

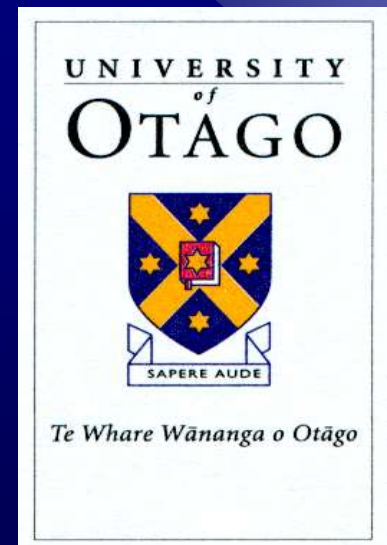
Development and Growth of the Neurocranium

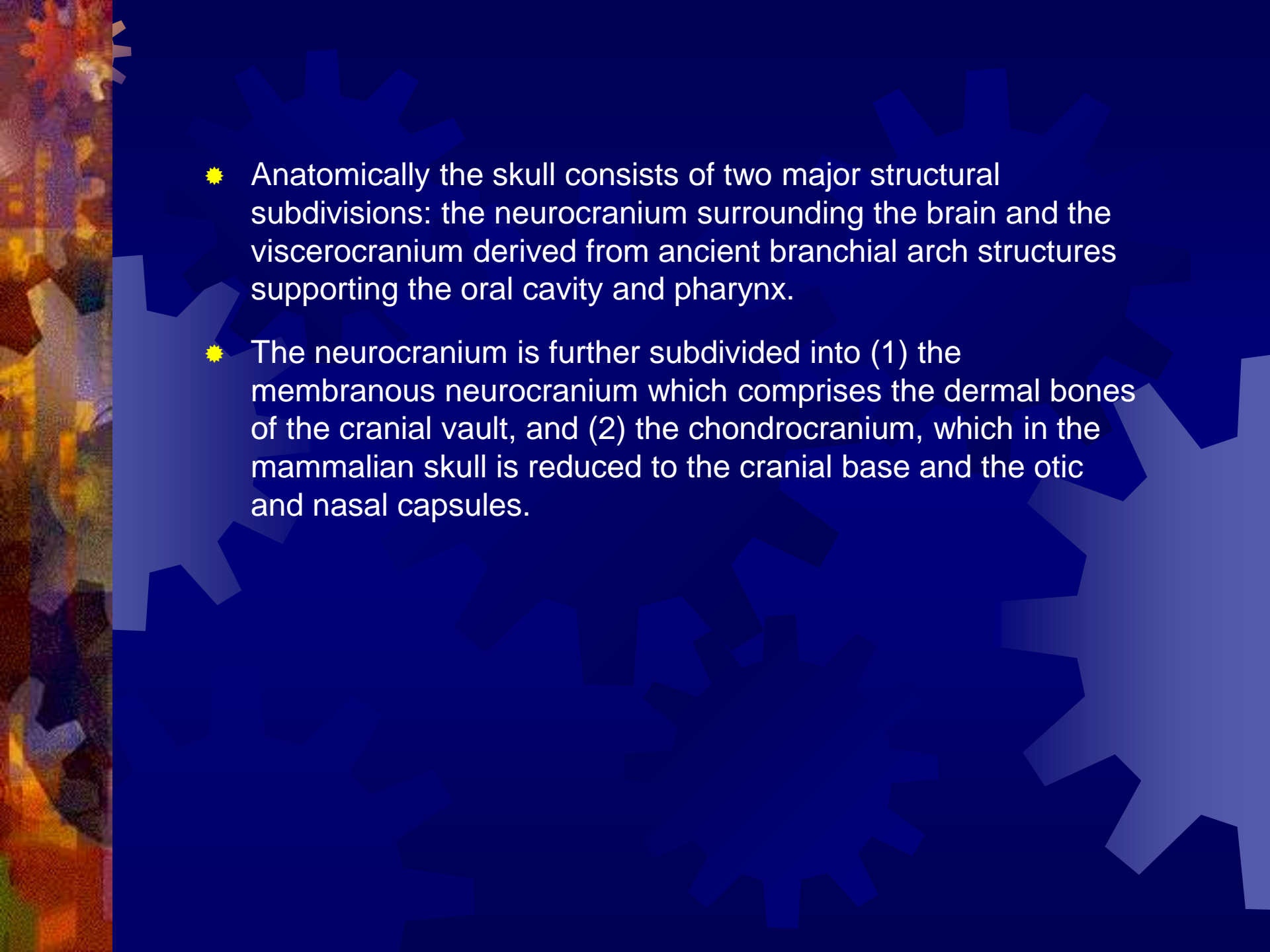
By Murray C. Meikle

Biological Foundations of Orthodontics
and Dentofacial Orthopaedics

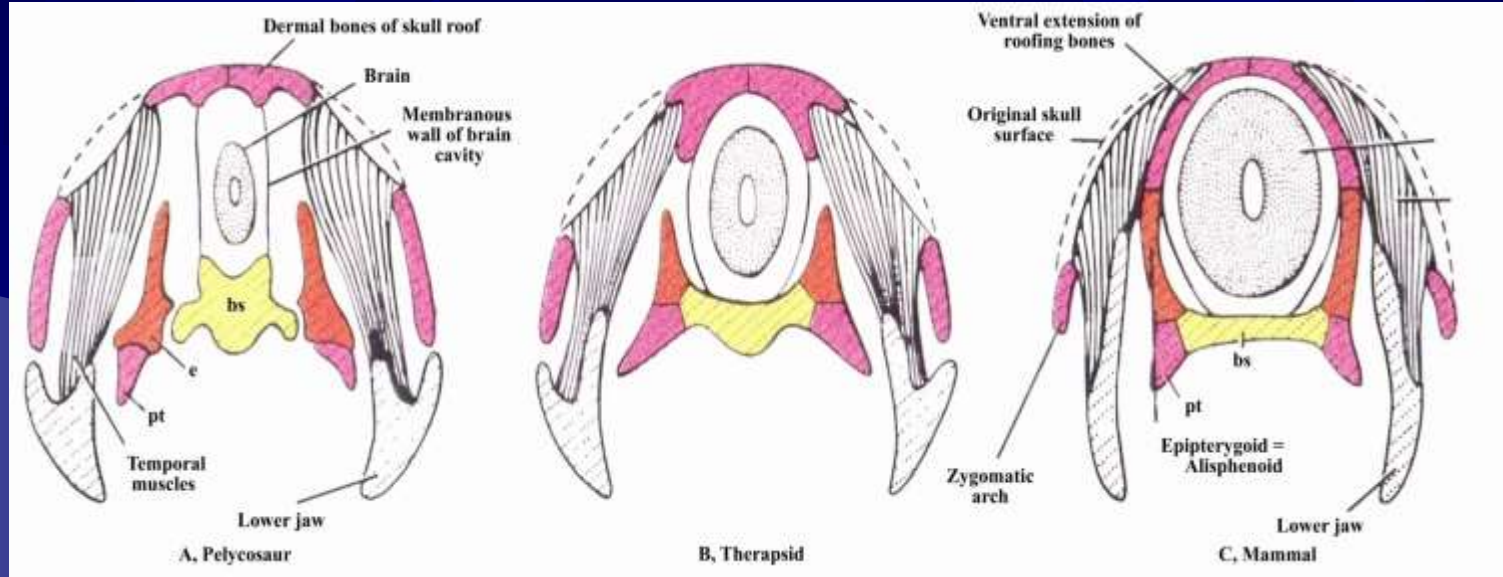
Seminar 5

2004



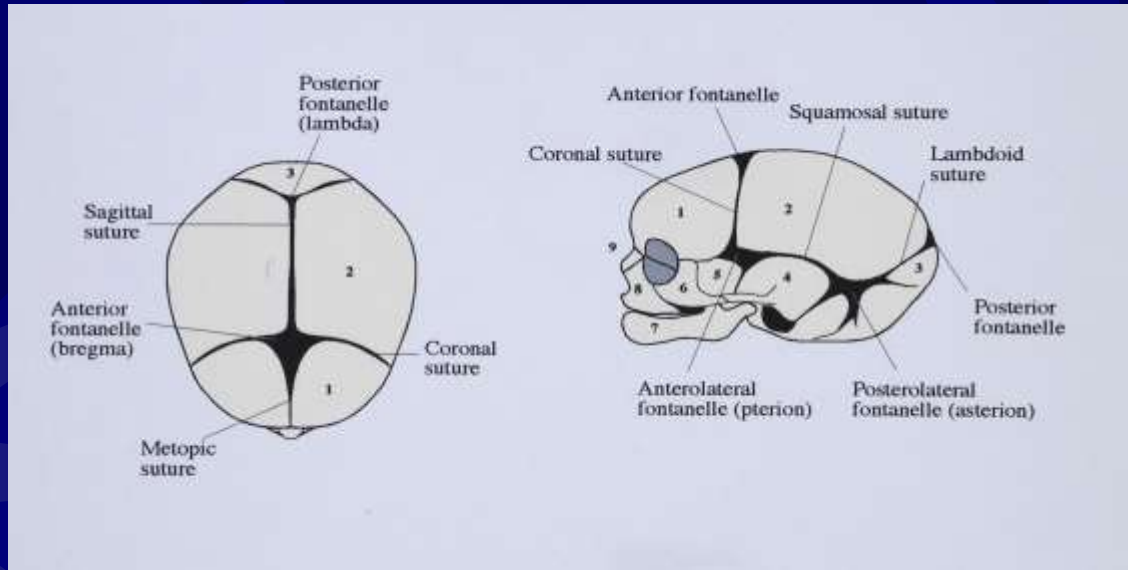
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- Anatomically the skull consists of two major structural subdivisions: the neurocranium surrounding the brain and the viscerocranium derived from ancient branchial arch structures supporting the oral cavity and pharynx.
 - The neurocranium is further subdivided into (1) the membranous neurocranium which comprises the dermal bones of the cranial vault, and (2) the chondrocranium, which in the mammalian skull is reduced to the cranial base and the otic and nasal capsules.

The membranous neurocranium



- ✿ In early reptiles the parietal and frontal bones formed a solid roof over the brain. With the expansion of the brain in mammal-like reptiles, downward extensions of the bones developed deep to the jaw muscles and together with the squamous temporal bone and the alisphenoid formed a new cranial vault; the temporal muscles thus came to lie external to the skull.
- ✿ In the mammalian skull the frontal and parietal bones between the temporal crests represent the original reptilian roof, while the zygomatic arches are remnants of the former lateral walls.
- ✿ From Romer (1977). *The Vertebrate Body*.

Development of the cranial vault



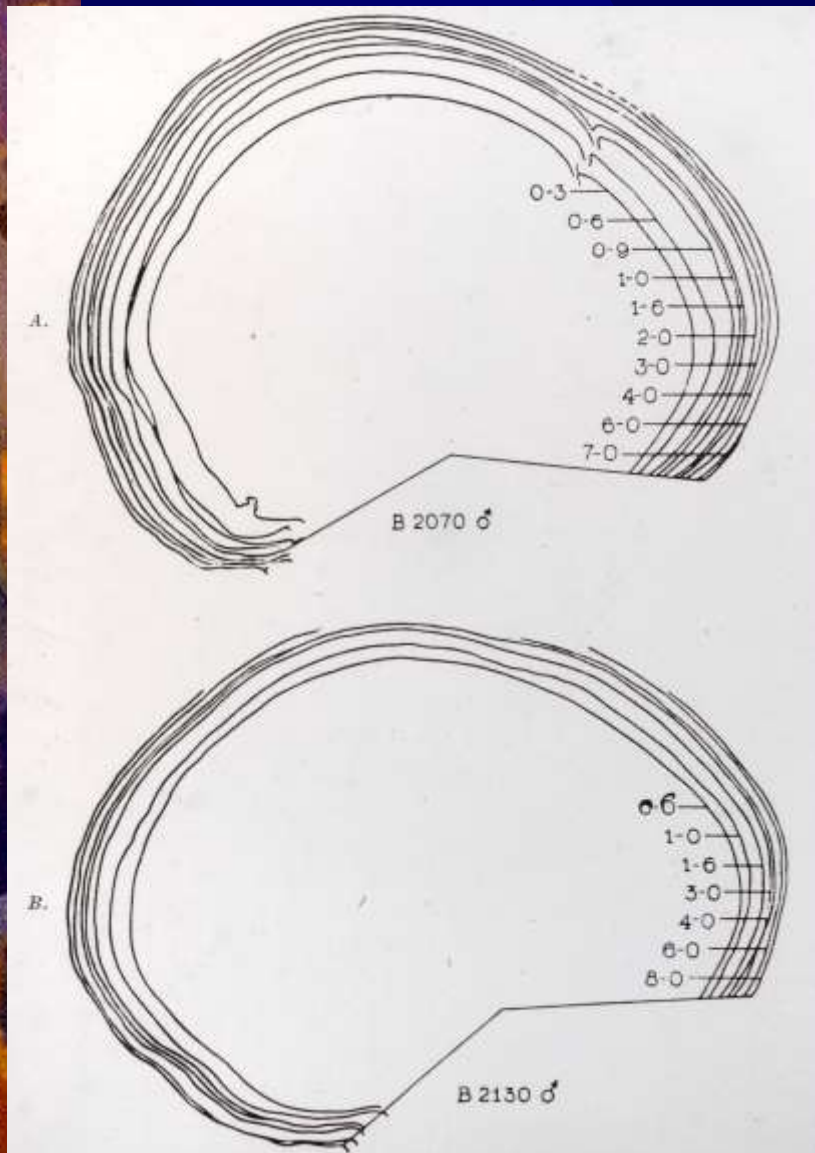
- ✿ The skull at birth showing the bones, sutures and fontanelles.
- ✿ The bones of the cranial vault develop from ossification centres at about 8 weeks *in utero*: one for each of the paired frontal bones, two for each of the paired parietal, temporal and occipital bones.
- ✿ Bone formation spreads outwards from these centres until the osteogenic fronts meet and cranial sutures are formed.
- ✿ From Meikle (2002), *Craniofacial Development, Growth and Evolution*.

The skull at birth



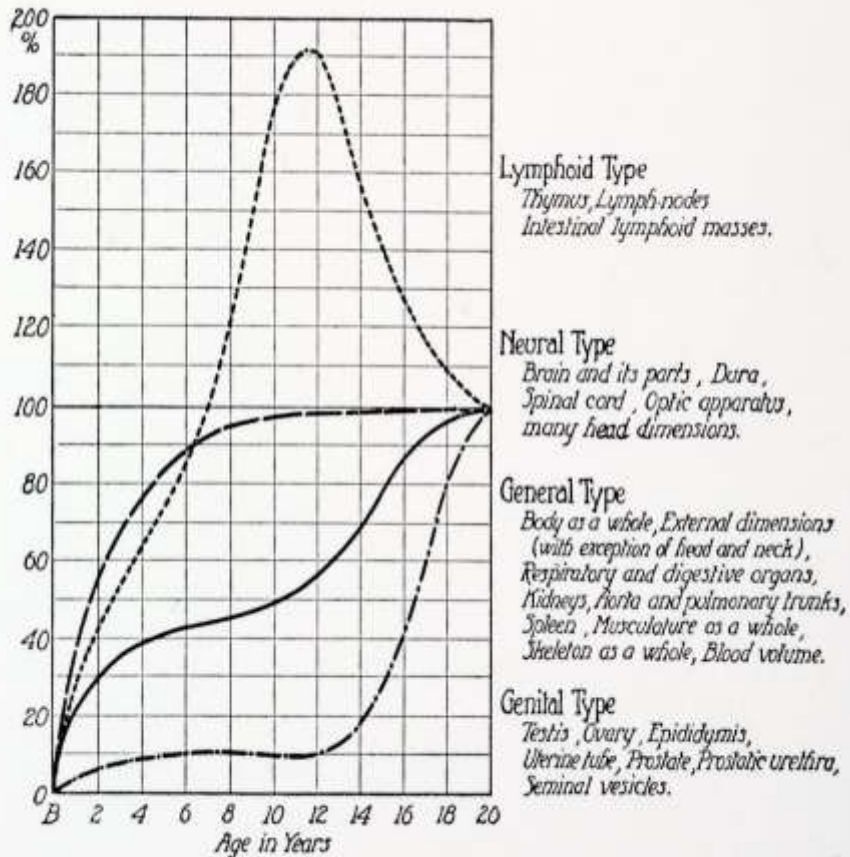
- ✿ The ratio of the neurocranium to the viscerocranium for the fetal skull is approximately 3:1 and for the adult skull roughly 1:1. The cranial vault has achieved more than 90% of adult size by the fifth year.
- ✿ The large diamond shaped fontanelle lying between the frontal bones (separated by the metopic suture) and the parietal bones (separated by the sagittal suture) – the anterior fontanelle is the last to close at about 18 months.

Growth and remodelling



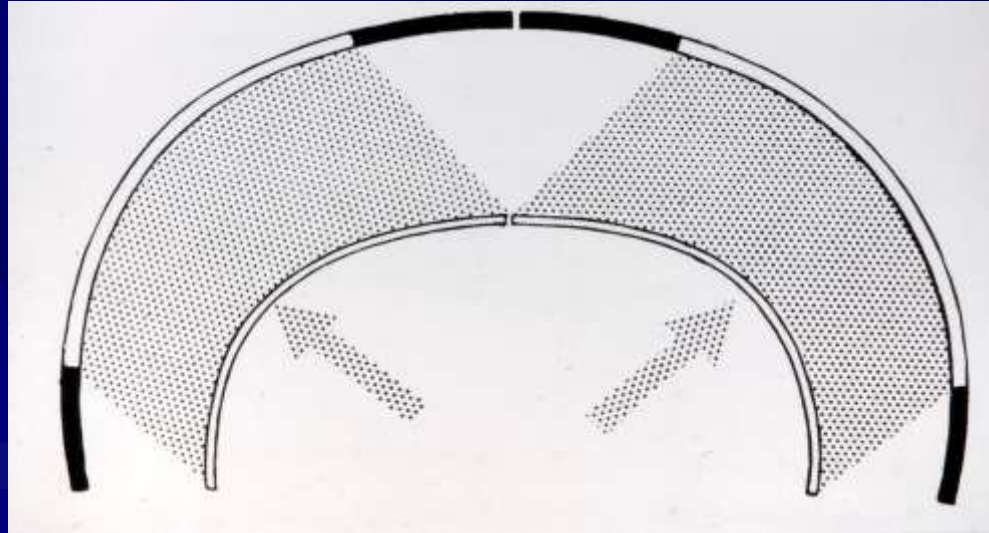
- The membranous neurocranium has achieved 25 percent of its growth at birth, 50 percent at 6 months and 75 percent at 2 years. In other words, it follows the neural growth curve in Scammon's famous illustration of 1930 shown next.
- These figures are from the first published longitudinal study of craniofacial growth using cephalometric radiography. They show growth increments of the cranial vault of two boys from 3 months to 7 years, and 6 months to 8 years of age.
- From Brodie (1941). *American Journal of Anatomy* 68, 209–262.

Growth curves of different tissues



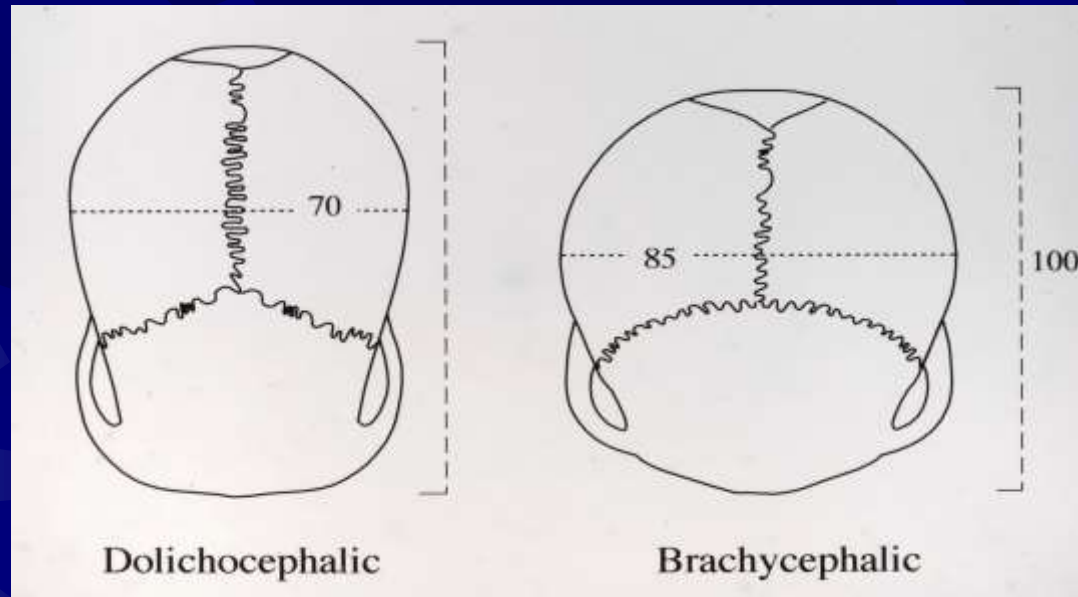
- Growth curves of the different parts and tissues of the body showing the four chief types.
- All the curves are of size attained and plotted as a percentage of total gain from birth to 20 years.
- The neural curve shows the early growth in the size of the brain and the dimensions of the cranial vault.
- From Scammon (1930). In: *The Measurement of Man*.

Growth of the cranial vault



- Growth of the cranial vault is co-ordinated with growth of the brain. As the bones (white) are carried passively outwards (stippled) by the growth of the brain, compensatory osteogenesis occurs at the calvarial sutures (black) to maintain structural integrity.
- As the brain grows the radius of curvature of the bones is increased, i.e. they become flatter. This accomplished by resorptive remodelling of the endocranial surface close to the sutural borders and deposition centrally, with concomitant deposition and resorption on the ectocranial surface.
- This well known figure from Moss (1962) in *Vistas in Orthodontics*, was used to illustrate the functional matrix hypothesis of craniofacial growth.

The cephalic index



- Heads vary in size and shape and when these variations are extreme, are regarded as deformities. A useful measure in clinical practice is the cephalic index (maximum width/maximum length x 100), originally devised by physical anthropologists to measure variation in head form.
- A skull is said to be brachycephalic when the cephalic index exceeds 80 and dolichocephalic when less than 75. Indices within the range 75–80 are said to be meso- or normocephalic.
- From Meikle (2002), *Craniofacial Development, Growth and Evolution*.

Craniosynostosis



- ✦ Craniosynostosis is the process of premature fusion of calvarial sutures, and the result is craniostenosis a term introduced by Virchow (1851) in his study of skull deformity. He observed that premature fusion of a suture resulted in compensatory overgrowth at the other sutures resulting in cranial malformation. Another legacy of Virchow is a complicated classification scheme based on the shape of the skull.
- ✦ This infant has trigonocephaly [Gr. *trigonos*, triangular] due to premature fusion of the metopic suture. Courtesy of R D Evans.

Plagiocephaly



- ✿ Craniosynostosis is a common developmental anomaly (1 in 2500 live births) and in the majority of cases occurs in patients with no other abnormalities.
- ✿ Isolated cases are rarely familial but when it does occur depends on the suture; isolated coronal synostosis is 14% and sagittal synostosis 6% familial. When isolated craniosynostosis is familial it is usually autosomal dominant with incomplete penetrance, meaning the trait can skip generations.
- ✿ CT scan of an infant with right-sided unilateral coronal synostosis. The result is plagiocephaly [Gr. *plagios*, oblique].
- ✿ Courtesy of W J C van Niekerk.

Syndromic craniosynostoses

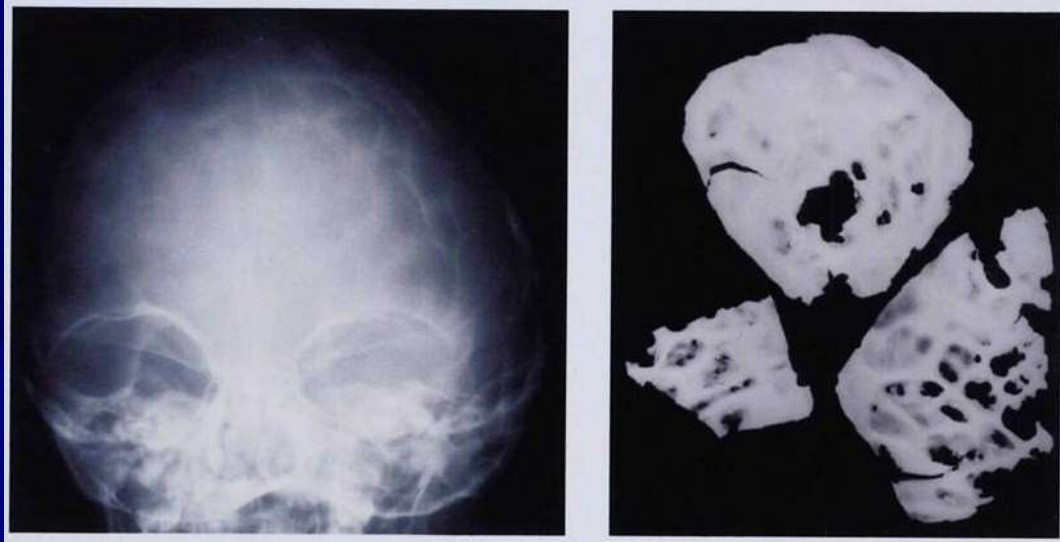
- More than 100 syndromes involving craniosynostosis are recognized (Winter and Baraitser, 1994), and several distinct forms are inherited in a Mendelian manner. Until recently, the delineation of such conditions has been purely phenotypic, producing an extensive literature on the unique and overlapping clinical features of each particular syndrome.
- The genetic basis of many of these conditions has now been established and shown to be associated with mutations in the *FGFR*, *MSX-2* and *TWIST* genes.
- The effect of these mutations is not confined to the cranial vault. The whole facial skeleton is distorted and there are many associated systemic effects; these include congenital heart disease, cleft palate, vertebral and renal anomalies.

Crouzon syndrome



- Crouzon syndrome (Crouzon, 1912) presents with varying degrees of craniosynostosis, midface hypoplasia and proptosis, but with normal limbs (radiography may reveal subtle limb defects). Occurs with a frequency of 1 in 25,000.
- The maxillary hypoplasia suggestive of faciostenosis results in hypertelorism and shallow orbits with consequent ocular proptosis, giving affected individuals a characteristic facial appearance.
- Maxillary hypoplasia results in relative mandibular prognathism; the palate is high-arched, short and sometimes cleft.
- Courtesy of R D Evans.

Crouzon syndrome



- ✦ Patients frequently develop raised intracranial pressure which may lead to papilloedema and visual failure necessitating surgery.
- ✦ Radiograph showing the “copper beaten” appearance of the skull characteristic of widespread craniosynostosis. Such convolitional markings result from the expansile growth of the brain in a skull leading to localized pressure and bone resorption.
- ✦ Bone specimens from a patient with clover-leaf deformity showing the scalloped appearance of the endocranial surface.
- ✦ Courtesy of W J C van Niekerk.

Acrocephalosyndactylies

- ✿ There are several craniosynostoses associated with syndactyly referred to collectively as the acrocephalosyndactylies. The group includes the Apert (1906), Pfeiffer (1964) and Jackson-Weiss (1976) syndromes.
- ✿ They share many of the craniofacial features of Crouzon syndrome, but are associated with specific digital abnormalities such as medially deviated toes and thumbs, with or without varying degrees of syndactyly (persistence of webbing or fusion) or brachydactyly (abnormal shortness) of other digits.

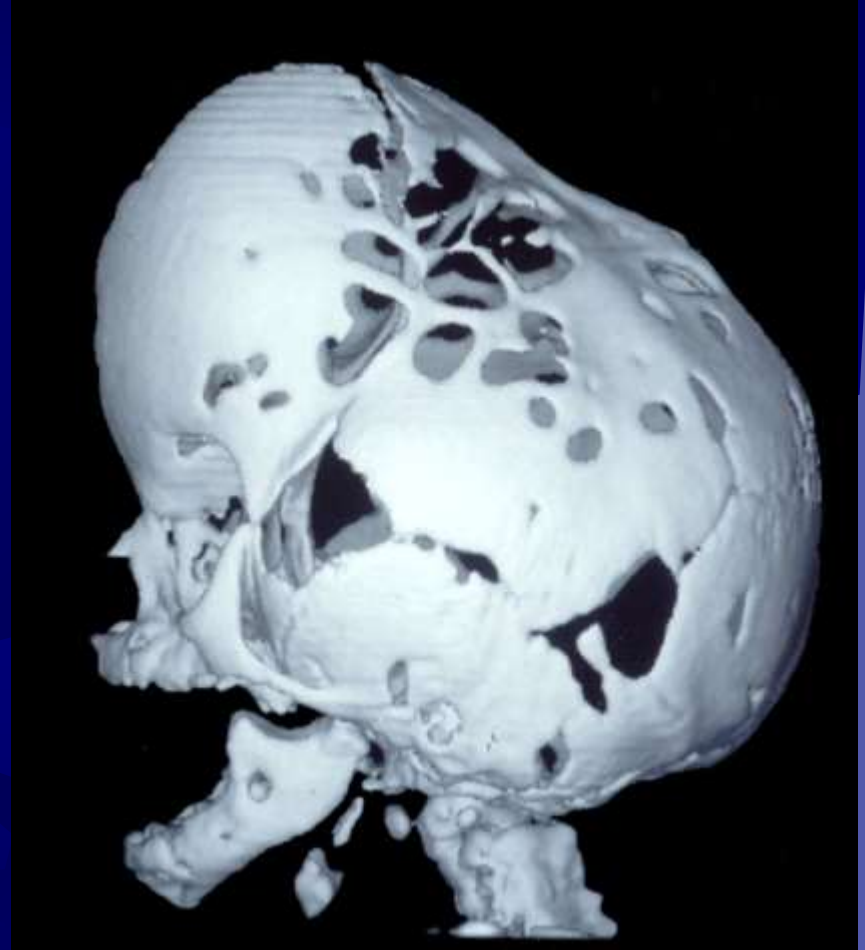
Apert syndrome



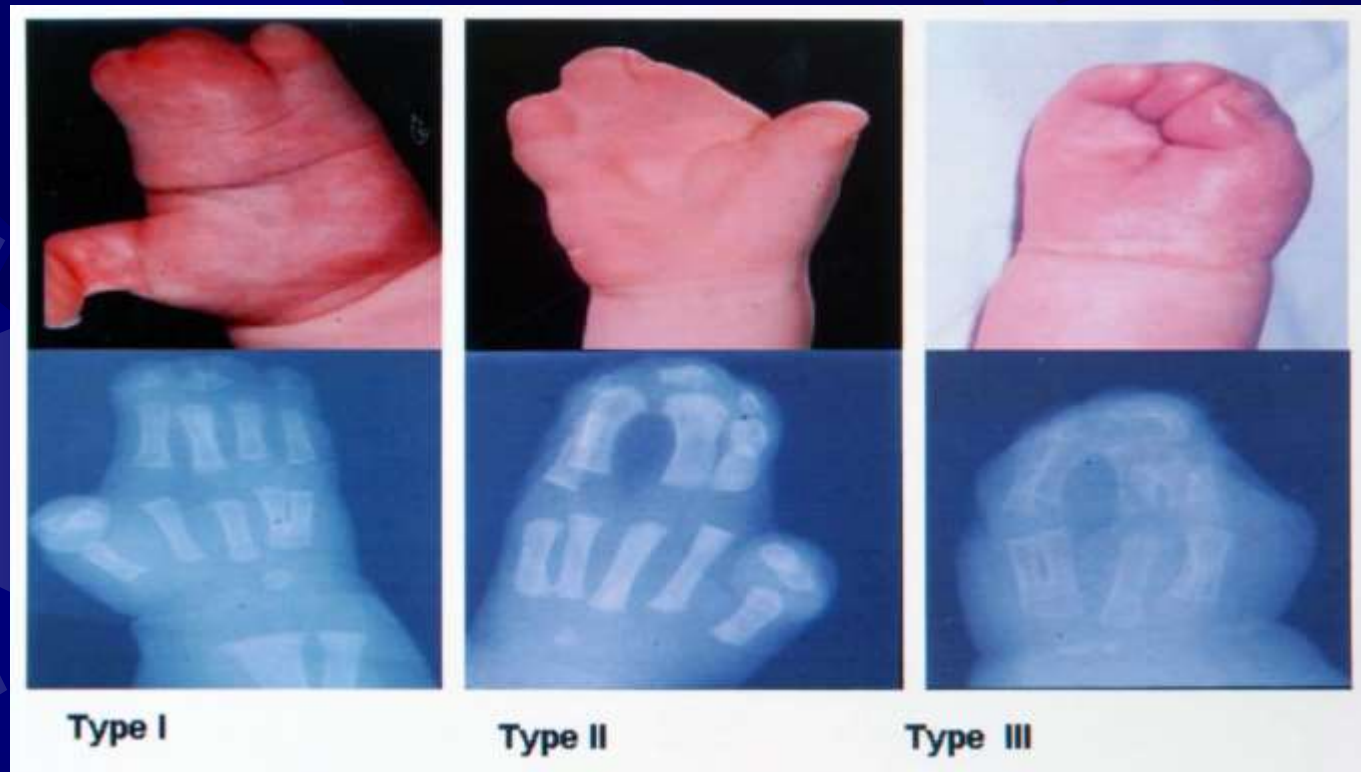
- ✦ In this patient with Apert syndrome, there is a slanting forehead with supraorbital retrusion and although not visible in these lateral views hypertelorism. The ears are set low and there is midface retrusion causing ocular proptosis and lagophthalmos (failure to close the upper eyelid). The hand displays a complex acrosyndactyly.
- ✦ Courtesy of J A Britto and R D Evans.

Apert syndrome

- CT reconstruction of the skull from a patient with Apert syndrome; The head is acrocephalic (turriccephalic) with a high forehead.
- The scan shows premature stenosis of the coronal and lambdoid sutures, plus numerous perforations in the calvarial bones. These perforations are developmental defects and not the result of raised intracranial pressure.
- Courtesy of R D Evans.



The Apert hand



- ✦ The Apert hand is characterized by acrosyndactyly. Metaphyseal fusions of metacarpals and distal phalanges are observed as well as soft tissue syndactyly; epiphyseal anomalies are common.
- ✦ From Britto *et al.* (2001), courtesy of J A Britto and R D Evans.

Pfeiffer syndrome



- Craniofacial features of the Pfeiffer syndrome include brachycephaly (turricephaly) with a high flat forehead, shortened cranial base and low set ears. The membrane bones of the midface are similarly synostosed, leading to maxillary hypoplasia and ocular proptosis. The orbits exhibit hypertelorism.
- Courtesy of J A Britto and R D Evans.

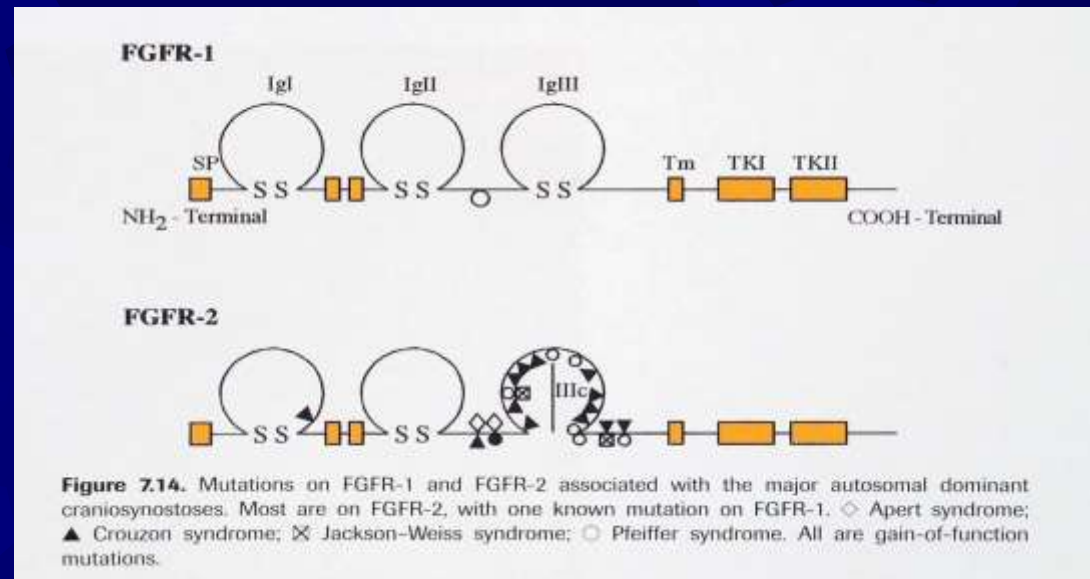
Cloverleaf skull deformity



- The cloverleaf skull deformity or *Kleeblattschädel* in this patient with Pfeiffer syndrome, describes the trilobar head seen from the front with frontal and temporal bulges; the abnormality results from multiple stenosis of the sagittal, lambdoid, coronal and temporal sutures.
- Courtesy of J A Britto and R D Evans.

FGF receptor mutations

From Meikle (2002),
*Craniofacial
Development, Growth
and Evolution.*



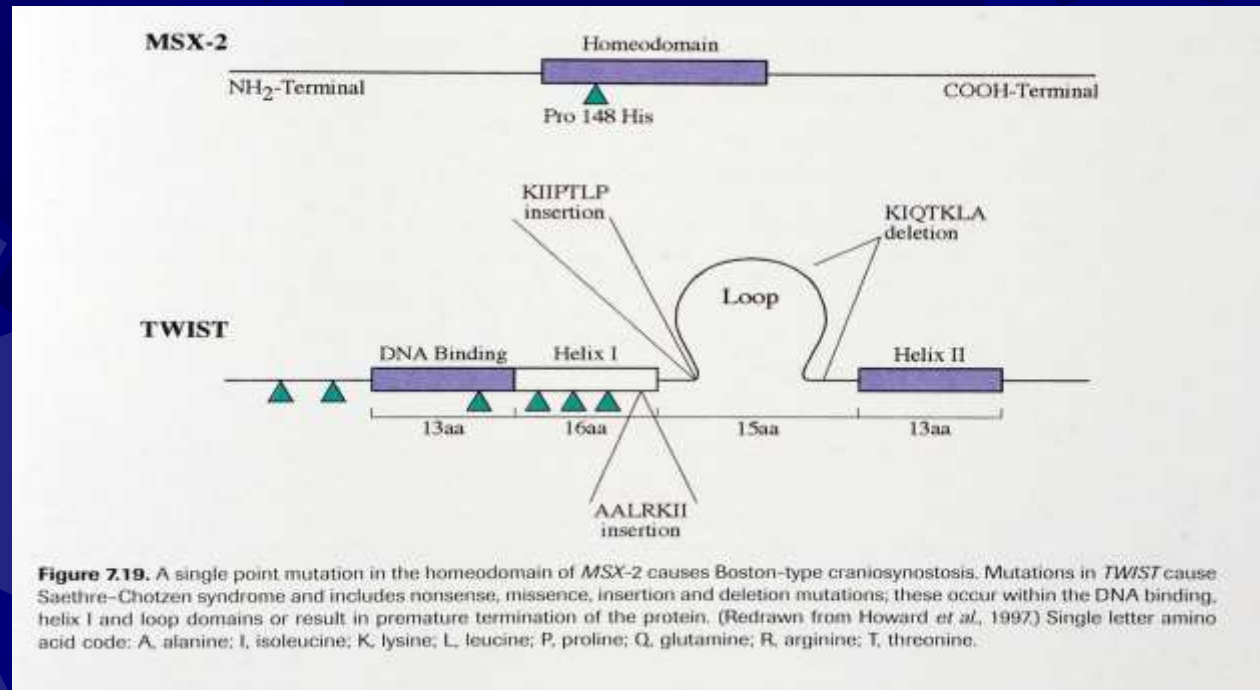
- Several autosomal dominant craniosynostoses are due to mutations in the fibroblast growth factor receptor *FGFR-2* gene on chromosome 10q25.3-q26. Most involve the immunoglobulin - Ig III domain and the regions linking the Ig II and Ig III domains, important for receptor binding.
- In some Crouzon patients the phenotype results from a Cys342Tyr substitution of the Ig III domain; cysteine replacement interferes with the tertiary structure of the receptor altering receptor binding with constitutive activation of tyrosine kinase, *i.e.* a gain-of-function mutation.

Saethre-Chotzen syndrome



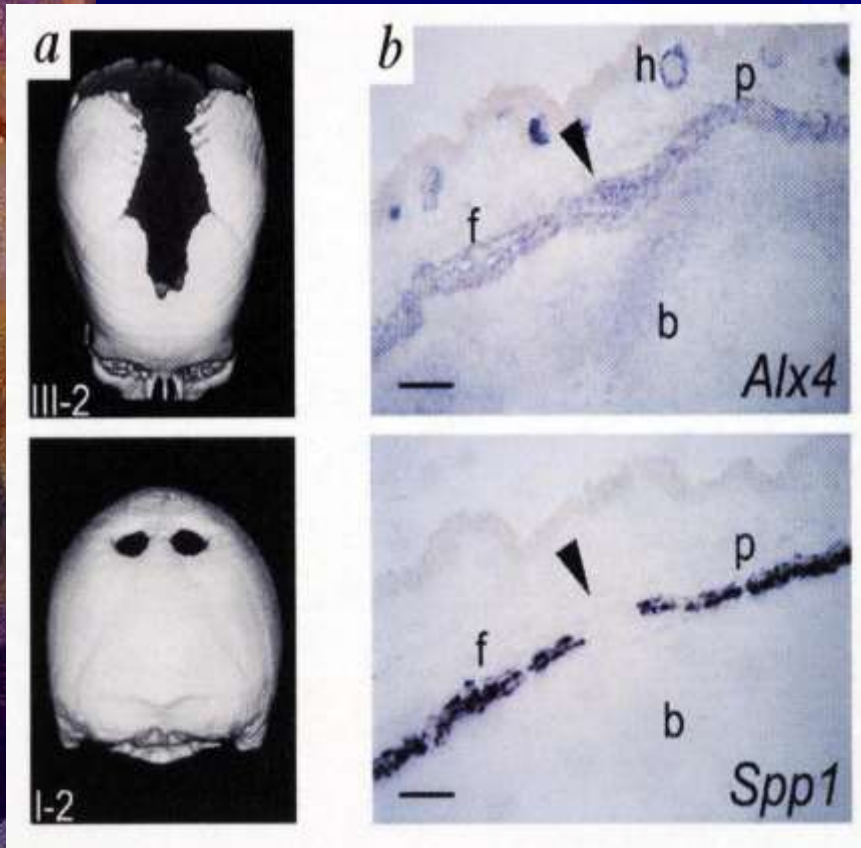
- ✿ This syndrome is an autosomal dominant combination of coronal synostosis with brachycephaly, facial abnormalities, limb abnormalities such as brachydactyly with variable soft tissue syndactyly. The prevalence is 1 in 25–50,000 live births.
- ✿ Facial dysmorphism in a patient with Saethre–Chotzen syndrome. She presents with maxillary hypoplasia, ptosis of the upper eyelids with an anti-mongoloid slope and small ears.
- ✿ Courtesy of R D Evans.

MSX-2 and TWIST mutations



- ☀ A gain-of-function mutation in the *MSX-2* gene results in Boston-type craniosynostosis. Loss-of-function *MSX-2* mutations have been shown to be associated with a different craniofacial phenotype called parietal foramina (see next slide).
- ☀ Saethre-Chotzen syndrome is due to mutations of the *TWIST* gene on chromosome 7p21-p22. *TWIST* mutations are largely loss-of-function (haploinsufficiency).

Parietal foramina

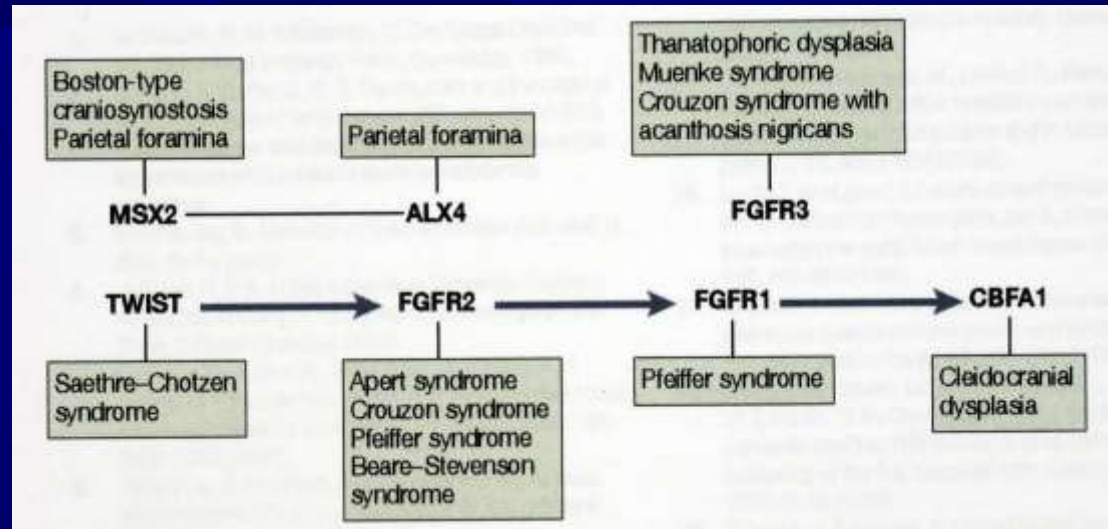


- The craniofacial phenotype parietal foramina is characterized by oval defects in the parietal bones and has been shown to be an allelic variant of the *MSX-2* gene (a loss-of-function mutation).
- Parietal foramina are also associated with heterozygous mutations (resulting in haploinsufficiency) of the *ALX-4* (*Aristaless homeobox-4*) gene on chromosome 11.
- The figures show CT scans of the human skull phenotypes associated with *ALX-4* mutations (a), and in (b) the expression of *Alx-4* and *Spp-1* in adjacent sections of the E16 mouse coronal suture.
- From Mavrogiannis *et al.* (2001). *Nature Genetics* 27, 17–18.



Molecular genetics of cranial suture development

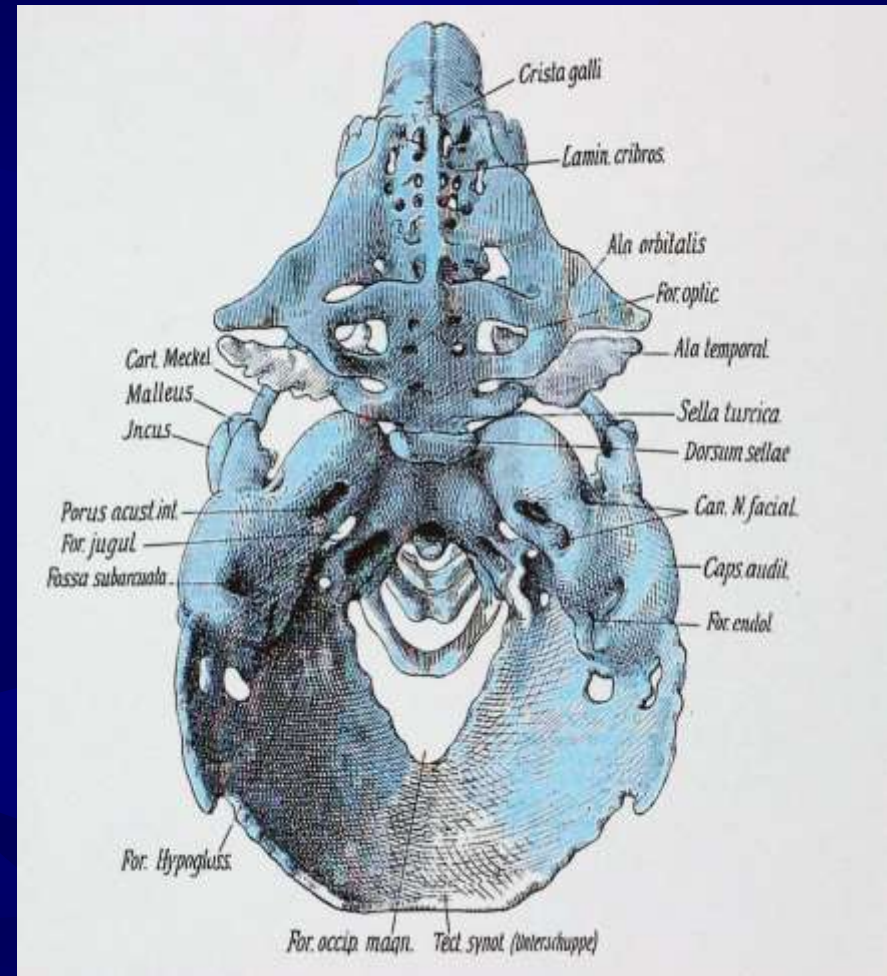
From Wilkie and Morriss-Kay
(2001. *Nature Reviews
Genetics* 2, 458–468.



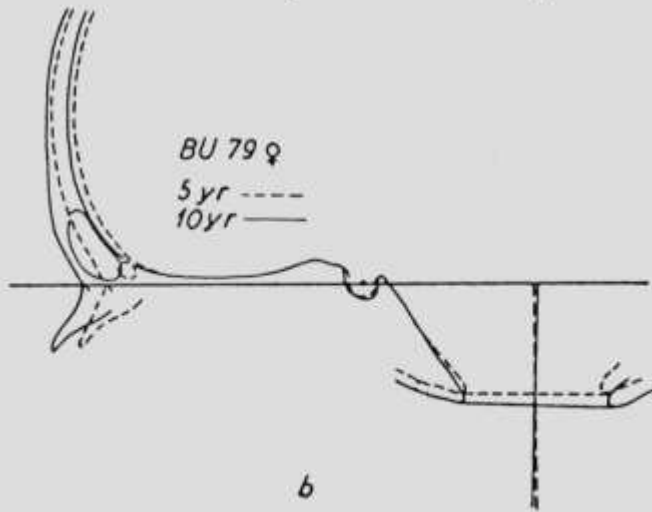
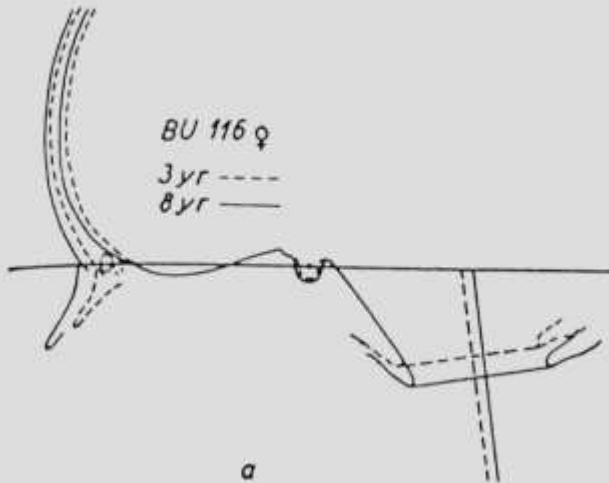
- ✪ The above pathways are based on human and mouse genetic evidence. Proteins are connected by solid arrows (pointing to the downstream target) according to whether the evidence for their placement in the pathway is strong or weak. The relationship of MSX-2, ALX-4 and FGFR-3 to the main pathway is uncertain.
- ✪ The boxes list the craniofacial disorders caused by mutations in the corresponding genes.

The chondrocranium

- In the mammalian skull, the chondrocranium is reduced to the cranial base and the otic and nasal capsules.
- This illustration is a model of the chondrocranium of a human embryo of 8 cm crown-rump length from the third month of pregnancy. The cartilage is blue.
- From Hertwig (1902). *Lehrbuch der Entwicklungsgeschichte des Menschen und der Wirbelthiere*.

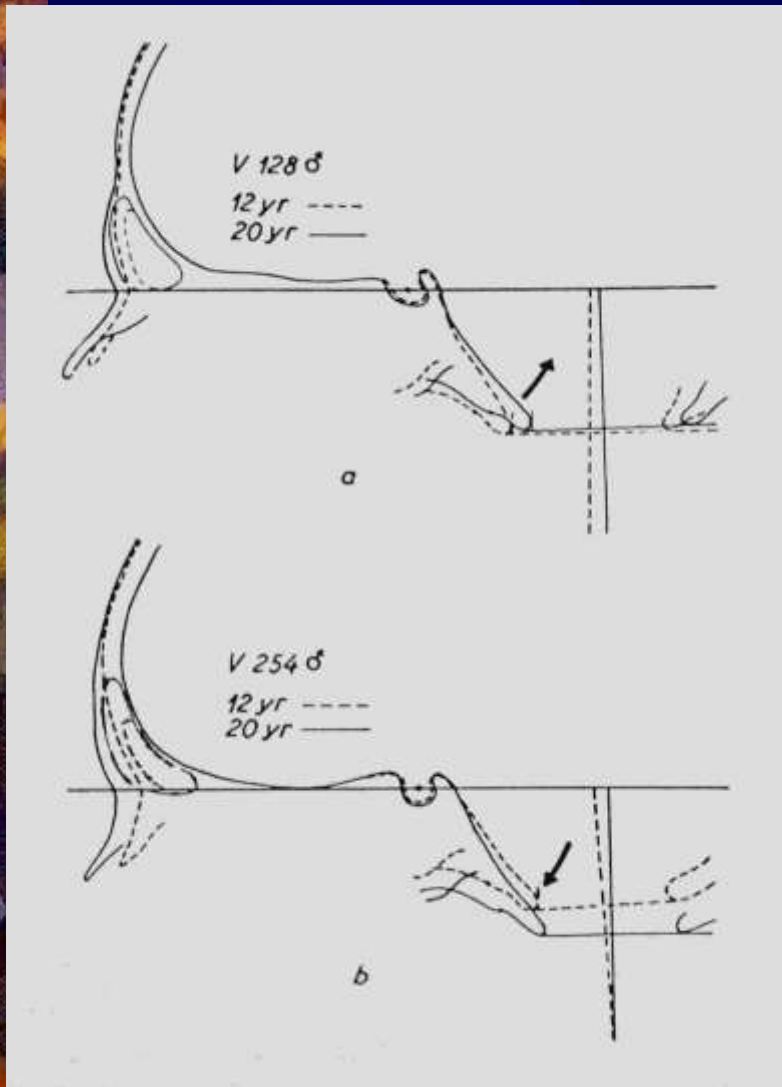


Growth pattern of the cranial base



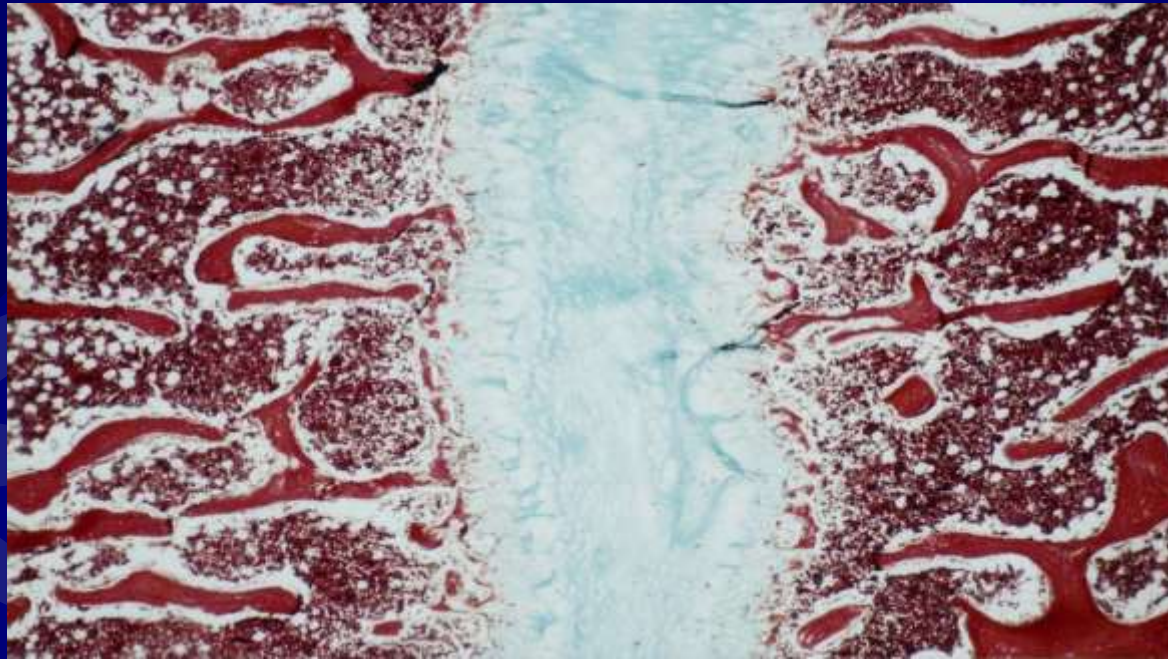
- The cranial base is important for two reasons: first, as a result of its influence on the growth of the middle third of the face and, second, as a reference area in cephalometry.
- Growth sites of the cranial base are: (1) foramen magnum (apposition at basion); (2) sphenoccipital synchondrosis; (3) sphenoccipital suture; (4) frontoethmoidal suture; (5) frontal bone (surface apposition). Enlargement of the anterior cranial fossa ceases around the age of 10. Increments in N-S are due to surface deposition at the frontal and nasal bones.
- From Björk (1955). *American Journal of Orthodontics* **41**, 198–225.

Variations in the growth pattern



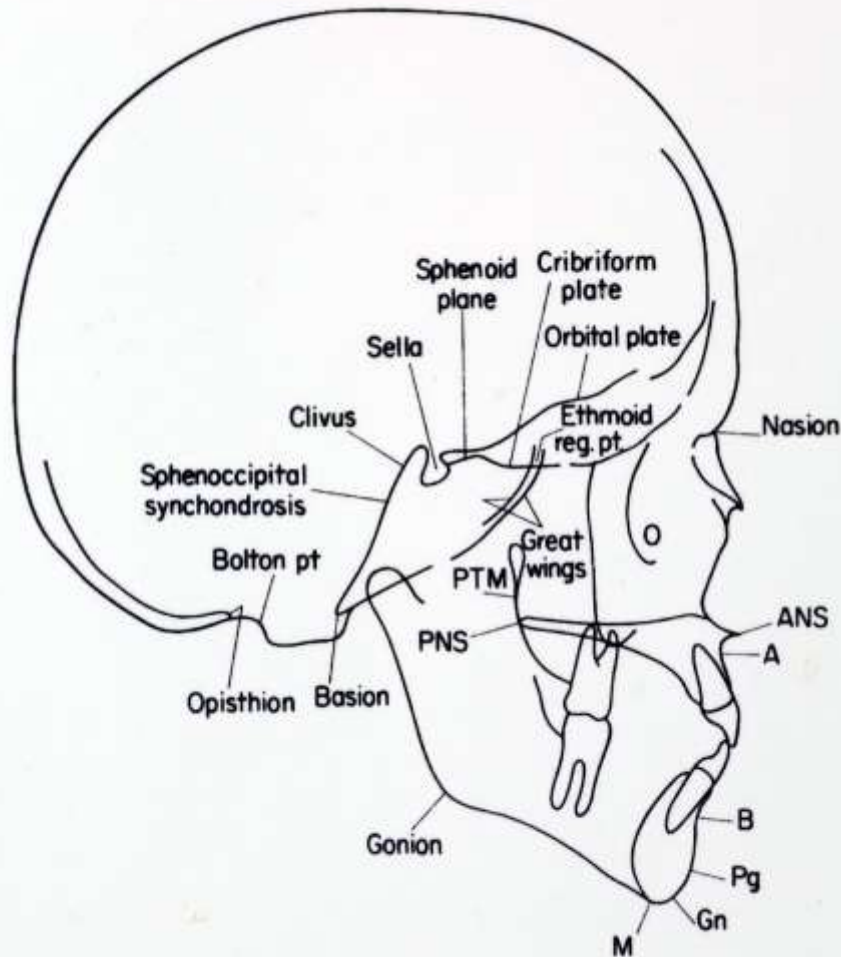
- Most cross-sectional studies have concluded that the cranial base angle (N–S–Ba) in man remains constant during postnatal growth.
- Individual variation does occur, however, as illustrated in two cases with (a) decreasing, and (b) increasing flexion of the cranial base angle during growth registered on the nasion–sella line.
- Björk also found that the anterior cranial base (N–S) increased on average 5mm due to surface deposition, and the posterior (S–Ba) by 4 mm due to growth at the sphenoccipital synchondrosis.
- From Björk (1955). *American Journal of Orthodontics* **41**, 198–225.

Spheno-occipital synchondrosis



- ✱ Spheno-occipital synchondrosis; human aged about 10 years. Structurally and functionally similar to the epiphyseal plates of long bones, but undergoes endochondral ossification on both surfaces.
- ✱ The SOS contributes to growth of the posterior cranial base until 15-17 years (males) and 13-15 years (females). However, contrary to earlier reports, there is no difference in the amount of growth at either the sphenoidal or occipital surfaces (Melsen, 1974). Original magnification x60.

Cephalometric radiography



- The most commonly used registration line in cephalometry is from sella to nasion. However, nasion is not a fixed point and moves upwards and forwards due to surface deposition and sutural growth. The sphenoid sinus also enlarges during growth; S–N will therefore give a slightly excessive estimate in vertical growth.
- To avoid such errors, de Coster (1951) suggested using the contour of the anterior cranial fossa; subsequently modified by adding the twin outlines of the greater wings of the sphenoid to form the ethmoid triad.
- Courtesy of A W Moore.

Achondroplasia



- Achondroplasia, the most common form of dwarfism is inherited as an autosomal dominant trait with 100% penetrance. The estimated frequency is 1: 26,000 and more than 80% of cases are sporadic; increased paternal age suggests that *de novo* mutations are paternal in origin.
- Characterized by a generalized defect in endochondral osteogenesis; the classical features include short limbs, lumbar lordosis, relative macrocephaly and underdevelopment of the middle third of the face due to impaired growth of the speno–occipital synchondrosis. Courtesy of R D Evans.

FGFR-3 mutations

From Meikle (2002),
*Craniofacial Development,
Growth and Evolution.*

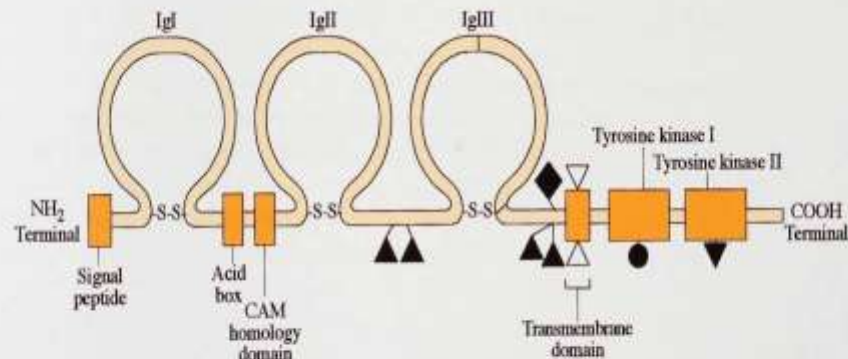
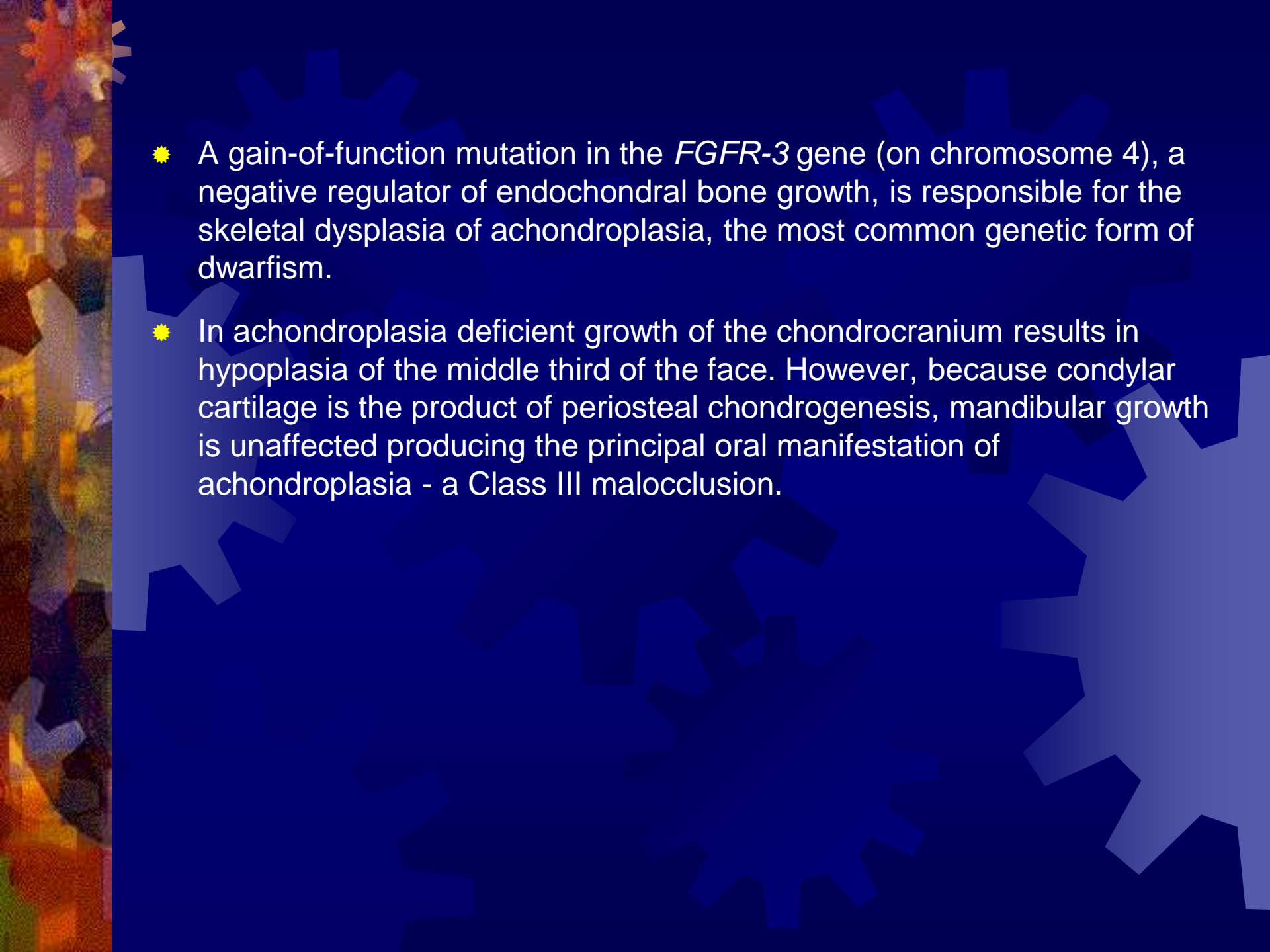


Figure 6.14. Diagrammatic representation of the structure of human growth factor receptor-3 (FGFR-3), showing positions of the mutations reported for the six known skeletal dysplasias. ▽ Achondroplasia; ● hypochoondroplasia; ▼ thanatophoric dysplasia type I and ▲ type II; △ Crouzon syndrome with acanthosis nigricans; ◆ Muenke-type craniosynostosis. See Table 6.2 for the exact positions of individual mutations.

- ☀ Achondroplasia is one of six known skeletal dysplasias resulting from dominant mutations in the *FGFR-3* gene. The clinical spectrum of these disorders ranges from mildly affected to embryonic lethality.
- ☀ Achondroplasia, hypochoondroplasia and the thanatophoric dysplasias are caused by abnormal endochondral ossification of the long bones and cranial base, resulting in short limbs and midface hypoplasia. In contrast, Crouzon syndrome with acanthosis nigricans, and Muenke-type craniosynostosis are characterized by abnormal osteogenesis and have craniosynostosis as their principal clinical feature.

Summary

- The growth of the cranial vault is co-ordinated with the growth of the brain. As the bones are carried passively outwards, compensatory osteogenesis occurs at the calvarial sutures to maintain structural integrity.
- Craniosynostosis, or premature fusion of one or more of the calvarial sutures, is the most common developmental anomaly (1 in 2500 live births) affecting the cranial vault.
- Several autosomal dominant craniosynostoses such as Crouzon, Apert, Jackson–Weiss and Pfeiffer syndromes have been shown to be due to gain-of-function mutations in the *FGFR-2* gene on chromosome 10.
- Mutations in the *MSX-2* (gain-of-function) and *TWIST* (loss-of-function) genes have been shown to cause Boston-type and Saethre-Chotzen syndromes respectively.

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- A gain-of-function mutation in the *FGFR-3* gene (on chromosome 4), a negative regulator of endochondral bone growth, is responsible for the skeletal dysplasia of achondroplasia, the most common genetic form of dwarfism.
 - In achondroplasia deficient growth of the chondrocranium results in hypoplasia of the middle third of the face. However, because condylar cartilage is the product of periosteal chondrogenesis, mandibular growth is unaffected producing the principal oral manifestation of achondroplasia - a Class III malocclusion.