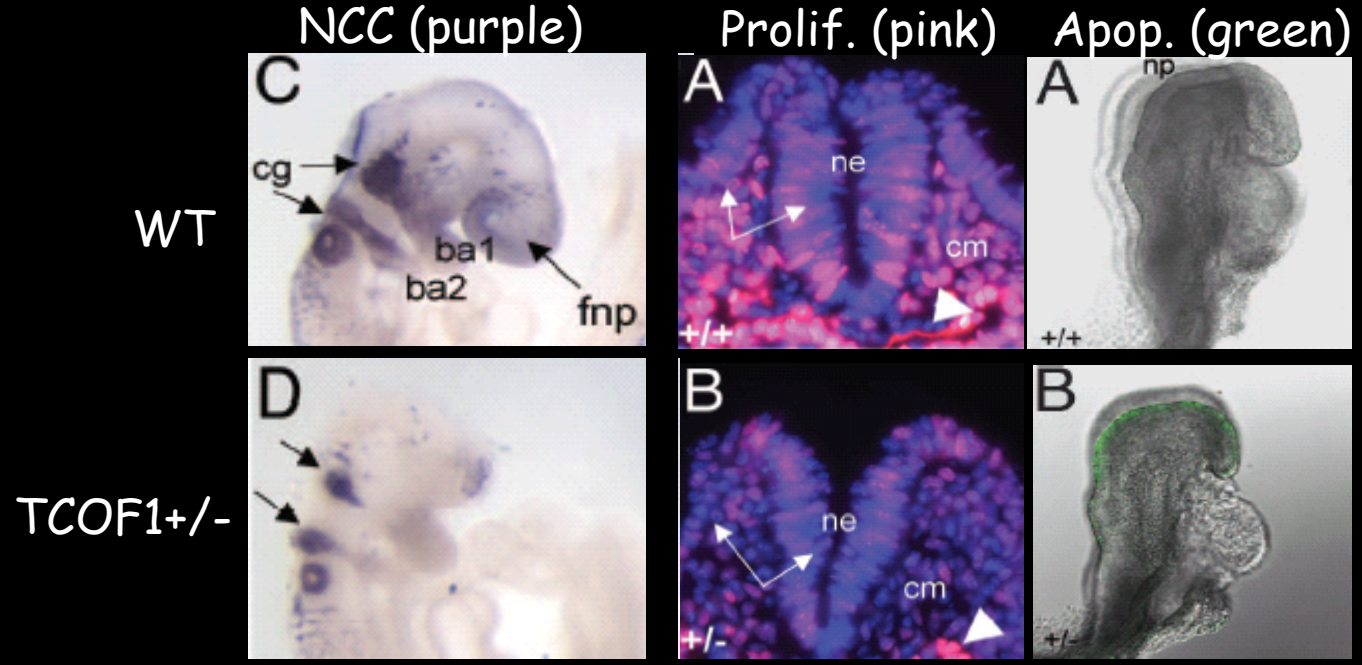
Proliferation



Apoptosis



Example: CNCC hypoplasia caused by decreased proliferation and increased apoptosis



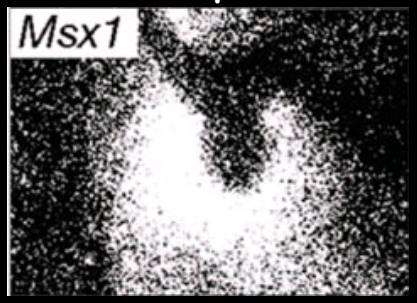
Dixon J. et.al., 2006

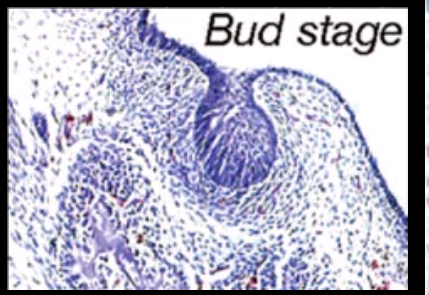
CNCC Proliferation in Tooth Agenesis

Proliferation

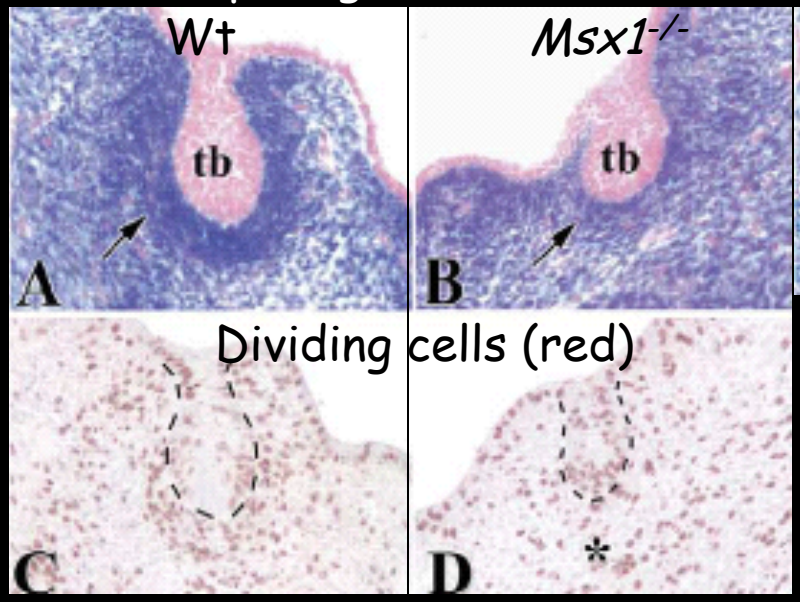
Example: Decreased proliferation of CNCC in early cap stage leads to tooth agenesis in *Msx1* knockout mice

Msx1 expression

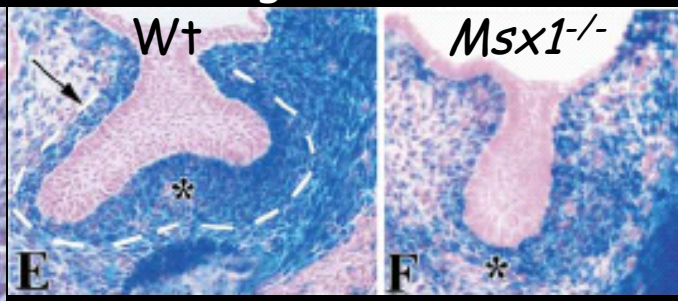




Cap stage, NCC (Blue)



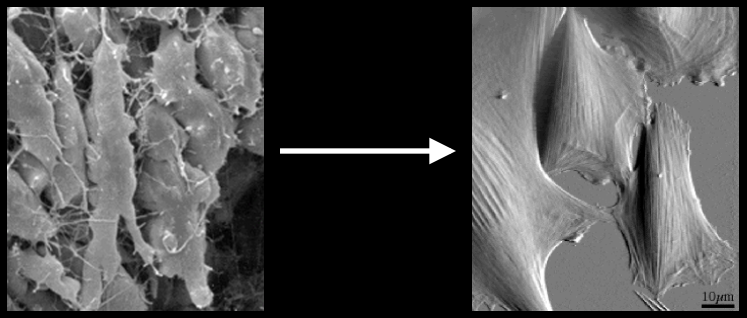
Bell stage, NCC (Blue)



Han et.al., 2003

CNCC Differentiation in Cleidocranial Dysplasia

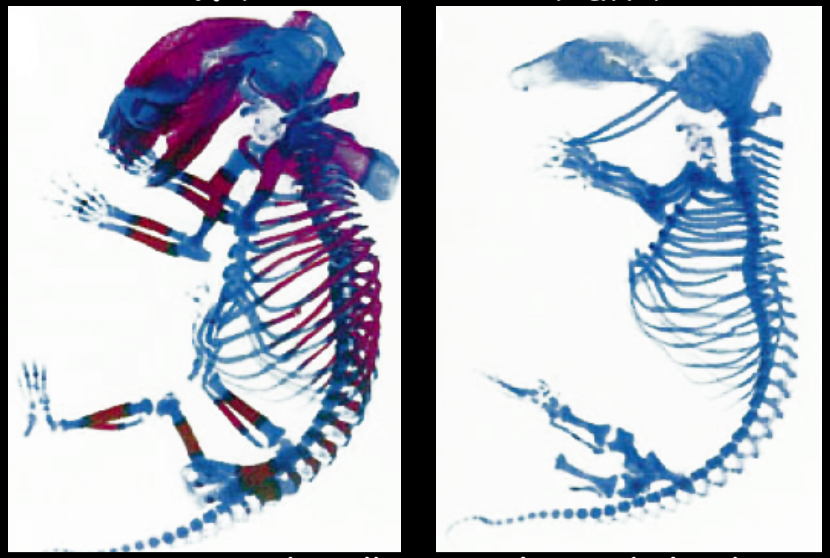
Differentiation into osteoblasts



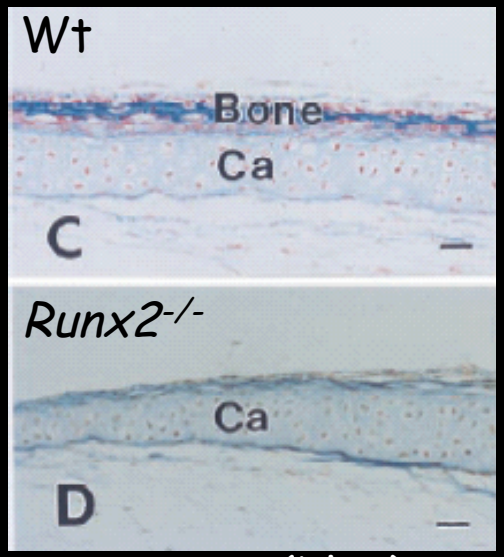
Example: Absence of osteoblasts in *Runx2* knockout mice

Wt

Runx2$^{-/-}$



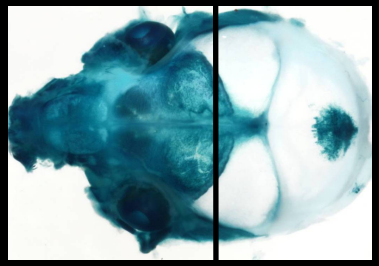
Bone (red) Cartilage (blue)

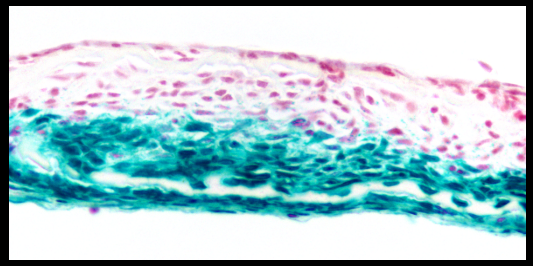


Bone (blue)

Hoshi et.al., 1999

CNCC Migration in Craniosynostosis

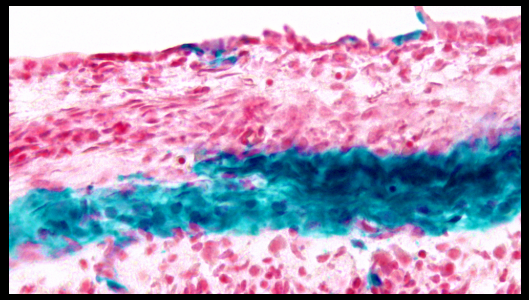


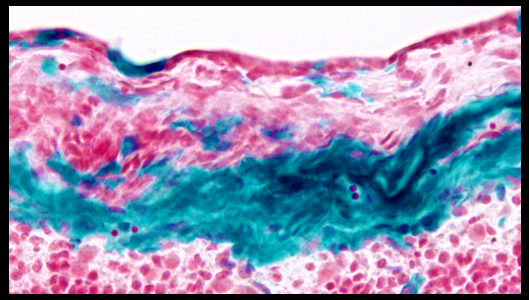


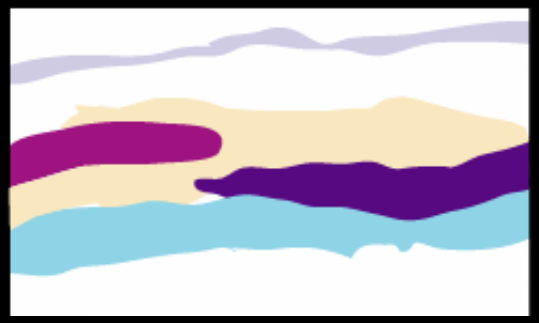
Example: Cell mixing at the suture boundary in craniosynostosis

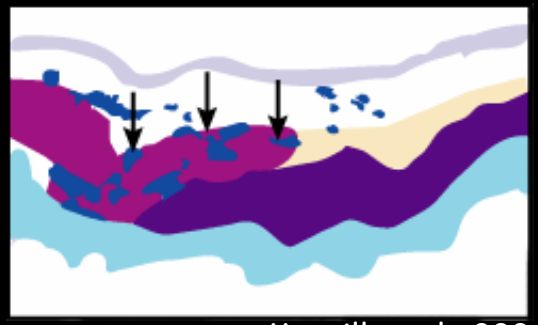
Wt

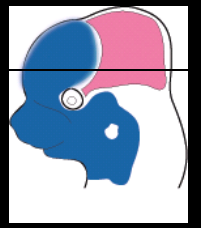
Twist$^{+/-}$



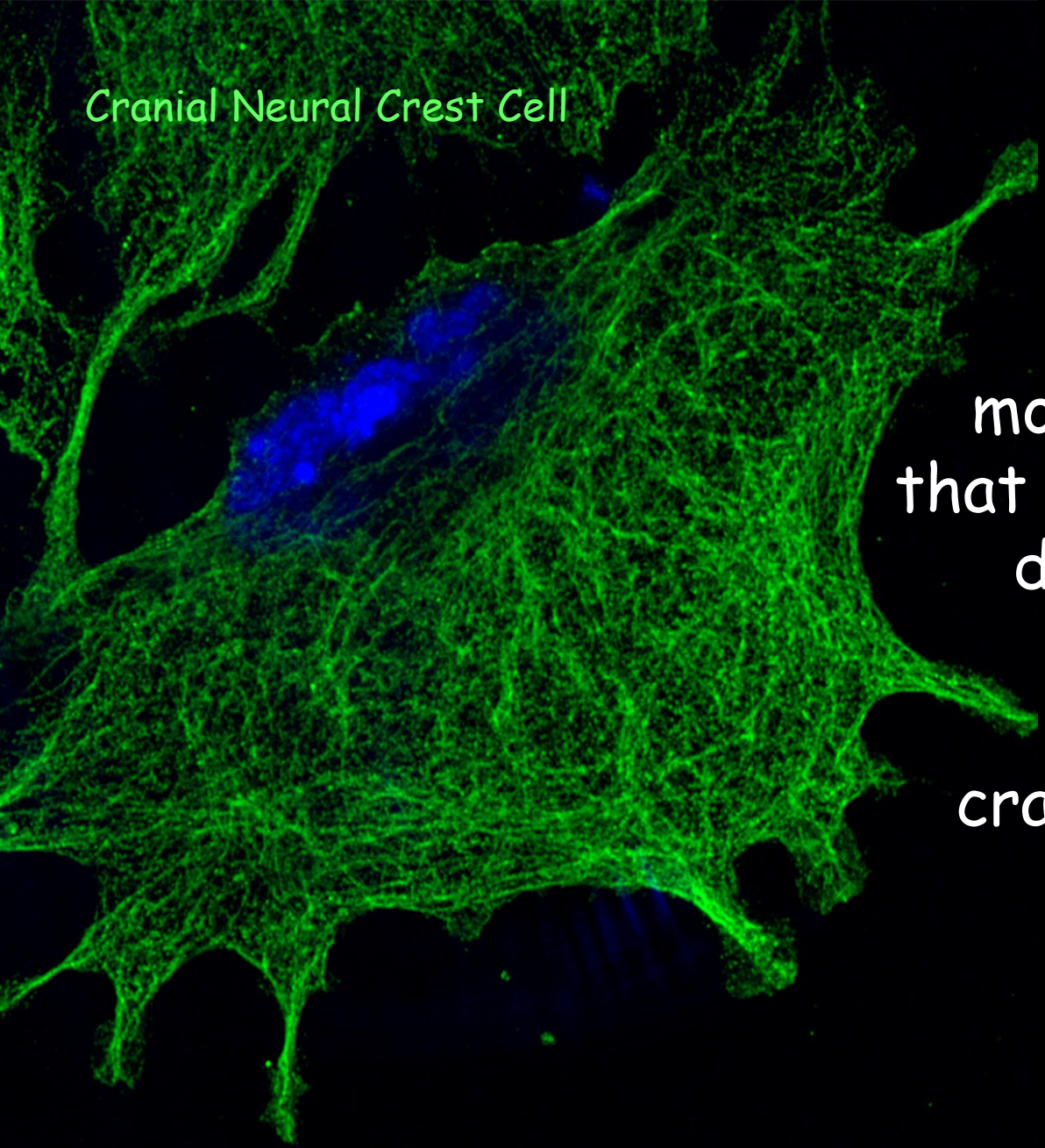








Merrill et al., 2006



The cellular and molecular mechanisms that control craniofacial development are key to understanding the etiology of craniofacial disorders.