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REVIEW

Cranial base in craniofacial development: Developmental features, influence on facial growth, anomaly, and molecular basis

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Abstract
The cranial base is of crucial importance in integrated craniofacial development. As distinct from facial bones, it is formed through endochondral ossification. The posterior and anterior cranial bases are derived from distinct embryologic origins and grow independently—the anterior cranial base solely from the neural crest, the posterior cranial base from the paraxial mesoderm. The anterior cranial base has more prolonged and active growth and exerts more influence on facial growth than does the posterior cranial base. Cranial base angulation is a unique feature in modern human beings. Cranial base anomalies have been identified in many genetic and developmental disorders. The molecular basis of cranial base development and growth is being clarified. In this review, these aspects of cranial base are discussed in detail, with a focus on developmental features, roles in craniofacial growth, anomalies, and the genetic basis of development.

Key Words: *Abnormalities, craniofacial development, genetics, skull base*

Introduction

The cranial base or basicranium, the ventral part of the cranium, is the most complex structure of the skeleton. Its main function is to protect and support the brain and to provide a platform for facial growth. Phylogenetically an ancient and conserved structure in the craniofacial skeleton, the cranial base has long been an interesting subject of research. In the past 50 years, extensive morphologic and developmental studies have been carried out on amphibia, birds, and mammals, including primates and human beings. This conserved structure has undergone evolutionary change that has endowed it with phylogenetic features. The most striking feature in the vertebra is the emergence of a neural crest integrated in the formation of the cranial base. The cranial base is therefore a key structure in ontogeny and phylogeny studies. The unique cranial base flexion in human beings and its pivotal position at the interface between the neurocranium and the face make it of particular interest to anthropologists as well.

The cranial base is important in integrated craniofacial development and growth—especially the anterior cranial base, which has direct connections with the upper-middle face and integrates with the facial elements into a growth complex (ethmomaxillary complex). Cranial base anomalies have been identified in human syndromes and developmental disorders such as Down's syndrome, Turner syndrome, craniosynostosis syndromes, cleidocranial dysplasia (CCD), cleft palate, and many others [1–11]. In some cases it has been proposed that the cranial base plays a primary role in leading to craniofacial anomaly [10].

The cranial base has distinct embryologic origins. The anterior cranial base is derived solely from the neural crest, similar to other facial bones, whereas the posterior cranial base is formed by the paraxial mesoderm [12,13]. Both these parts also develop and grow with distinct features. Unlike other craniofacial bones that are mostly formed through intramembranous ossification, the cranial base is formed through endochondral ossification, in which a cartilage plate, known as the chondrocranium, is formed first and soon replaced by bones. Individual bones are then connected by cartilaginous structures, termed synchondroses, which are morphologically similar to long bone growth plates. Even though the cranial base shares a common

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ossification mechanism with axis and appendicular bones, there are considerable differences in their development and growth regulations. In gross morphology, the cranial base is more like flat bones and indeed has more interaction with flat bones.

All those aspects make the cranial base an interesting and unique structure. However, its anatomic complexity and embryologic amalgamations make study of this structure a difficult task. Recently emerging molecular and imaging techniques have motivated new endeavors in cranial base research. In particular, the genetic approach provides much information about the molecular basis of development and disorders in the past decade. In this review, the above-mentioned aspects are discussed in detail, with a focus on advances in cranial base research.

Developmental features of the human cranial base

The cranial base is mainly a midline structure composed of basioccipital, sphenoid, ethmoid, and frontal bones in the midline and temporal bones laterally (Figure 1). The early embryologic precursor of the cranial base was a cartilaginous plate, also known as the chondrocranium, which was soon replaced by bones through endochondral ossification.

Fetal development of the cranial base

Initially, the cranial base was condensed as individual elements. The paired anlagen from caudal to rostral are sclerotome cartilages, parachordal cartilages (precursor of basioccipital), hypophyseal cartilages (precursor of basisphenoid), presphenoid (trabecular) cartilages, orbitosphenoid (precursor of less wing) and alisphenoid cartilages (precursor of great wing). In most, the front is a single mesethmoid cartilage.

These cartilages extend and fuse with each other. Cartilage structures that are similar to long bone growth plates, termed synchondroses, are developed connecting the cartilages and functioning as growth centers. Finally, the initially separate centers of cranial base chondrification fuse into a single, irregular and much-perforated base plate, which is the chondrocranium. The chondrocranium undergoes progressive ossification from caudal to rostral initiating from numerous ossification centers. However, large areas of the cranial base remain cartilaginous throughout early fetal life and many cartilages persist into the third trimester and postnatal life in humans [14–17].

The cranial synchondrosis

The synchondrosis is composed of well-organized cell bands. Morphologically, it is similar to the long bone growth plate except that it is bipolar, i.e. it looks like two growth plates sharing one common resting zone (Figure 2). From the middle to the distal ends, a resting zone, proliferation zones, and hypertrophic zones are distributed. The resting zone, homologous to the reserve zone of the growth plate, is composed of chondrocyte precursors which direct formation and organization of the synchondrosis [18]. The chondrocyte cycle is demonstrated through progressive differentiation from the resting zone to the hypertrophic zone.

Three synchondroses are present in the midline cranial base: spheno-occipital synchondrosis, midsphenoidal synchondrosis, and spheno-ethmoidal synchondrosis. In human beings, the sequence of synchondroseal fusions is: perinatal fusion of

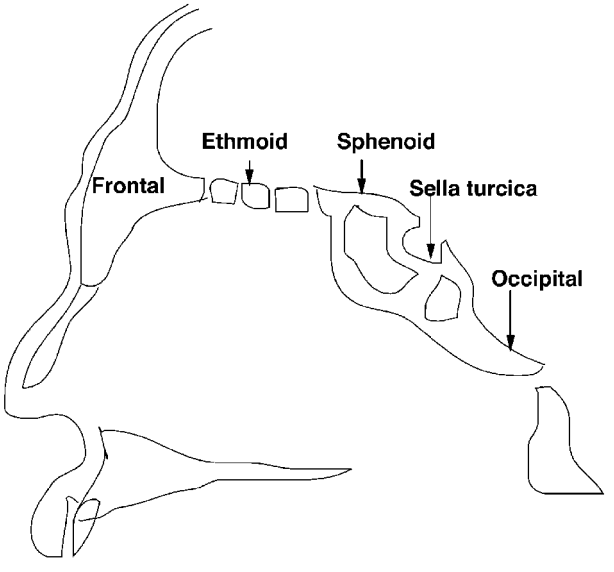

Figure 1. Diagrammatic representation of human cranial base in the sagittal midline. The cranial base is composed of basioccipital bone, sphenoid bone, ethmoid bone, and frontal bone in the midline.

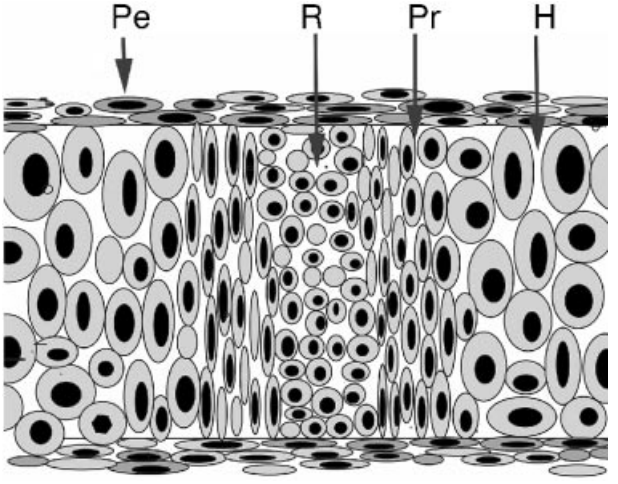

Figure 2. Diagrammatic illustration of cranial base synchondrosis. Cranial base synchondrosis consists of a common resting zone located in the middle region, two proliferation zones on its sides and next hypertrophic zones on its distal ends. R: resting zone; Pr: proliferation zone; H: hypertrophic zone; Pe: perichondral mesenchyme.

midsphenoidal synchondrosis, fusion of spheno-ethmoidal synchondrosis around the juvenile or adolescent, and fusion of the spheno-occipital synchondrosis [15]. The spheno-occipital synchondrosis is considered to be particularly important because of its late ossification and major contribution to postnatal cranial base growth. However, there are diverse results concerning the exact fusion time of this synchondrosis due to the uncertainty of radiography and tomography in determining the status of the synchondrosis. Dry skull inspection will ascertain whether the synchondrosis is fused; however, it is difficult to determine the exact chronological age. On investigating the human skull, Ford found that the sphenoid-occipital sychondrosis closes at the time of eruption of the 3rd molar; concurring with this, Melsen reported that closure occurs after eruption of all the canines, premolars, and 2nd molars [15,19]. By histological observation, Ingervall and Thilander demonstrated that the average age of closure in females is around 14 years; the corresponding age for males is 16 years [20]. Closure age determined by tomographic study, on the other hand, is 1 or 2 years younger than that of dry skull and histological observation [21].

Cranial base angulation

During the developmental process, the anterior and posterior cranial base flexes at the sella turcica in the middle sagittal plane and thus constitutes an angle in the cranial base, termed cranial base angle or saddle angle. Cranial base flexion is a unique cranial feature of modern human beings (Figure 3). Consequently, in modern human beings the petrous pyramids are oriented more coronal, the foramen magnum is positioned more inferiorly, and the posterior cranial fossa is deeper and wider.

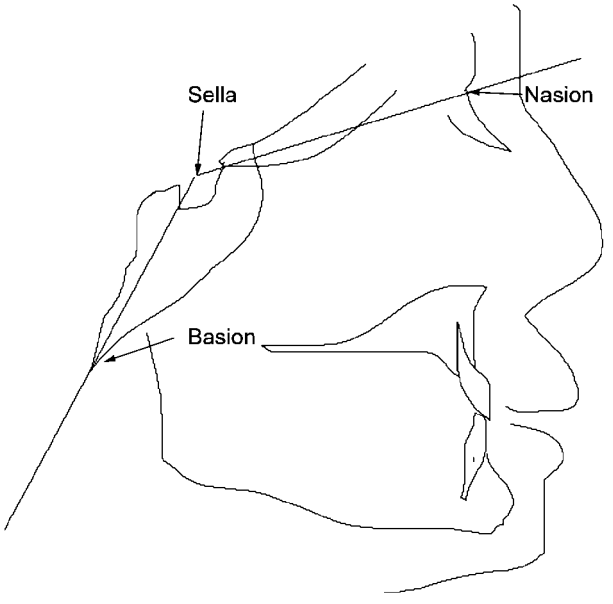

Figure 3. Diagrammatic illustration of the human cranial base angle. The anterior cranial base and posterior cranial base constitute an angle at the sella turcica, as illustrated by the Nasion-Sella-Basion (NSB) angle.

The angulation or flexion in the cranial base has been widely believed to be the consequence of gradual brain expansion during evolution. A well-known explanation of the high flexion in the human cranial base is the spatial-packing hypothesis, which proposes that cranial base flexion might be a result of an adaptive rearrangement of the skull to accommodate the successive phylogenetic increases in brain size. Consequently, base flexion and petrous reorientation are the solutions to the spatial-packing problem created by the phylogenetic increase of relative brain size. The spatial-packing hypotheses were substantiated by numerous studies and not supported by some others, because modern human beings having a less flexed basicranium than expected for their relative brain size [22–28].

In a similar well-known ontogenetic model, Enlow proposed that cranial base flexion during human prenatal and postnatal ontogeny is due to the increased brain growth relative to slower growth of the midline basicranium [29]. This hypothesis is supported by human fetal studies showing that growth along the cranial base is significantly slower than along other parts of the skull, and that fetal brain expansion is markedly rapid in the same period. However, this has been challenged in studies demonstrating that the cranial base retroflexes rather than flexes in this human fetal period [17,26,30].

So what are the major determinants? It seems that cranial base angulation is not determined simply by the size or pace of growth of the brain. An alternative explanation is that the cranial base is an intrinsic feature of the modern human being that is predominantly genetically determined.

The cranial base angle is measured by three points at the sagittal plane. One of the most commonly used methods is to measure the nasion-sella-basion angle (Figure 3). However, the conventional sella-nasion plane is problematic in that the nasion is located in the facial structure and moves relative to the cranial base throughout the period of facial growth [31]. Therefore, the nasion is not a fixed point in cephalometric analysis. However, satisfactory results can be obtained by using the nasion-sella line, because both nasion and sella rise in relation to the cribriform plane that maintains the nasion-sella line still relatively parallel to the cribriform plane. An alternative is the cribriform plane, which does not change from 3 years onwards [15,32]. Many researchers also define the prechordal plane using the planum sphenoideum, which extends from the sphenoidal to the planum sphenoideum point [33].

This angulation further influences craniofacial dimension. As discussed below, there have been extensive studies examining the relationship between cranial base angles and dentofacial complex.

Differential growth between the anterior base and the posterior cranial base

It has long been observed that growth of the cranial base is not homogeneous. Growth of its elements follows either the pattern of the skeleton or the neural [34]. Further studies show that the anterior and posterior parts of the cranial base, demarcated by the sella turcica, grow at different paces. Growth of the posterior cranial base is far slower than that of the anterior cranial base. Linear growth of the anterior cranial base is approximately twice that of the posterior skull base [15,16,30,35–37]. Growth of the anterior cranial base has even been found in adulthood [38]. This discrepancy arises due to the early ossification and maturation of the posterior cranial base. In contrast, the anterior cranial base ossifies much later. The cribriform plate completes its growth at the end of the second year postnatally [15]. Thereafter, growth of the anterior cranial base takes place in the sphenoethmoidal synchondrosis and the cartilage between mesethmoid and frontal bones as long as the cartilage persists. During adolescence and onwards, the enlargement of frontal and ethmoid bones through a mode of periosteal growth due to increased pneumatization contributes predominantly to the rest of the growth [15,34]. The active and prolonged growth of the anterior cranial base is consistent with that of the upper-middle face and essential for integrated craniofacial growth. This independent growth also reflects their distinct embryologic origins.

Dual embryologic origins of the cranial base

Facial bones and the cranial vault are mostly of neural crest origin. However, the cranial base is derived from distinct embryologic origins. The chondrocranial precursors anterior to the notochord are formed through neural crest migration, while the posterior precursors are derived from the paraxial mesoderm similar to the vertebra [12,13]. Using the quail-chick chimera technique, Couly demonstrated that the chondrocranium included elements that originated from the mesoderm and others from the neural crest [12]. He further stated that the occipital bone as a whole could be considered as a giant vertebra enlarged to support the brain [12]. The middle of the basisphenoid body marks the division between the anterior base and posterior cranial base of distinct originations. This bone therefore crosses the limit between the chordal and the prechordal chondrocranium. The anterior limit of the notochord then corresponds to the limit where the mesoderm skeleton ends and the neural crest derived skeleton begins.

More recently, this finding has been further corroborated by the use of genetically modified mice. Sox9 is an essential transcriptor for chondrogenesis. Conditioned knockout of this gene in the murine neural crest results in absence of cartilage formation of neural crest origin [39]. In such mice, the occipital bone derived from the mesoderm develops normally, but the sphenoid bone originating from the neural crest is missing. Thus, the chordal cranial base, more like an enlarged vertebra, is postulated to be the ancient and conserved cranial floor in phylogeny, whereas the prechordal cranial base, derived from the neural crest, is postulated to be phylogenetically a new portion and is regarded as part of the new head [12,40].

Cranial base in integrated growth of craniofacial structures

As the interface between brain and face, the cranial base has long been suggested as a key structure in integrating craniofacial growth. First, development and growth of the cranial base is regulated by that of the brain. Since the growth of the cranium is to accommodate the expanding brain, it is reasonable to believe that development of the brain controls the growth rate, final size, and shape of the cranium. As mentioned above, the relationship between brain and cranial base morphogenesis has been investigated extensively [22–28]. Even though the cranial base flexion cannot be satisfactorily explained by brain size and pace of growth alone, there is still general agreement on the significant influence of the brain on development of the cranial base.

How the expanding brain regulates the development of the cranium is not completely known. A possible mechanism is through the dura mater. It has been showed that the dura mater plays an important role in regulating cranial vault sutures [41,42]; similarly, it may regulate the cranial base synchondrosis. During development, many developmental genes are continuously expressed in the dura mater [41,42]. When the brain expands it therefore presses the dura mater into direct contact with the cranium, thus triggering the growth signal pathway of the cranium. The mechanical force itself is a stimulating factor to growth of the cranial base, as demonstrated in animals [43,44].

The cranial base, on the other hand, exerts considerable influence on facial growth, and plays an integrated role in coordinated craniofacial growth. In this aspect, the anterior cranial base is more important than the posterior cranial base. It has direct connection with the upper-middle face and integrates with the upper-middle face into a growth complex (ethmomaxillary complex). During its longitude growth, it carries the upper-middle face forward, inferiorly and laterally. Deficiency in the anterior cranial base growth is often accompanied by midfacial deficiency [45–50]. The mandible, articulating with the posterior cranial base, is influenced mainly by that; variations in length and inclination of the posterior cranial base affect mandible position and are related to prognathism [49–52].

Cranial base angle and length have been proposed as key factors in influencing the face projection. Facial retraction in modern humans compared to other

primates might be the result of cranial base flexion [53]. Conversely, the cranial base is under the influence of facial structures and the cranial vault, but to a far less extent.

Cranial base and dentofacial complex

Many authors have argued about the relationship between the cranial base and dentofacial features [51,54–62]. The maxillary and mandible articulate with different parts of the cranial base and therefore variations in growth and orientation of the cranial base may lead to differential movement of the position of the jaws and thus also influence the occlusion. Bjork, using cepholometric radiographs, demonstrated the existence of a relationship between cranial base morphology and jaw position [34]. Later, the relationship of the cranial base with jaw position and classification of malocclusion has been examined extensively. Cranial base variations have been identified in class I to class III subjects [51,54–62]. In class II malocclusion, subjects tend to have open cranial base angles, whereas in class I and class III malocclusion, subjects tend to have smaller angles [50,57]. In class III malocclusion, major changes have been identified at the posterior cranial base [51,55,62]. However, in many studies the etiological relationship between cranial base flexion and types of malocclusion is not supported [51,54,55,59–62]. It therefore appears that the cranial base angle is not a pivotal factor in determining malocclusion. But those results do imply that length and inclination of the cranial base are controlling factors of jaw position. Abnormalities of the posterior cranial base are more related to mandibular prognathism, and those of the anterior cranial base to retrusive maxilla.

The relationship between non-syndromatic facial retrognathia and the cranial base needs further clarification. Recently, sphenoethmoidal complex has been suggested as a mechanism of midfacial retrognathism [61]. Abnormal growth in the presphenoid component was detected in a mouse model for midfacial retrognathia (3H1 Br/+) [63]. In a further investigation testing responsiveness to epithelial growth factor, these researchers demonstrated that there is a primary growth defect in the sphenoethmoidal region [64]. It therefore seems that the intrinsic growth defect of the cranial base is the primary cause of facial retrognathia in some cases.

Cranial base anomalies in human beings

The cranial base appears to be strongly genetically determined and subject to minimal environmental influence. Therefore, cranial base anomaly occurs less than that of the intramembranous bones. The anterior cranial base, the relatively new part of the cranial base in evolution, is more often affected than the posterior part.

Cranial base anomalies have been identified in human syndromes, craniosynostosis, CCD, cleft palate, and many other pathologic conditions (Table I). In anencephaly, a lethal condition due to failure to close the anterior neural tube during development and in many cases with notochordal anomalies, the chondrocranium is characterized by a short and narrow basioccipital bone [65]. In microcephaly, reduced size of the brain is accompanied by a change in the remodeling pattern of the internal and external surfaces of the cranial base, leading to flattening and shortening of the cranial base [66,67]. In hydrocephalics, the cranial base angle is obtuse and changes markedly during shunt treatment [68,69]. The cranial base is even more flexed than normal subjects following the treatment; the sella turcica also becomes shallow and "J" shaped [68,69]. In achondroplasia, the cranial base is characterized by a striking shortening of the posterior part and an acute cranial base angle [34,70]. In the anterior cranial base, even though the general length is normal, the cribriform plate length is reduced and compensated by overgrowth of the presphenoid bone [70]. In CCD, the most significant findings include delayed ossification, distortion of the clivus and foramen magnum [7–9,71]. In Cretinism syndrome, Turner syndrome [45,47,48,72] and Down's syndrome [73], the craniofacial structure is characterized by a short retrognathic face due to reduced cranial base length and increased angulation. In Klinefelter syndrome and Williams syndrome, the major craniofacial changes are located in the cranial base [74,75].

Cranial base anomalies identified in craniosynostosis syndromes or non-syndromatic craniosynostosis are generally believed to be the secondary changes following abnormal growth of the cranial vault. However, in some cases it seems that anterior cranial base abnormalities in the embryo stage play a primary role leading to craniofacial deformities [10]. Some even suggest that primary malformations of cranial base cartilage cause craniosynostosis secondarily. Animal experiment with rabbits also imply that cranial base fusion alone may account for many of the dysmorphic features seen in craniofacial synostosis and confirms both a primary directive and translational role of the cranial base in craniofacial growth [76]. Also, in a rabbit model for familial coronal suture synostosis, suturectomy did not normalize cranial base growth pattern due to possible primary malformations in the cranial base [77,78]. Thus, it seems that in some cases the craniofacial malformations are caused by primary anomalies of the cranial base.

The relationship between cleft palate and cranial base anomaly has been extensively investigated. In complete clefts of lip and palate (CLP), cranial base deviations in dimension and shape have been described [5,6,79,80]. The data indicate that cleft lip and palate is not an isolated malformation localized to the jaws, but a malformation also involving the cartilaginous cranial base.

Table I. Cranial base anomalies in human beings

Diseases and OMIM number	Mutated genes	Craniofacial features	Cranial base anomalies
Boston type craniosynostosis, #604757	MSX2, 5q34–q35	Forehead retrusion, frontal bossing, turribrachycephaly, and the Kleeblattschaedel deformity (cloverleaf skull anomaly; trilobular skull with craniosynostosis)	Shortening of anterior cranial base
Apert syndrome, #101200	FGFR2, 10q26	Craniosynostosis, midface malformation	Malformed often asymmetric short anterior cranial base
Cleidocranial dysplasia (CCD), #119600	CBFA1, 6p21	Delayed closure of fontanelles and sutures, midface hypoplasia, delayed union of mandibular symphysis, unrupted or supernumery teeth	Severely retarded ossification of cranial base, distorted clivus, and foramen magnus
Pfeiffer syndrome, #101600	FGFR1, 10q26	Craniosynostosis, midface hypoplasia	Shortening of anterior cranial base
Saethre-Chotzen, #101400	FGFR2, FGFR3	Craniosynostosis	Shortening of posterior cranial base
Thanatophoric dysplasia (TD), #187600	FGFR3, 4p16.3	Megalocephaly or craniosynostosis	Severe shortening of cranial base due to prematurely fused synchondrosis
Crouzon syndrome, #123500	FGFR2, 10q26	Craniosynostosis, midface hypoplasia	Short anterior and posterior cranial base, prematurely fused synchondroses
Achondroplasia (ACH), #100800	FGFR3, 4p16.3	Macrocephaly, frontal bossing, nasal bone short and depressed	Cribriform plate length reduced, anterior sphenoid length increased, posterior cranial base length greatly reduced, cranial base angle reduced, spheno-occipital synchondrosis prematurely fused
Campomelic dysplasia (CD), #114290	SOX9	Micrognathia, cleft palate	Small chondrocranium and the disproportionately large neurocranium
Turner syndrome	X chromosome	Short stature and maxillary retrognathism	Short posterior cranial base and increased cranial base angle
Down syndrome, #190685	Xp11.23, 21q22.3, 1q43	Mental retardation, retrognathic face	Short anterior cranial base
Cohen syndrome, #216550	8q22–q23	Mental retardation, microcephaly, short philtrum, forward-inclined upper incisors and maxillary prognathia	Short cranial base, but normal cranial base angle
Klinefelter syndrome	47, XXY	The length of the maxillary base was greater and more prognathic. The mandible was longer and more prognathic	Variations of cranial base dimension and cranial base angle
Williams syndrome, #194050	7q11.2	Retrognathic or micrognathic mandible	Short anterior cranial base

OMIM = Online Mendelian inheritance in man.

Endocrine and mechanical regulation of cranial base growth

The independent growth between the chordal and prechordal cranial base and the different fusion time of synchondroses suggest that there are multiple regulation mechanisms for development and growth of the cranial base.

First, growth of the cranial base, like other primary cartilage sites, is subject to systematic factors and, more specifically, to the hormones. Pubertal growth in the cranial base and the ensuing fusion of sphenoid-occipital synchondrosis indicate a systematic control of this structure in humans [81]. Early closure of other synchondroses demonstrates a complicated regulation mechanism in the cranial base coupled with systematic and local factors.

Patients with growth hormone (GH) deficiency show an abnormal sphenoid bone and cranial base angle indicating the influence of GH on growth of the cranial base [82]. However, GH therapy to patients with Turner's syndrome and growth retardation had only a minor effect on the dimension of the cranial base, but an obvious effect on mandible growth [83,84]. This was probably due to the fact that development of the cranial base is completed at a relatively early stage. A low dose of testosterone greatly improved the craniofacial dimension including the cranial base shortening in boys of delayed puberty, suggesting an important role of this hormone in regulating cranial base growth [85].

Secondly, the cranial base is also under mechanical influence from surrounding structures. Mechanical stress exerted *in vivo* increases chondrocyte

proliferation in rabbit synchondrosis [43,44]. Mechanical expansion of the anterior cranial base performed on rabbits indicates that cranial base sychondrosis growth can be manipulated mechanically and that growth changes can be attained secondarily in the cranial vault skeleton [86].

Genetic approach in deciphering cranial base development and growth

As has been suggested, development of the cranial base might be determined more by genetics than by related structures. The genetic approach is essential in elucidating the mechanism of its development and clarifies its role in craniofacial development and human disorders. Moreover, genetic information also provides a basis for comparative analysis among different species and further clarifies its evolutionary changes. Identification of the unique signal pathway or signal pathway uniqueness in the cranial base would be informative for our understanding of its developmental features. The specificities of its signaling most likely exist at patterning and early developmental stages. The anterior and posterior cranial bases are patterned differently and hence might have different genetic control in future development.

The use of genetically modified mice has provided much information about some of the most crucial signal pathways, such as Bmp, Fgf/Fgfr, Shh, Sox9 families, which have all turned out to be essential for cranial base development [39,87–92]. The effect of the Bmp signal pathway on the regulation of synchondrosis was specifically analyzed using an organ culture system [93]. Synchondroses were cultured as explants in the presence of Bmp4, which promoted cartilage growth by stimulating chondrocyte proliferation and matrix deposition in a dose-dependent manner. Fgfr expressions have been analyzed in developing mouse cranial base at specific stages [91,94]. Transcripts of Fgfr1 and Fgfr2 are both localized in the perichondrium and periosteum; Fgfr3 is expressed at proliferation chondrocytes of the sychondroses [91,94].

The role of hyaluronan on cranial base expansion was specifically investigated in the cranial base as well. It is required to mediate the expansion of lacunae in the hypertrophic zones of the synchondroses and in doing so plays an important part in the expansion of the cranial base [95].

PTHrP (parathyroid hormone-related peptide) inhibits chondrocyte differentiation and in doing so regulates the pace of skeleton growth in the developing limb. It might also play a role in governing the distinct differentiation pace between the anterior and posterior cranial base. In PthrP null mutant mice, accelerated chondrocyte differentiation and endochondral ossification were observed in the posterior part of the anterior cranial base, and the major part of the anterior cranial base appeared to be normal [96]. Therefore, PTHrP is not the only gene regulating the pace of development of the anterior cranial base.

Compared to other sites, investigation of the genetic basis of the cranial base has just started. More work directly targeting the cranial base needs to be done to unravel the molecular cascade at this site. However, those limited results do provide convincing evidence of the role of the cranial base in human disorders in which the cranial base is also affected. For example, in Apert, Crouzon, and Pfeiffer syndromes, caused by mutations of FGFR1 or FGFR2, anomalies in the cranial base appear to be primary affections indicated by genetic information. These two genes are crucial for proper development of the cranial base; their mutations will simultaneously affect development of the cranial base as evidenced by the generation of Fgfr2c knockout mice in which both the cranial vault and base show simultaneous deformities [91]. In the Boston syndrome, caused by MSX2 mutations, the changes in the cranial base are probably secondary to abnormal growth of the cranial vault, because MSX2 does not play any significant role in cranial base development implied by knockout mice [97].

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