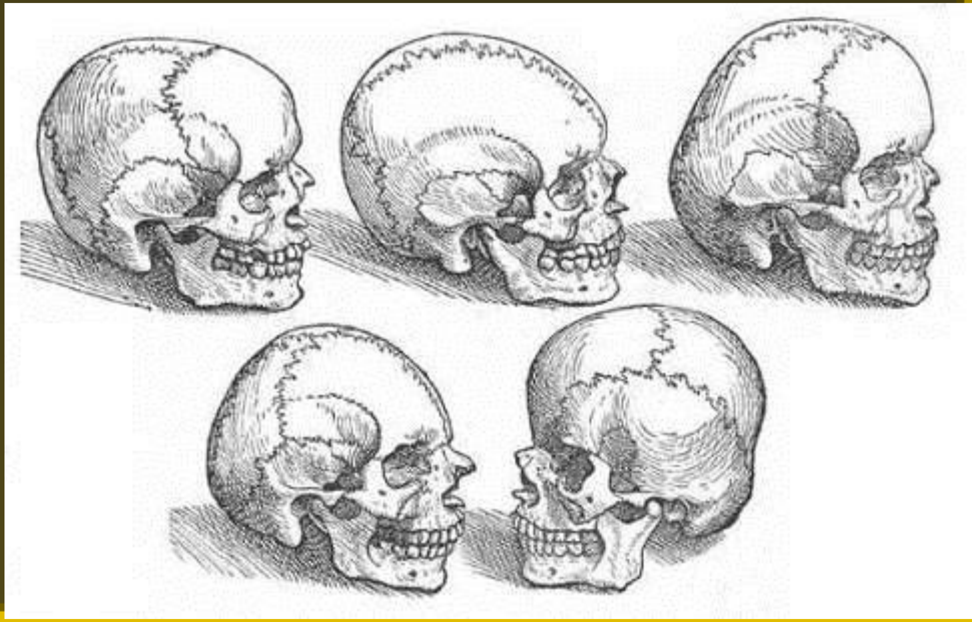
Development of the skull

Ágnes Nemeskéri

2017



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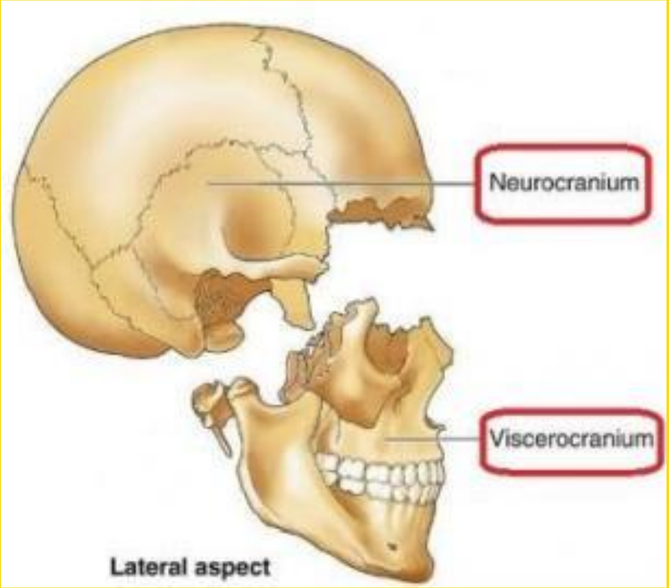
Subdivisions of skull

Facial bones   Bright green: Inferior nasal concha (2)   Bright blue: Lacrimal bone (2)   Purple: Mandible (1)   Yellow: Maxilla (2)   Pink: Nasal bone (2)   Red: Palatine bone (2)   Blue: Vomer (1)   Dark green: Zygomatic bone (2)

1. NEUROCRANIUM

protect the brain and sensory organs



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By Polygon data is from BodyParts3D - Polygon data is from BodyParts3D, CC BY-SA 2.1 jp, https://commons.wikimedia.org/w/index.php?curid=37620562

2. VISCEROCRANIUM

skeleton of the face – lower and anterior part of the skull

Craniofacial structures are derived:

- **from the cranial neural crest (CNC)**
- **cranial mesoderm**

Development of human skull

Morphogenesis of the bones of the cranial vault is a long developmental process initiated during early embryogenesis and completed during adulthood!

All bones of the skull pass first through a mesenchymatous phase or precondensation phase.

1. **EMBRYONIC PHASE - period of membrane formation**

   - development of the cranial bones begins with condensation of mesenchymal cells that surround the developing brain and contain osteoprogenitor cells.

   - condensation of mesenchyme also marks the beginning of selective genes specific for either chondro- or intramembranous osteogensis.

   - during 4th week, head mesenchyme develops to form the base of the ectomeningeal capsules (membrane) - earliest evidence of skull formation

   - during 5th week, mesenchyme that gives rise to membranous neurocranium (calvaria) is first arranged as a capsular membrane around the developing brain

   - at 37 days post ovulation, first phase of the period of membrane formation is completed

Development of human skull

1. EMBRYONIC PHASE

2. FETAL PHASE – osteogenesis

Endochondral

- from the **40th day** conversion of ectomeninx mesenchyme into **cartilage** is the beginning of chondrocranium

- **by 8 weeks**, through endochondral ossification, the **desmocranium is replaced with cartilage**

- at **13 weeks** (day 88) **ossification begins**, initially **within the chondrocranium**, forming part of occipital bone

Intramembranous

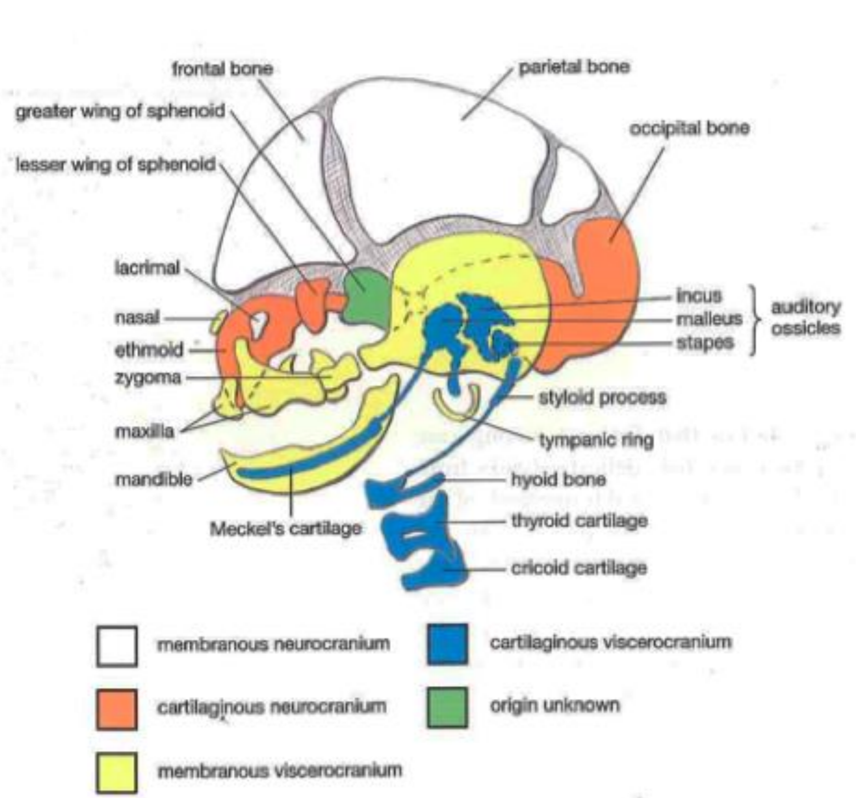
- osteogenesis starts by developing the **ossification centers in the outer layer of the ectomeninx**

- **7th and 8th week** - ossification centers first appear in areas corresponding to the future eminences and with bone formation spread centrifugally.

Development and Growth of the Normal Cranial Vault : An Embryologic Review
Sung-Won Jin, M.D.,1 Ki-Bum Sim, M.D., Ph.D.,2 Sang-Dae Kim, M.D., Ph.D.
J Korean Neurosurg Soc 59 (3) : 192-196, 2016

Development of skull

1. NEUROCRANIUM



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CHONDROCRANIUM
cartilaginous base of neurocranium
cartilaginous model
endochondral ossification

DESMOCRANIUM
membranous neurocranium
membranous model
intramembranous ossification

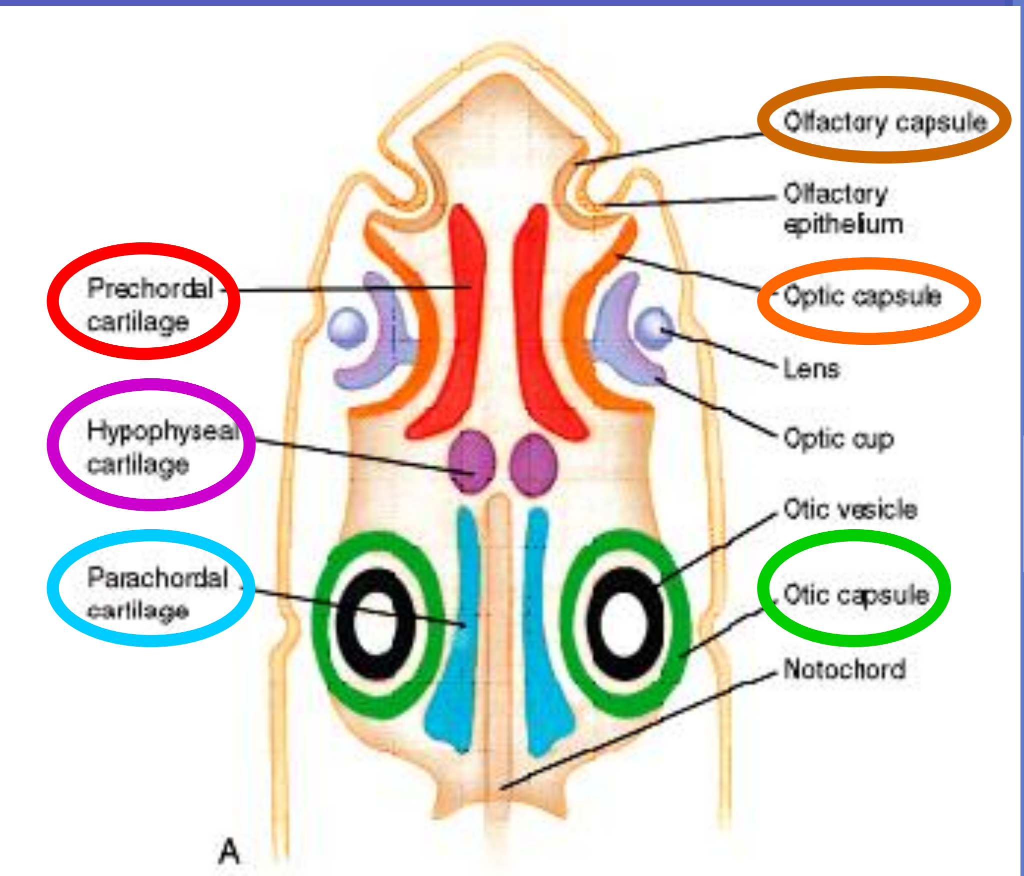
2. VISCEROCRANIUM

CHONDROCRANIUM
cartilaginous model
endochondral ossification

DESMOCRANIUM
membranous model
intramembranous ossification

Neurocranium - cartilaginous neurocranium

cartilaginous base of neurocranium – 6th week of gestation



1. along the midline: paired cartilages

- prechordal (trabeculae cranii)

-hypophyseal cartilage

-parachordals
(derived from the occipital sclerotomes + first cervical sclerotome, derived from mesoderm)
➔base of occipital bone

2. laterally: cartilages associated with epithelial primordia of sense organs

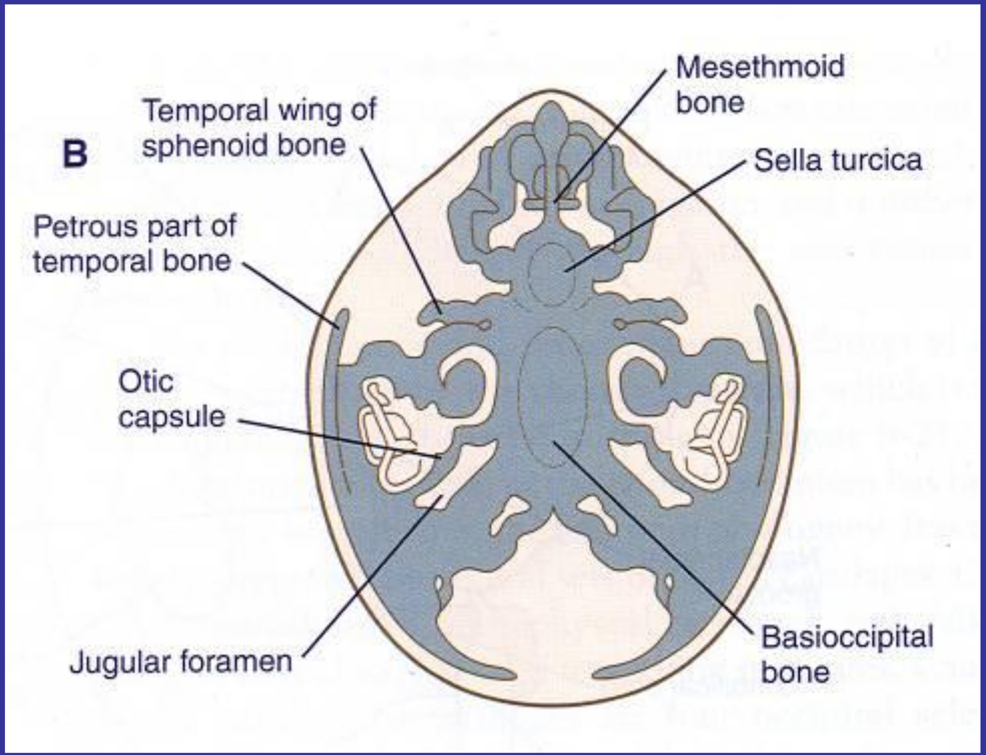
-olfactory capsule
(ala orbitalis – orbitosphenoid + ala temporalis – alisphenoid)

-optic capsule
(ala orbitalis – orbitosphenoid + ala temporalis – alisphenoid)

- otic capsule
(periotic cartilage)

Cartilaginous neurocranium

cartilaginous base of neurocranium – 8th week of gestation



growth and fusion:

BASICRANIUM

Occipital - basis

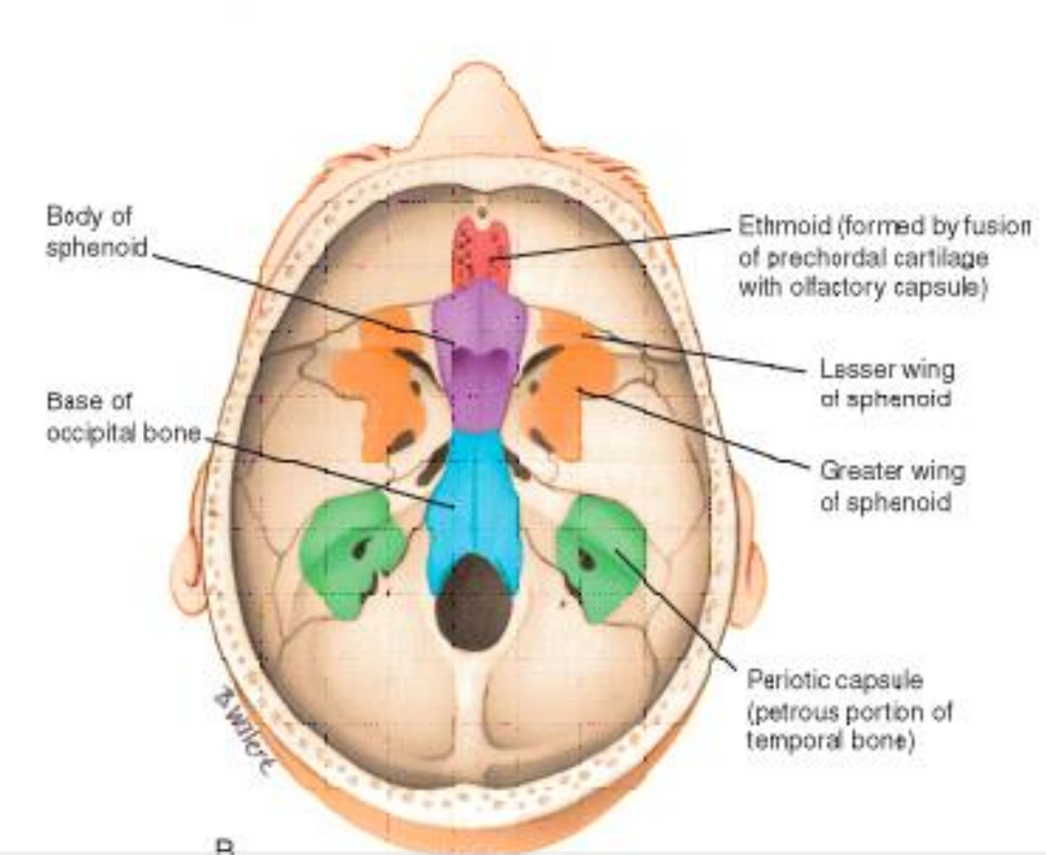
sphenoid,

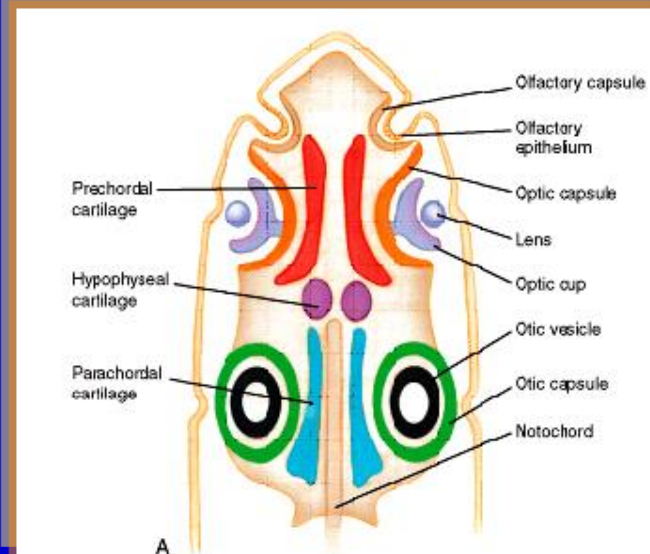
temporal – petrosal part

ethmoid

- cartilaginous precursors of the endochondral bones form around the pre-existing cranial nerves and blood vessels, so that in the mature skull the foramina for these connections between the brain and the rest of the body lie within the endochondral skull base

Base of the skull





-olfactory capsule + prechordal cartilage ➔ ethmoid bone

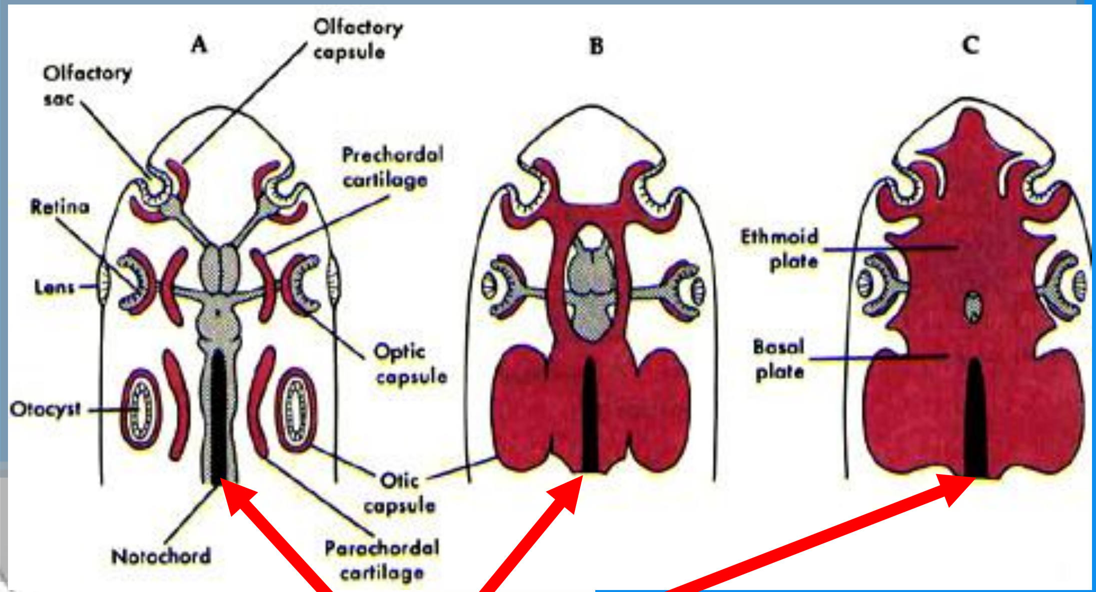
-optic capsule ➔ greater and lesser wings of sphenoid

-hypophysiseal cartilages ➔ body of sphenoid bone

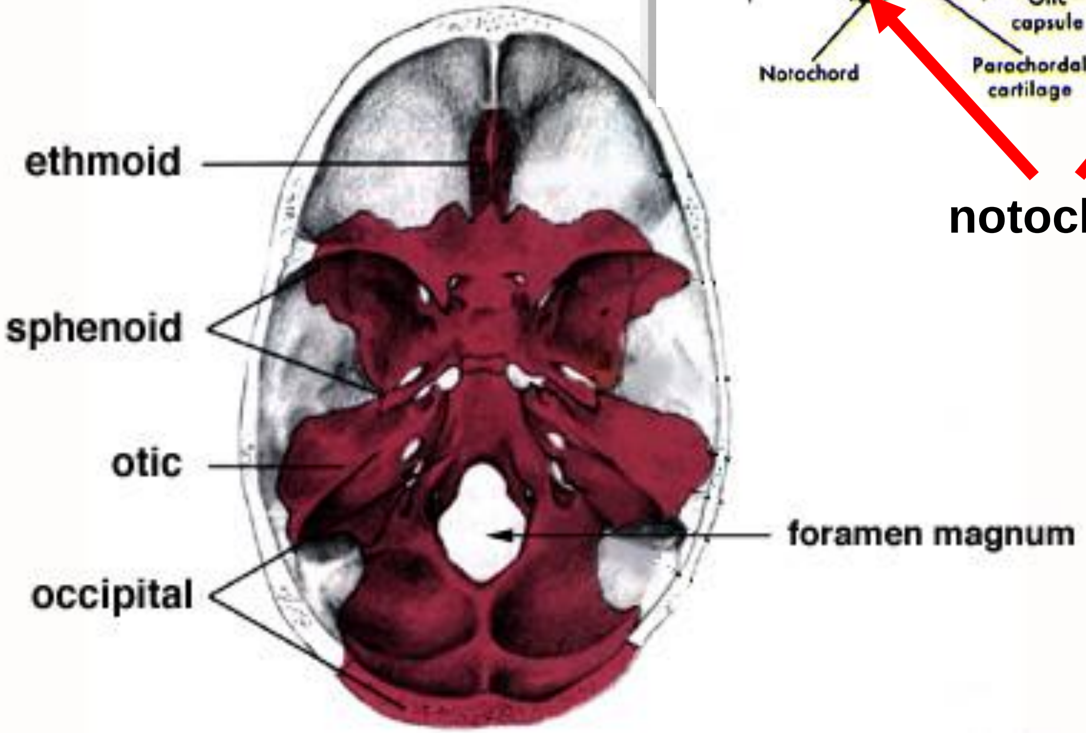
-periotic capsule ➔ petrous portion of temporal bone

-parachordal cartilage ➔ base of occipital bone

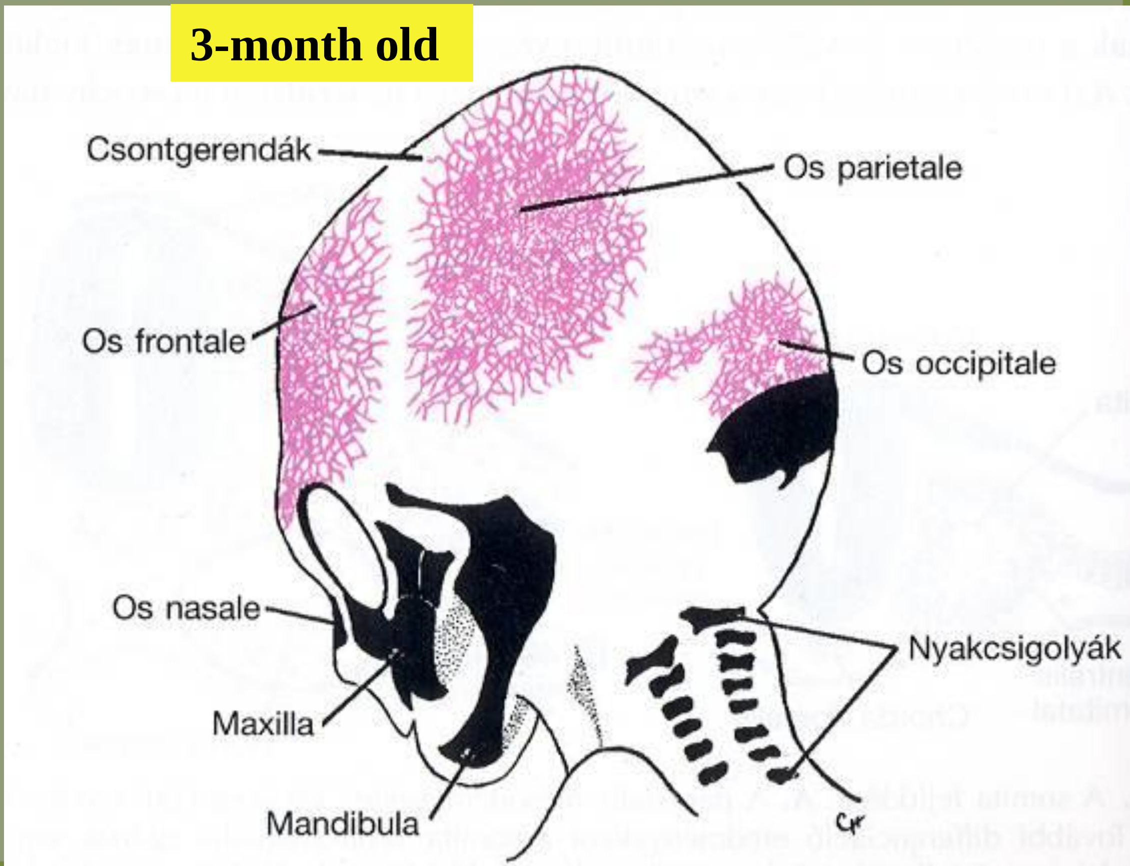
Basicranium



notochord



Membranous neurocranium - desmocranium



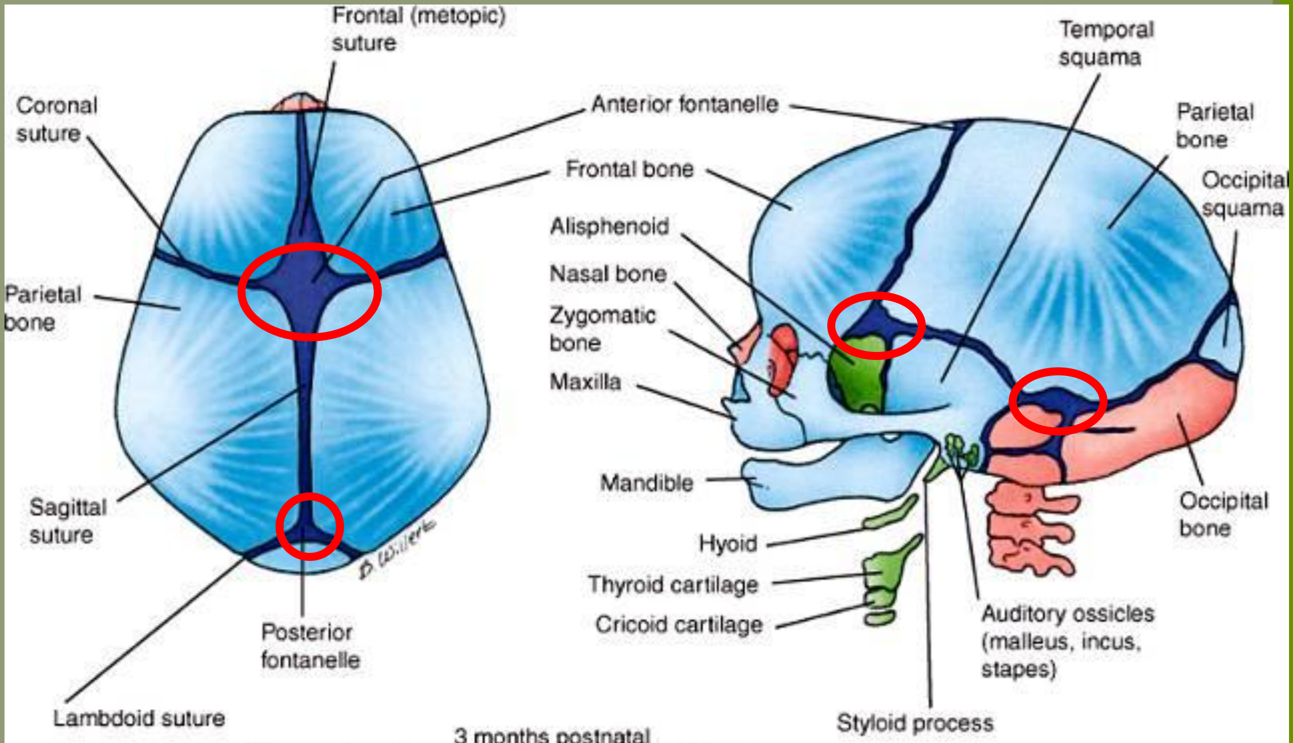
-primary ossification center

-radier bony trabeculae: spiculum

-flat bones

-bones develop from an <u>ossification directly in the mesenchyme</u> - intramembranous ossification membrane or dermal bone
-bones of cranial vault do not complete their growth during fetal life

Membranous neurocranium
Sutures and fontanelles



Schoenwolf et al: Larsen's Human Embryology, 4th Edition.

anterior fontanelle

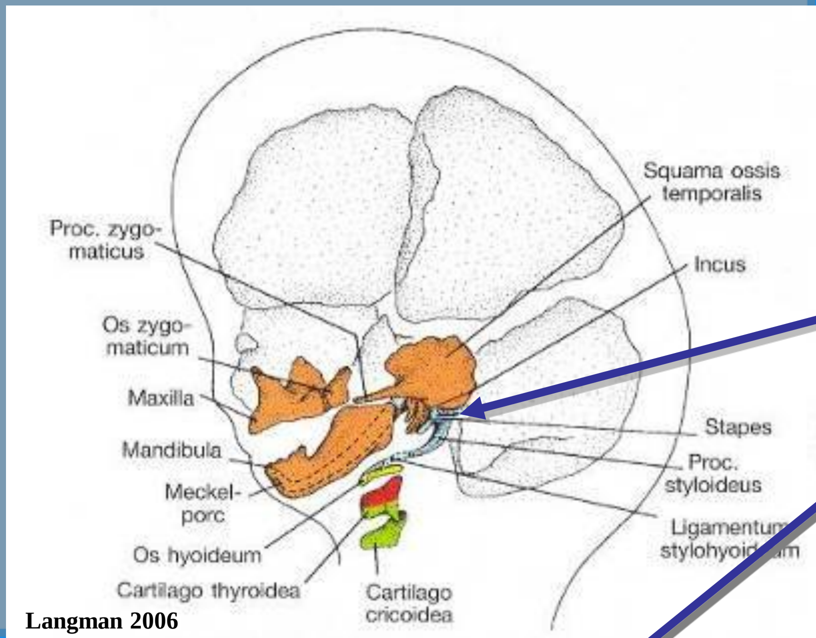
posterior fontanelle

anterolateral fontanelle

posterolateral fontanelle

sutures are fibrous
- permit the skull vault to deform as it passes through the birth canal
- allow it to continue growing throughout infancy and childhood

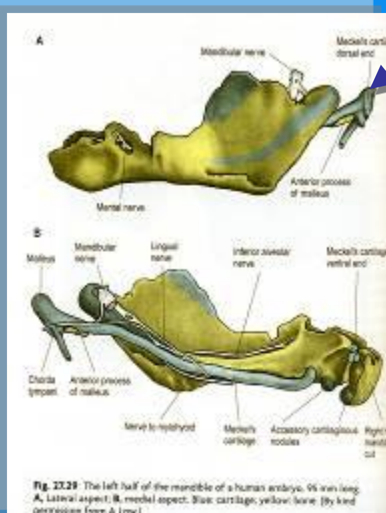
Cartilagenous viscerocranium – bones of face



Langman 2006

Circumoral first pharyngeal arch
mandibular prominence

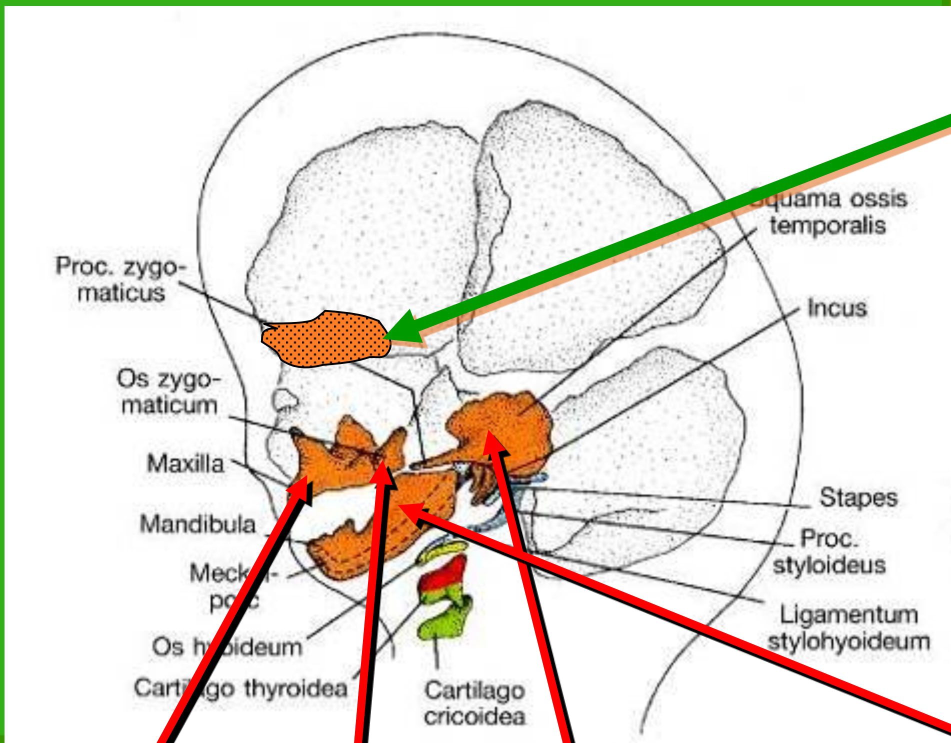
Meckel's cartilage
dorsal end
rudiments of incus, malleus



Second pharyngeal arch
Reichert's cartilage

stapes, temporal styloid process

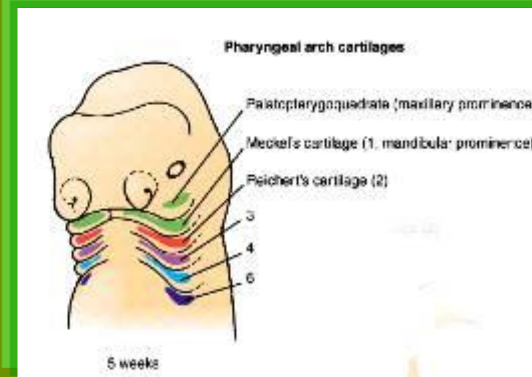
Membranous viscerocranium – bones of face



frontonasal prominence

frontal bone

orbital and nasal parts



Circumoral first pharyngeal arch
two prominences:
mandibular and maxillary prominences

maxilla, zygomatic, temporal squama

membrane bones

maxillary prominence

mandible

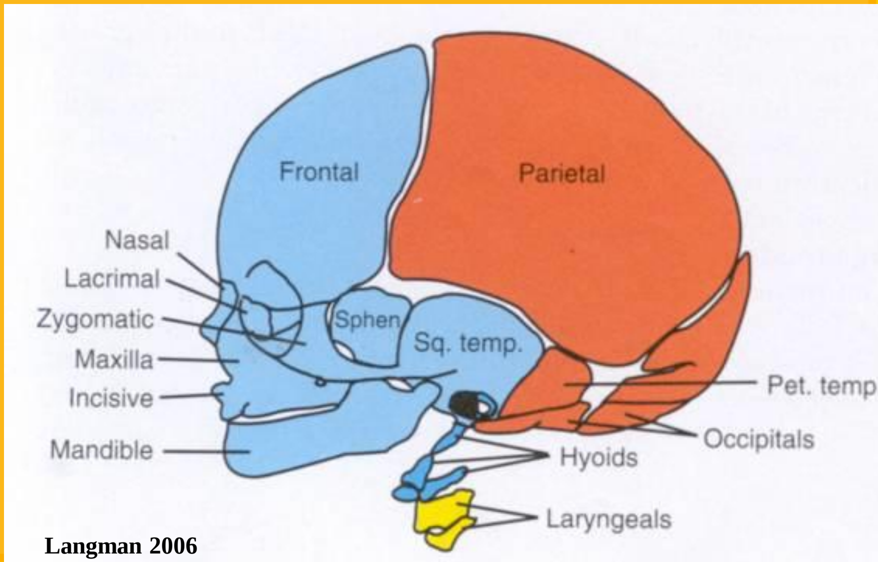
intramembranous ossification!!!
around the ventral part of Meckel's cartilage

mandibular prominence

Neurocranium, viscerocranium

neural crest mesenchyme origin

paraxial mesoderm origin



Langman 2006

Cranial neural crest cells

- contribute to all the elements of the viscerocranium (lower jaw, upper jaw and snout),

- frontal bones

- anterior skull base,

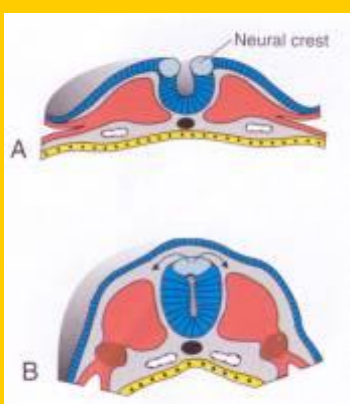
- connective tissues, cranial ganglia and smooth muscle of the blood vessels in the head

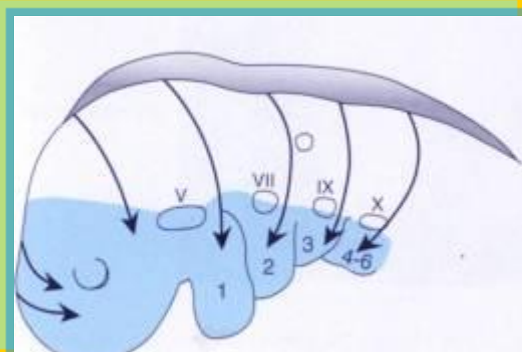
(Developmental Biology 374 (2013) 295–307)

- coronal suture forms at the interface between the neural crest-derived osteogenic mesenchyme of frontal bone and mesoderm-derived osteogenic mesenchyme of parietal bone.

Amy E. Merrill et al. 2006

- **a small line of the neural crest derived mesenchyme remains between the two parietal bones and contributes to the signaling system that governs growth of the cranial vault at sutures and to the development of the under lying meninges**





Origin of chondrocranium

in front of rostral end of notochord

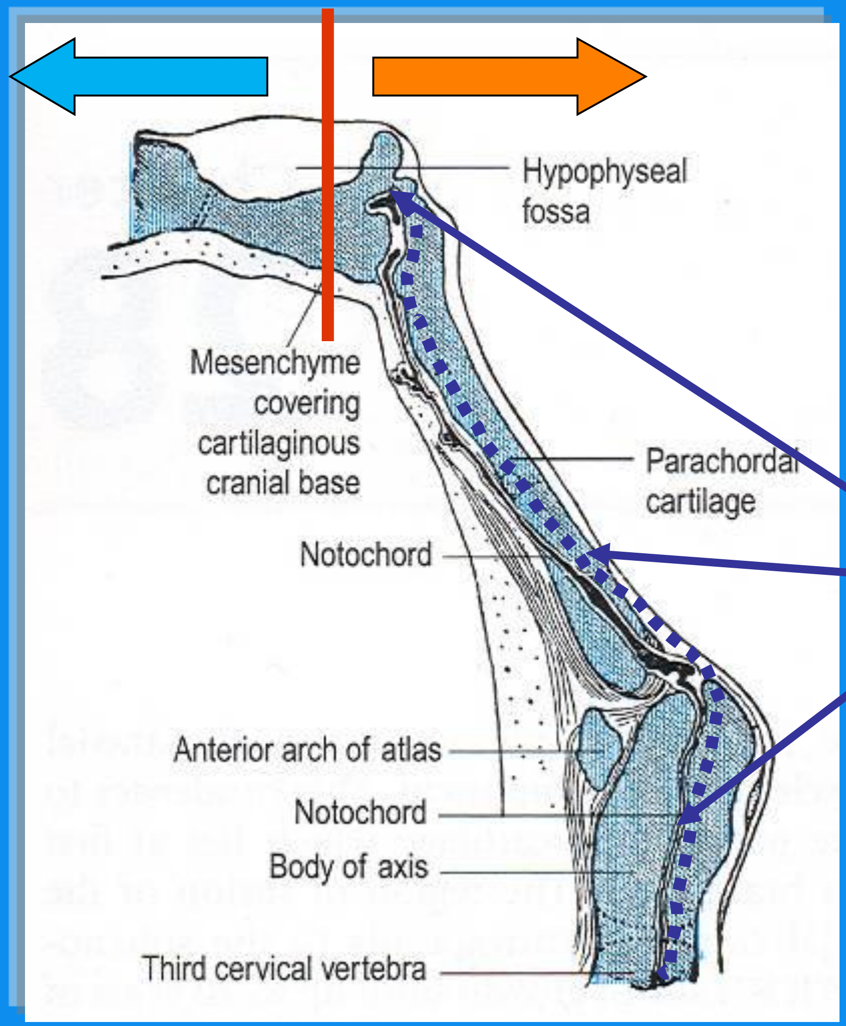
neural crest

praechordal chondrocranium

at the level of notochord

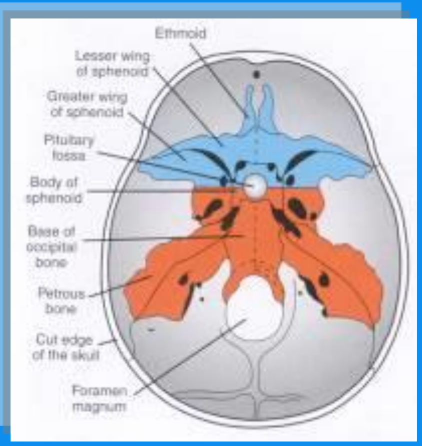
paraxial mesoderm

chordal chondrocranium



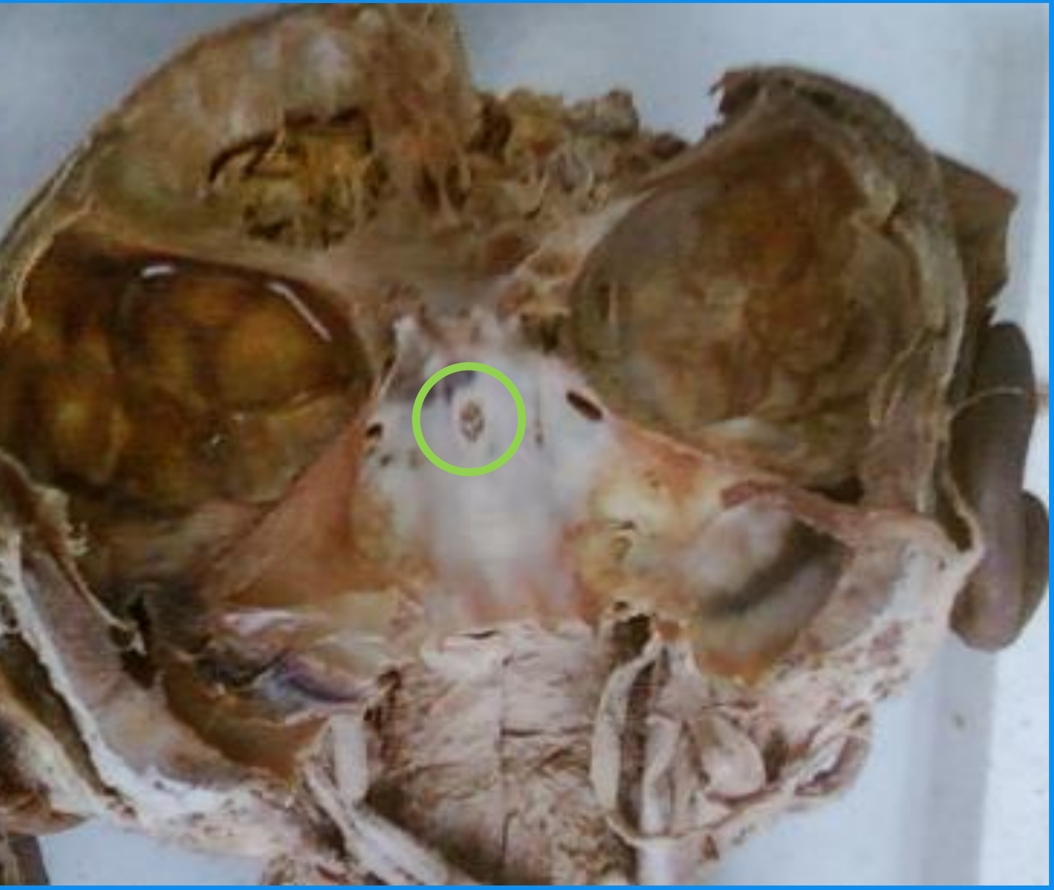
Research suggests that the notochord is a major signaling center for patterning the parachordal cartilage
(Nie et al., 2005b; Young et al., 2006)

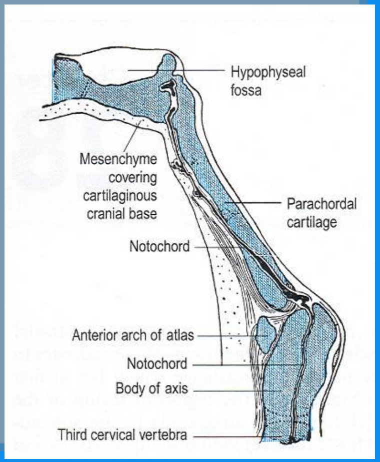
notochord



Remnant of notochord in the dissecting room

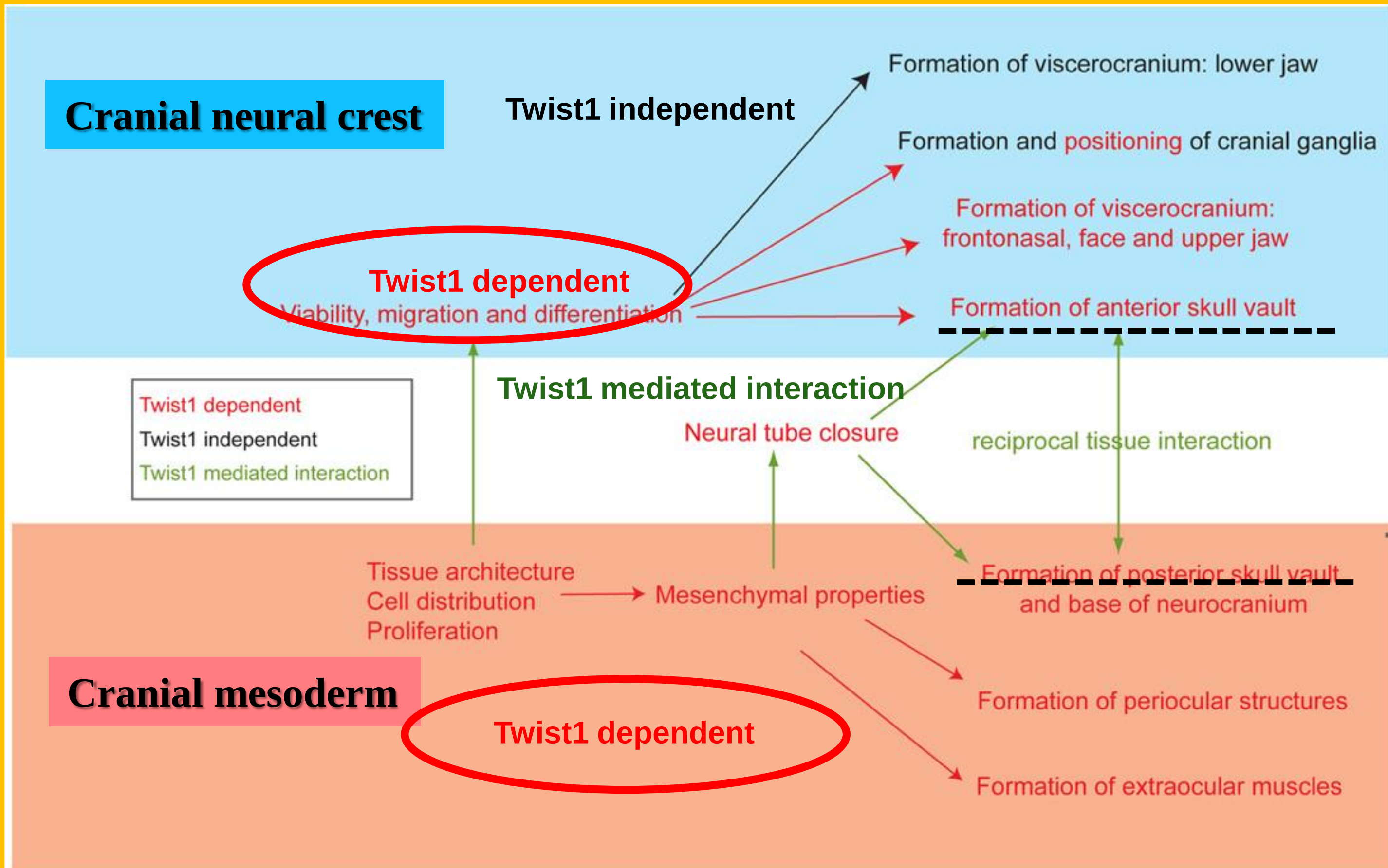
https://www.google.hu/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&ved=0ahUKEwjTm_Ooxf_XAhWDCOwKHalnBq0QjRwIBw&url=https%3A%2F%2Fcanaray.com%2Fcanaray%2Fmobile%2Freport%2F106153&psig=AOvVaw2LPJ5rvbFFsf2FThqozq5v&ust=1512998527879025





The inferior median clival canal (canalis basilaris medianus) is a rare anatomical variant of the clivus, which passes in the sagittal plane from the intracranial surface of the clivus to its retropharyngeal surface. It is generally thought to represent a remnant of the notochord. This is a non-significant anatomic variant, which does not require treatment or further attention.

Origin of neurocranium, viscerocranium



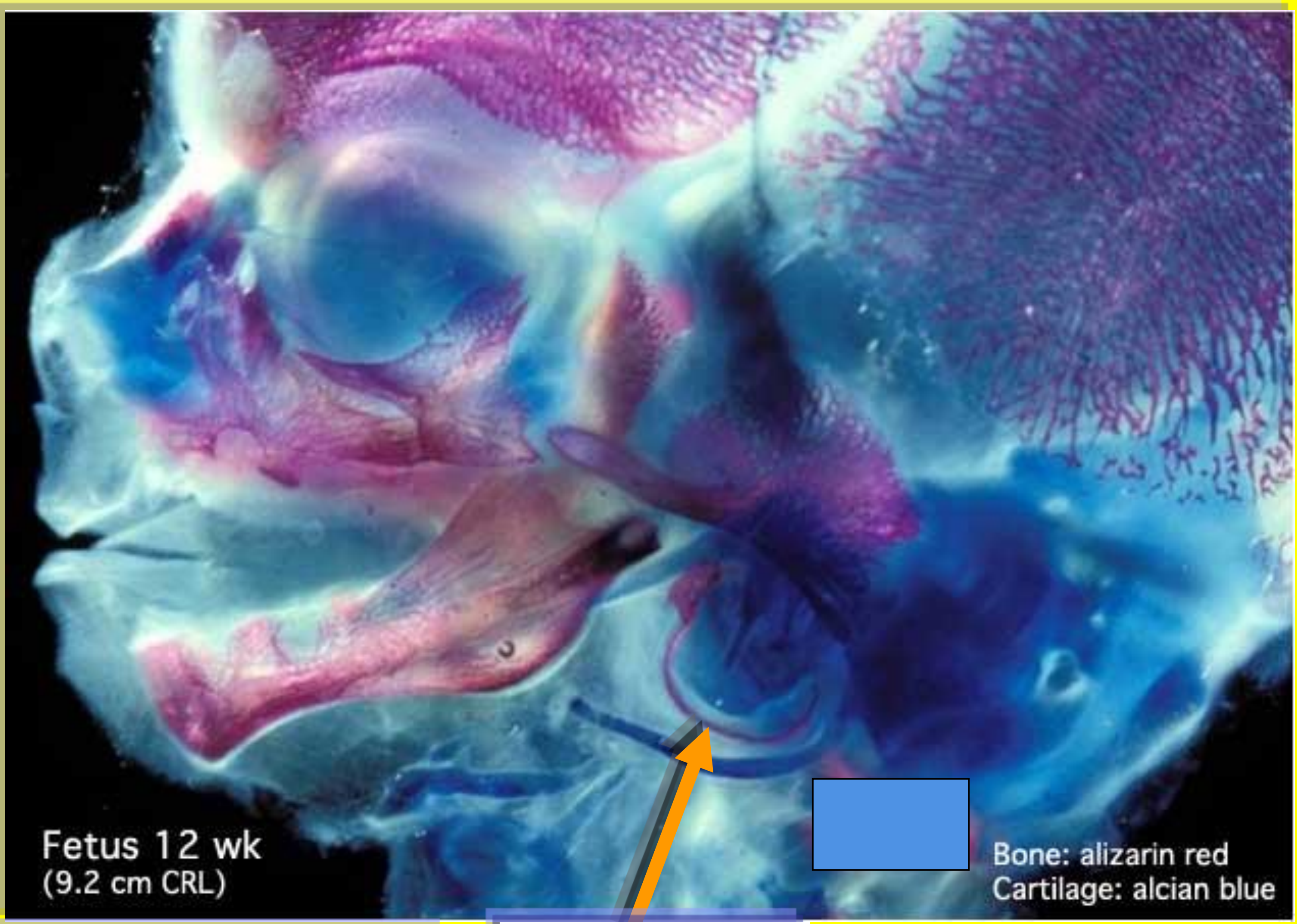
2012

Twist1 encodes a **transcription factor** that is expressed in both the **cranial neural crest** and the **cranial mesoderm** during craniofacial development

The mesenchymal architecture of the cranial mesoderm of mouse embryos is disrupted by the loss of Twist1function. Heidi Bildsoe et al. 2012 Dev Biol

- in the peri-orbital skeleton is the **hypochiasmatic cartilage**, which develops as an **isolated mesoderm-derived** structure is **embedded in the CNC-derived anterior skull base**.
- this cartilage forms a bridge between the orbital cartilage and the skull base, to which the ExtraOcularMuscles attach.
- it has been proposed, based on their spatial association, that the EOM and the hypochiasmatic cartilage share a common origin in the anterior cranial mesoderm. Developmental Biology 374 (**2013**) 295–307

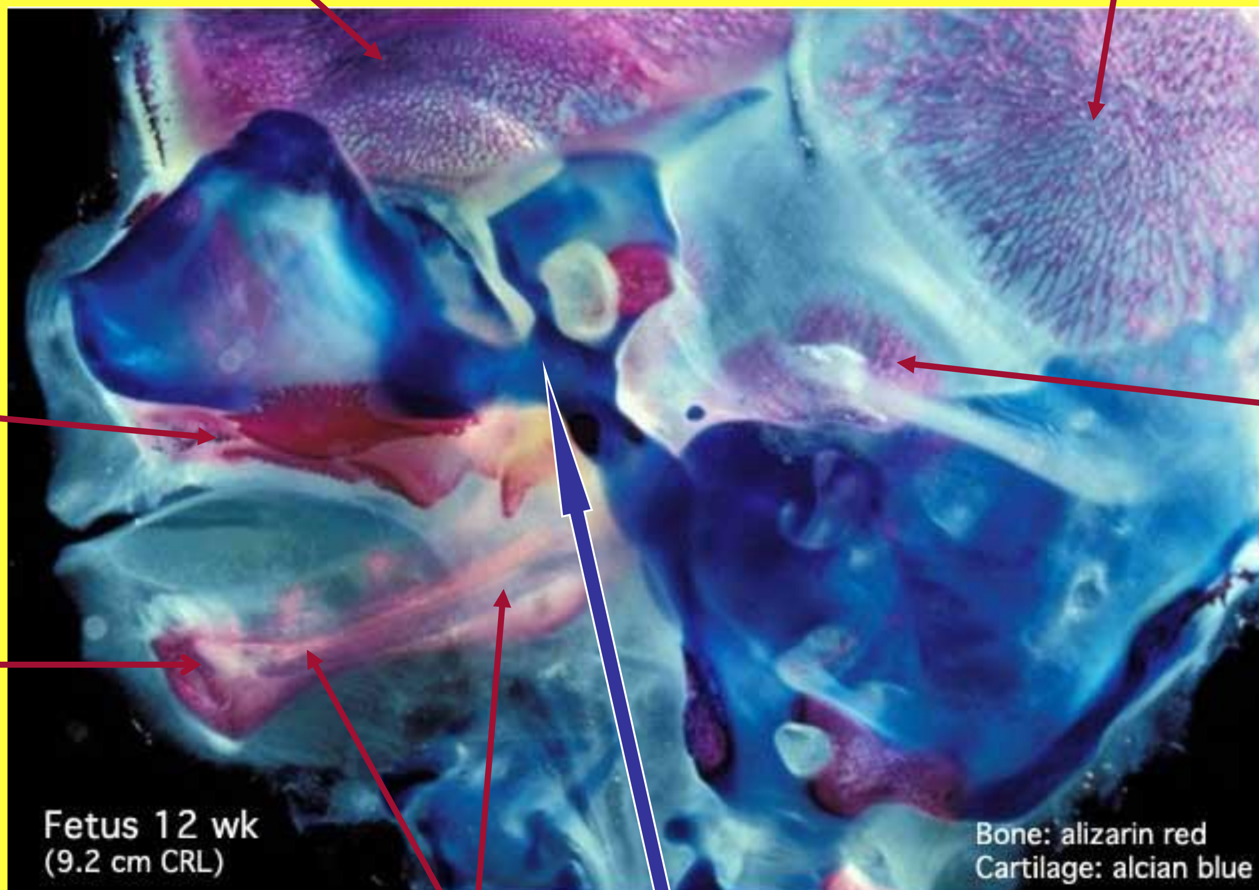
12-week-old fetus



-tympanic annulus

Pink – intramembranous ossification

12-week-old fetus



!! Pink: bone

endochondral and intramembranous

Box 9-2 Embryological Origins of Bones of the Cranium

NEUROCRANIUM

Chondrocranium
- Occipital
- Sphenoid
- Ethmoid
- Petrous and mastoid part of temporal

Membranous neurocranium
- Interparietal part of occipital
- Parietal
- Frontal
- Squamous part of temporal

VISCEROCRANIUM

Pharyngeal Arch I

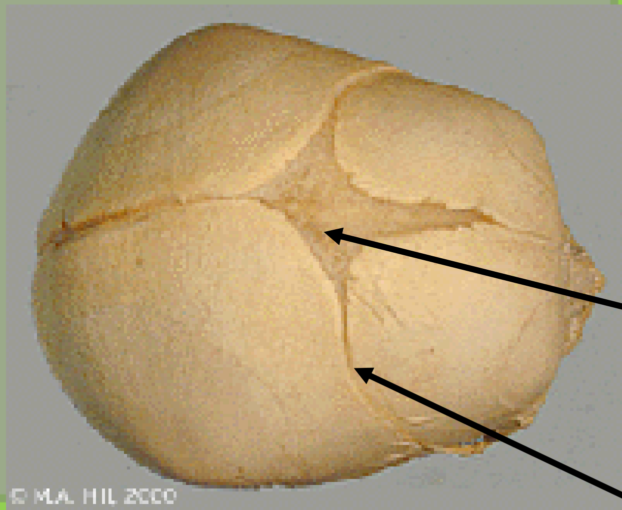
Cartilaginous viscerocranium
- Meckel's cartilage
  - Malleus
  - Incus

Membranous viscerocranium
- Maxillary process (superficial)
  - Squamous part of temporal
  - Zygomatic
  - Maxillary
  - Premaxillary
  - Nasal?
  - Lacrimal?
- Maxillary process (deep)
  - Palatine
  - Vomer
  - Pterygoid laminae
- Mandibular process
  - Mandible
  - Tympanic ring

PHARYNGEAL ARCH II

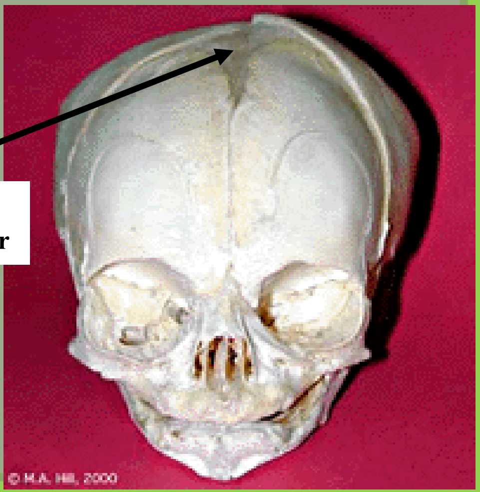
Cartilaginous viscerocranium
- Reichert's cartilage
- Stapes
- Styloid process

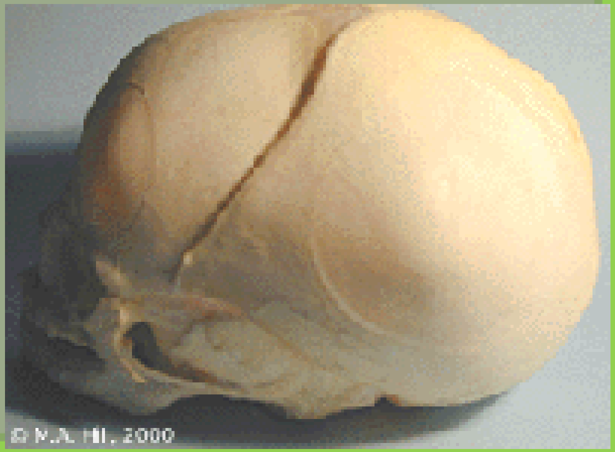
Newborn skull



anterior fontanelle
-"fills in" in the middle of 2th year

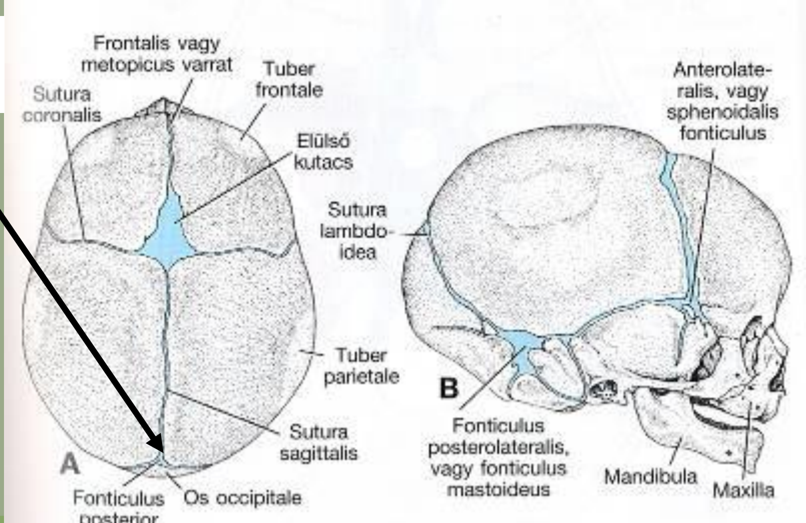
-fibrous sutures





Fontanelles and fibrous sutures during birth,
enable the bony plates of the skull to flex,
allowing the child's head to pass through the birth canal!!!!

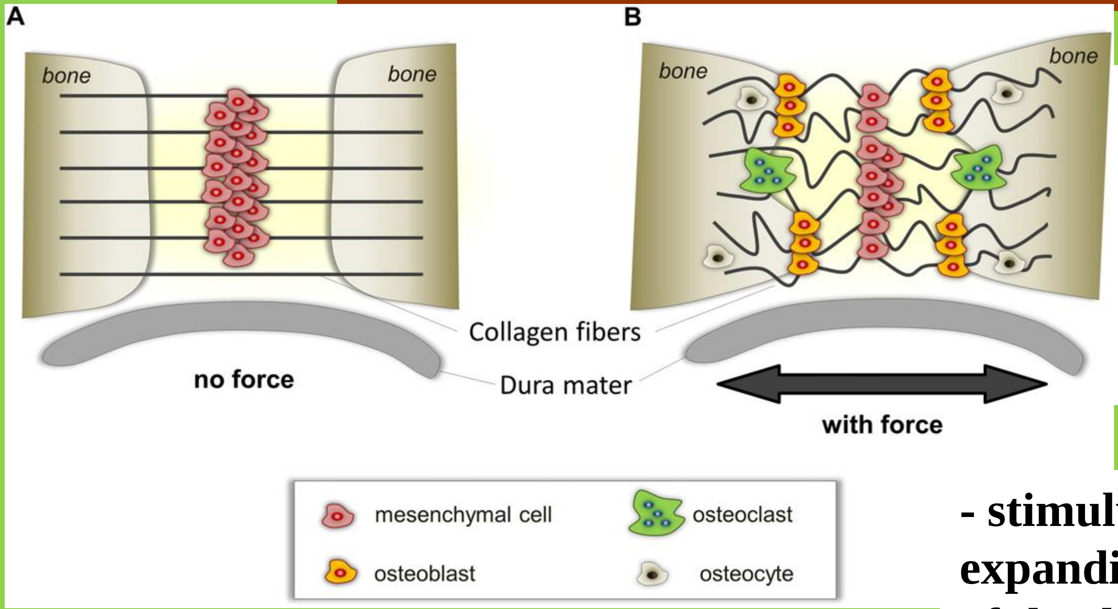
-posterior fontanelle
fills in after 3rd month



- fibrous membrane forming the cranial vault before ossification, is unossified at the angles of the parietal bones: 6 fontanelles

viscerocranium/neurocranium at birth comprises ~ one-eighth of head, by adulthood becomes one-half!!!

Formation of sutures



FGFR1, FGFR2, FGFR3

bone morphogenetic protein (BMP),

TGFß,

noggin

- stimulus arises primarily from the expanding brain, sending signals by means of the dura mater

- development of full mental capacities in the growing child depends on longterm expansion of the skull to allow free growth of the brain.
- in some individuals (approximately 1 in 2500 live births) this mechanism fails due to craniosynostosis, the premature loss and ossification of sutural growth centres
(J. Anat. (2005) 207, pp637–653)

- **normally, obliteration of the calvarial sutures begins between 30 and 40 years internally**
- **and 10 years later externally**

Regulation of skull development

1. All the bones of the neurocranium arise as the result of an inductive influence of an epithelial structure

2. Interactions are mediated by growth factors and the extracellular matrix

3. At the site of developing sutures the osteogenic fronts of two adjacent bones meet and overlap.

Important role of FGF, bone morphogenetic protein, TGFß, noggin, TWIST

FGFR signaling pathway remains the most important molecule in the pathological development of craniosynostosis, as mutations were initially found in FGFRs. Moreover, FGFR signaling is a critical player in osteogenesis.

Craniofacial malformations

Early ossification of one or more sutures – Craniosynostosis

-2500 birth/1 craniosynostosis

-increased intracranial pressure, blindness, mental retardation

Fibroblast Growth Factors (FGFs) –FGF family, 9 factors

Fibroblast Growth Factors Receptors (FGFRs) – 4 receptors

-proliferation + differentiation + migration regulation

FGFR1, FGFR2, FGFR3 (tyrosin kinase receptor)

- mutations of these receptors ➔ different kinds of craniosynostosis
- receptor becomes constantly activated because of mutation ➔ no binding of FGF

TWIST-gene codes a DNA-binding protein

- mutation of this gene induces proliferation and early differentiation in the coronal suture
- normally, inhibits the differentiation of primary osteogenic cells at the edge of the suture

Craniofacial malformations

TABLE 9.1 Genes Associated with Skeletal Defects

Gene	Chromosome	Abnormality	Phenotype
FGFR1	8p12	Pfeiffer syndrome	Craniosynostosis, broad great toes and thumbs, cloverleaf skull, underdeveloped face
FGFR2	10q26	Pfeiffer syndrome	Same
		Apert syndrome	Craniosynostosis, underdeveloped face, symmetric syndactyly of hands and feet
		Jackson-Weiss syndrome	Craniosynostosis, underdeveloped face, foot anomalies, hands usually spared
		Crouzon syndrome	Craniosynostosis, underdeveloped face, no foot or hand defects
FGFR3	4p16	Achondroplasia	Short-limb dwarfism, underdeveloped face
		Thanatophoric dysplasia (type I)	Curved short femurs, with or without cloverleaf skull
		Thanatophoric dysplasia (type II)	Relatively long femurs, severe cloverleaf skull
		Hypochondroplasia	Milder form of achondroplasia with normal craniofacial features
MSX2	5q35	Boston-type craniosynostosis	Craniosynostosis
TWIST	7p21	Saethre-Chotzen syndrome	Craniosynostosis, midfacial hypoplasia, cleft palate, vertebral anomalies, hand and foot abnormalities
HOXA13		Hand-foot-genital syndrome	Small, short digits, divided uterus, hypospadias
HOXD13	2q31	Synpolydactyly	Fused, multiple digits

Craniofacial malformations
Craniosynostosis

Scaphocephalia

-sagittal suture closes early
-skull long, narrow, wedge-shaped
-frontalis és occipitalis terjeszkedés
-57%

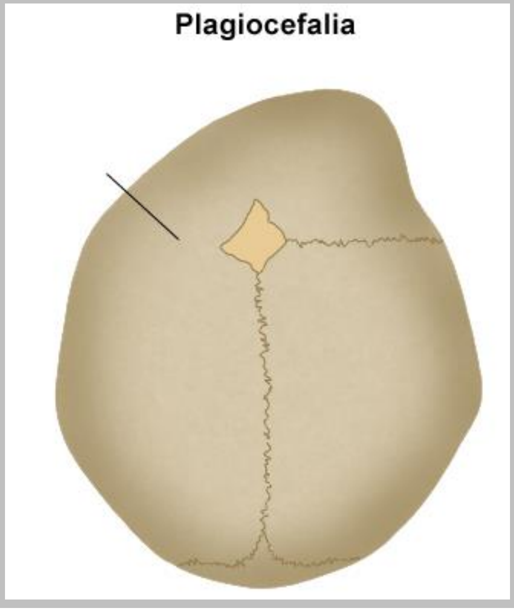
Turrycephaly

-coronoid + lambdoid sutures close early

-high tower-like skull

Langman 2006

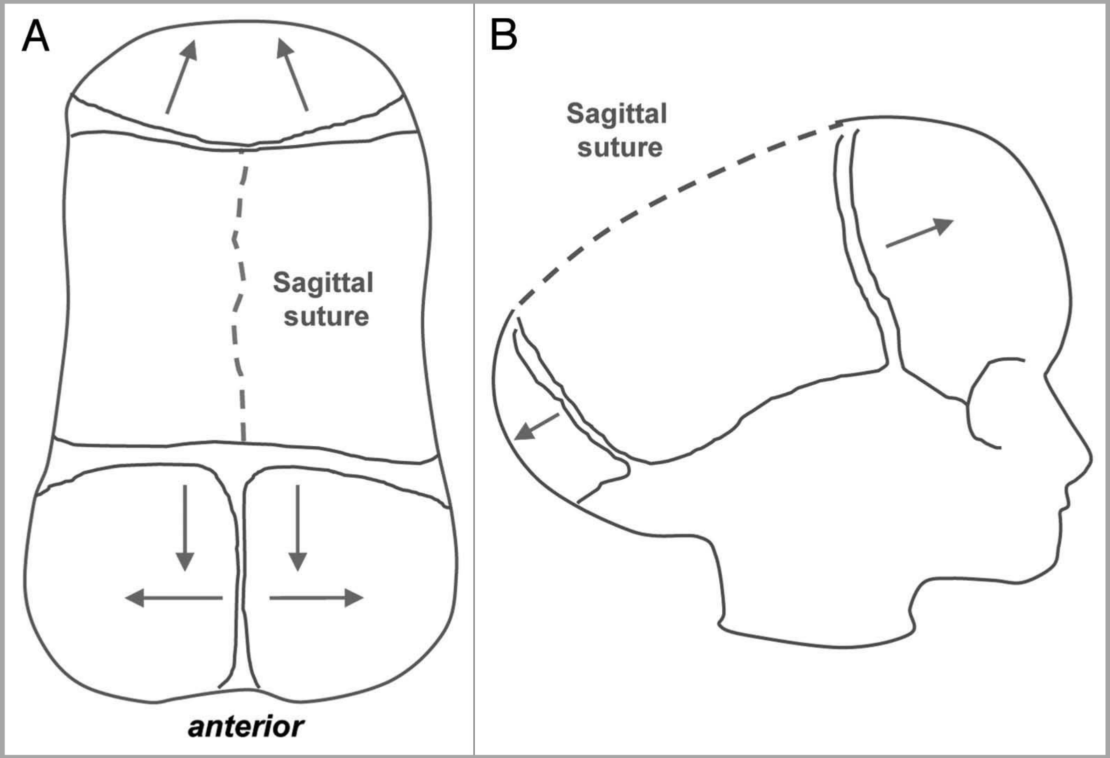
Langman 2006



http://emedicine.medscape.com/article/1281182-overview#aw2aab6b4

- growth is restricted in a direction perpendicular to the fused suture
- remaining sutures undergo compensatory growth

Scaphocephalia



Organogenesis 8:4, 103–113; October/November/December 2012

Cranial malformations

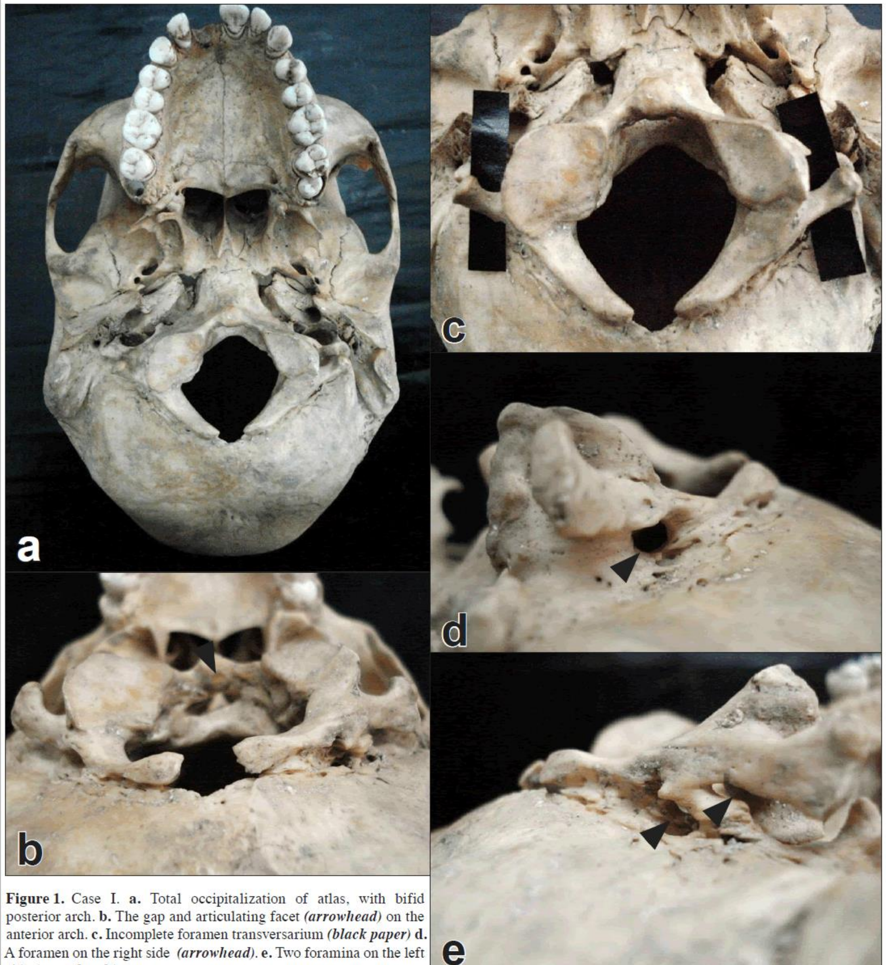
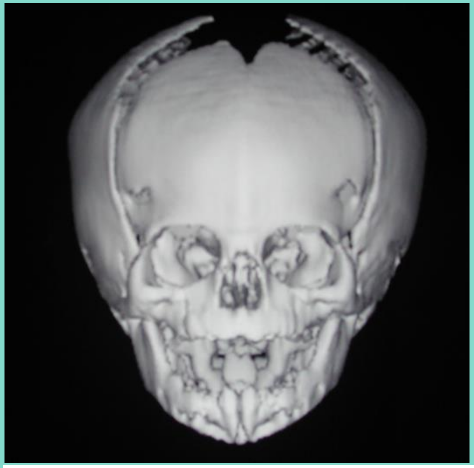
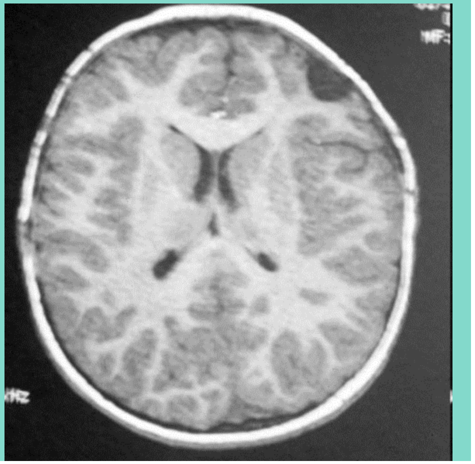


Figure 1. Case I. **a.** Total occipitalization of atlas, with bifid posterior arch. **b.** The gap and articulating facet *(arrowhead)* on the anterior arch. **c.** Incomplete foramen transversarium *(black paper)* **d.** A foramen on the right side *(arrowhead)*. **e.** Two foramina on the left side *(arrowheads)*

occipitalizaton of the atlas

Craniosynostosis – diagnosis, managements





http://search.incredimail.com/?q=craniosynostosis+therapy&lang=hungarian&source=017104062045105

- Measure head circumference longitudinally
- and monitor development.

Ensure normal brain growth in patients with primary craniosynostosis.

- **Carefully monitor signs and symptoms of elevated intracranial pressure.**

Examine the fundi and alert parents to report persistent vomiting or lethargy promptly.

Should elevated intracranial pressure be suspected, an emergent neurosurgical consult would be appropriate.

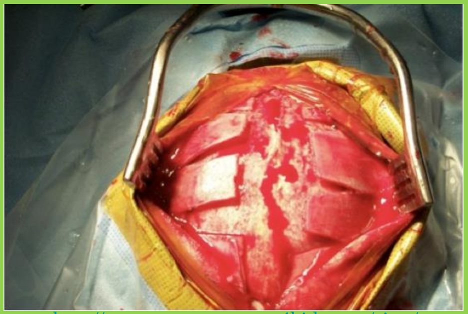
- **To preserve visual function in patients with elevated intracranial pressure, an emergent ophthalmological consult would be appropriate.**

surgical intervention is the primary treatment modality: correction of deformity

Surgical management of craniosynostosis

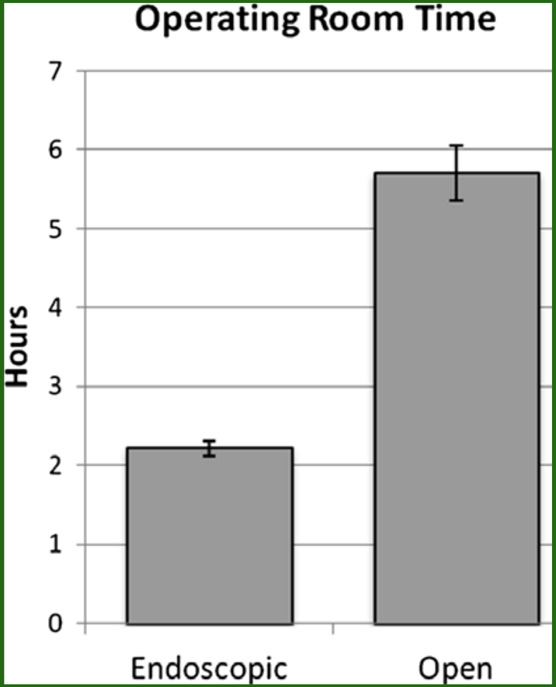
In the final configuration (see the image below), the frontal bones have been reshaped and reoriented for the best cosmetic result.
The sagittal suture and coronal sutures have been removed and cut into smaller pieces. They are reconfigured into the final construct, being attached to the skull with absorbable plates and sutures.

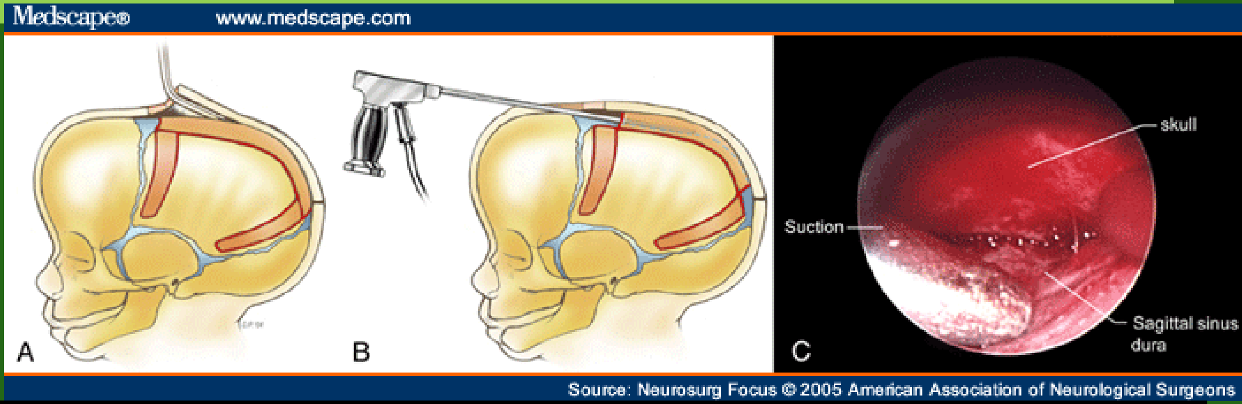
Sagittal craniosynostosis repair. Final configuration secured in place.
javascript:refImgShow(15)

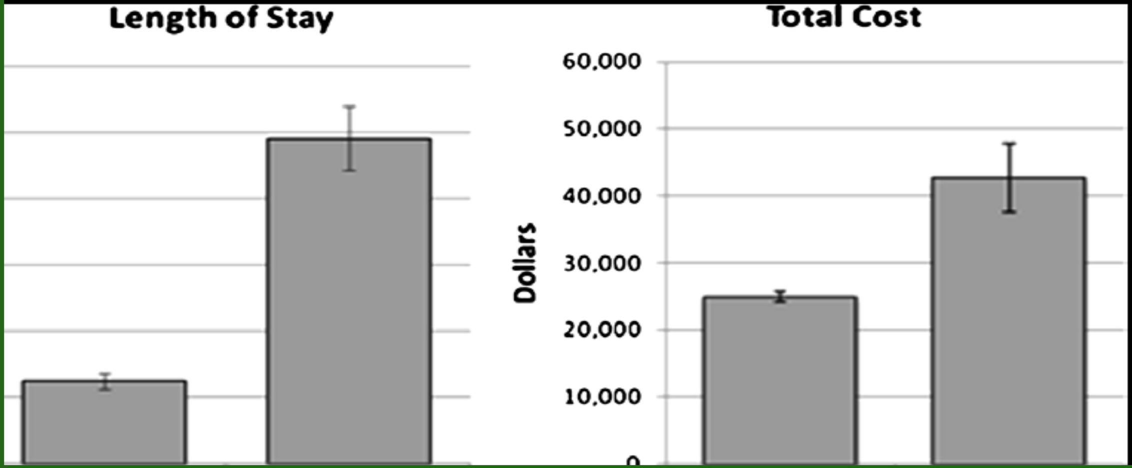


http://www.neurosurgeons4kids.com/sites/www.neurosurgeons4kids.com/files/craniofacial-15.png

Endoscope-Assisted Versus Open Repair of Craniosynostosis:
A Comparison of Perioperative Cost and Risk







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Hugo St. Hilaire, MD, DDS,*Ţ Lori McBride, MD,ţ and Michael H. Moses, MD- 2013

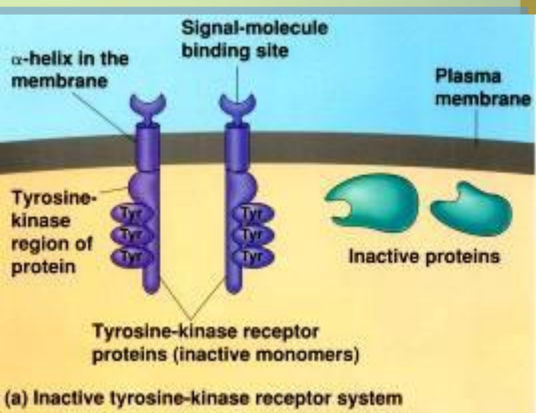
2006

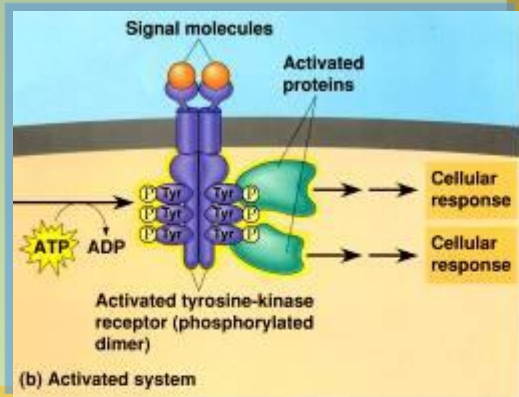
New data

FGF Receptor inhibition in vitro prevented the early synostosis. Selective separation of the binding protein (Frs2α) from the activated FGF Receptor 2c in vivo normalized the skull development and does not disturbed other developmental processes.

V. P. Eswarakumar, F. Ozcan, E. D. Lew, J. H. Bae, F. Tome, C. J. Booth. J. Adams, I. Lax, and J. Schlessinger 2006

2012





„With continued studies in clinical genetics and biomolecular mechanisms involved in premature suture fusion, new insights will undoubtedly be made which could, the in the future, usher in a new era of non-surgical therapy for craniosynostosis. „

Organogenesis 8:4, 103–113; 2012

2016

Still the surgical therapy…

In the near future certain types of craniosynostoses can be treated!!

-tyrosin kinase inhibitor has already been successfully applied in chronic myeloid leukaemia

-the cause of this disease is also the activated receptor tyrosin kinase

FGF signaling pathways in endochondral and intramembranous bone development

-the expression of FGFs and FGFRs is temporally and spatially regulated during craniofacial development.

-during intramembranous bone formation, *Fgf2*, *Fgf4*, and *Fgf9* are expressed in sutural mesenchyme in early craniofacial skeletogenesis, suggesting that they may be involved in regulating calvarial osteogenesis

-*Fgfr2* is expressed at sites of ossification in differentiating osteoblasts

-FGF2 activates osteocalcin transcription (Osteocalcin is secreted solely by osteoblasts and thought to play a role in the body's metabolic regulation and is pro-osteoblastic, or bone-building, by nature)

-FGF2 increases the number of osteogenic cells and promotes calvarial osteogenesis FGF signals control the balance among skeletal cell growth, differentiation, and apoptosis

FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease.David M. Ornitz1,3 and Pierre J. Marie2
Genes Dev. 2002 16: 1446-1465

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