Relationship of Premaxillary Bone and Its Sutures to Deciduous Dentition in Nonhuman Primates

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Objective: **The relationship of the human premaxillary bone (Pmx) to neighboring craniofacial structures is clouded by its embryonic union with the maxillary bone proper. Only humans among all primates have such early fusion of the premaxillomaxillary suture (PS). This study surveyed the relationship of the PS to the upper deciduous dentition in nonhuman primates, and describes the distribution of bone cells along the osseous margins of the Pmx.**

Method: **Twenty-eight subadult primates were studied using gross, CT, and histologic observations. Location of the anterior deciduous dentition relative to the PS was assessed. In sections of selected specimens, observations of bone cells on the osseous boundaries of the Pmx were made. Osteopontin (OPN) immunohistochemistry was used to isolate osteoclastic binding sites along the Pmx boundaries.**

Results: **The PS was consistently found between deciduous incisor and canine in strepsirrhines of all ages, whereas the suture passed variably closer to the incisor or canine in haplorhines. In all species, the anterior part of the Pmx was nonarticulating and mostly osteoblastic, except for osteoclastic margins adjacent to dentition and the nasal fossa. Superolaterally, the osteogenic fronts of the PS were osteoblastic, while more inferiorly, at the level of the deciduous canine, the PS was often osteoclastic. Results from OPN immunohistochemistry support the findings on bone cell distribution.**

Conclusion: **Bone cell distribution patterns in perinatal nonhuman primates resemble those described for the prenatal human Pmx, suggesting that differences among species relate to magnitude rather than the pattern of osteogenesis.**

KEY WORDS: *maxillary bone, premaxilla, osteogenesis*

In human craniofacial anatomy, no bony element has stirred as much controversy as the premaxilla (Pmx). Some authors maintain humans do not possess a Pmx bone based on lack of evidence for a separate ossification center (Jacobson, 1955; Wood et al., 1969). However, others regard the Pmx as a transiently present element, with its own ossification center(s), which is subsequently fused with the maxillary bone proper (Chase, 1942; Woo, 1949; Shepherd and McCarthy, 1955; Kraus and Decker, 1960; Kvinnsland, 1969; Mauser et al., 1975; Mooney et al. 1991). There has been disagreement regarding the fate and the very existence of a suture between fetal premaxillary and maxillary bones. Two major theories have been advanced in this regard. The ''fusion theory'' suggests that the two bones fuse on the ectofacial aspect during late embryonic/early fetal development (Chase, 1942). The ''overgrowth theory'' holds that the maxillary bone completely covers the Pmx on the facial surface between 12 and 16 weeks of fetal development (Ashley-Montagu, 1935; Woo, 1949). The validity of these theories is still in debate, but many authors consider the premaxillomaxillary suture (PS) to be a transient, functional growth site in the human fetal midface (Kraus and Decker, 1960; Mooney and Siegel, 1986; Mooney et al., 1991).

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This paper, in part, was presented at the 2006 annual meeting of the American Association of Physical Anthropologists.

Submitted September 2006; Accepted April 2007.

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DOI: 10.1597/06-197.1

TABLE 1 Species and Source of Sample

Specimen Number	*Species*	*Age (Days)*	*Source**
P384	*Mirza coquereli* (Coquerel's dwarf lemur)	2	DLC
P1690	*Cheirogaleus medius* (dwarf lemur)	0	DLC
CM3913	*Perodicticus potto* (potto)	?	CM
CM69182	*Perodicticus potto*	?	CM
CM6303	*Galago crassicaudatus* (thick-tailed greater bushbaby)	?	CM
CM5678	*Galago elegantulus* (needle-clawed bushbaby)	?	CM
P3097	*Galagoides demidoff* (dwarf galago)	2	DLC
CM 14919	*Galago demidoff*	?	CM
P3080	*Galago moholi* (Mohol's galago)	1	DLC
EM1	*Eulemur mongoz* (mongoose lemur)	0	CMZ
P6778	*Eulemur macao* (black lemur)	1	DLC
P6834	*Lemur catta* (ring-tailed lemur)	5	DLC
CM2710	*Alouatta seniculus* (red howler monkey)	?	CM
CM658	*Cebus albifrons* (white-fronted capuchin)	?	CM
CM3452	*Cebus albifrons*	?	CM
CM6314	*Cercopithecus albogularis* (Sykes's monkey)	?	CM
CM40611	*Cercopithecus petaurista* (Lesser white-nosed monkey)	?	CM
CM18695	*Cercopithecus pygerythrus* (Southern African vervet monkeys)	?	CM
CM5846	*Cercopithecus pygerythrus*	?	CM
CM1479	*Pan troglodytes* (common chimpanzee)	?	CM
Cg1	*Colobus guereza* (colobus monkey)	0	CMZ
SG3	*Saguinus geoffroyi* (Geoffroy's tamarin)	0	CMZ
SG4	*S. geoffroyi*	0	CMZ
SG5	*S. geoffroyi*	0	CMZ
MM105	*S. geoffroyi*	1 month, 23 days	CMZ
LR1	*Leontopithecus rosalia* (Golden lion tamarin)	3	CMZ
LR2	*L. rosalia*	4	CMZ
LR4	*L. rosalia*	9	CMZ

* CM, Carnegie Museum; CMZ, Cleveland Metroparks Zoo; DLC, Duke Lemur Center.

The potential importance of the PS as a growth site is evidenced by its variable relationship to the upper dentition. In humans, the PS may extend between the canine and the lateral incisor or may intersect the canine (Ferenczy, 1958; Lisson and Kjaer, 1997). This, in turn, may relate to the variable position of primary palatal clefts to the upper dentition. Unfortunately, the sutures of the human Pmx are uniquely difficult to study since the bone is at least partly inseparable from the maxilla for most of development (Barteczko and Jacob, 2004). Although the human PS is elusive subsequent to 10 weeks' gestational age (Kvinnsland, 1969), later developmental stages have been examined in nonhuman primates (e.g., Schwartz, 1983; Wei et al., 2000; Wang et al., 2006). In humans, the medial nasal process/maxillary process fusion area has been suggested to be medial to the lateral incisor or to intersect the lateral incisor (Ooe, 1957; Ferenczy, 1958; Lisson and Kjaer, 1997), though the position relative to the PS is less certain. In the macaque, Wei et al. (2000) demonstrated that the medial portion of the Pmx and the central incisor are derived from both the medial nasal process, whereas the lateral portion of the Pmx and lateral incisor are derived from the maxillary process. Furthermore, the lateral incisor is found at the PS until late fetal development. Subsequently, the Pmx bone expands laterally in late fetal and early postnatal development, thus shifting the PS lateral to the lateral incisor. These findings bear on variation in the locus of the defect in cleft lip and palate. In humans, the lateral incisor may be located medial or lateral to the cleft.

The aforementioned studies raise the possibility that nonhuman primates may provide indirect but informative insights into the development of the human Pmx, its sutures, and their bearing on palatal morphogenesis and dysmorphogenesis. However, a comparative microanatomical perspective is needed to assess whether nonhuman primates can provide models to augment our understanding of the human Pmx. This study provides a comparative perspective of the Pmx using nonhuman primates by surveying the position of the PS relative to the deciduous dentition. We also assessed the distribution of bone cells along external and alveolar surfaces of the premaxilla of neonatal nonhuman primates. These data were examined to infer resorptive and appositional surface characteristics of the Pmx as they relate to the position of neighboring facial bones and the deciduous upper dentition.

Materials and Methods

Twenty-eight subadult primates were studied (Table 1), including 12 strepsirrhine and 16 haplorhine species (Strepsirrhini = lemurs and lorises; Haplorhini = monkeys, apes, humans, and tarsiers). Of these, 13 skeletal specimens of unknown age were examined at the Carnegie Museum of Natural History, Section of Mammals. For this sample, skulls were examined if five or fewer teeth were erupted. Fifteen were specimens of known postnatal age obtained from natural deaths in captivity and were used for histology. These specimens were acquired after natural deaths at zoos (Table 1). Use of deceased nonhuman

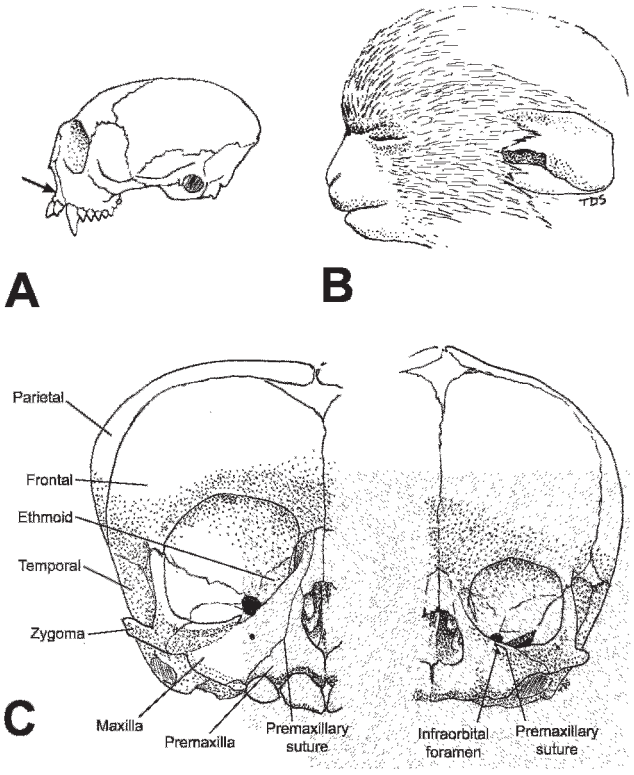

FIGURE 1 A: Lateral view of an adult marmoset cranium, indicating the position of the premaxillary bone (arrow) and its relationship to the incisors. B: Head of a neonatal marmoset, showing facial characteristics at birth in one of the species used in the present study. C: Comparison of the anterior surface of the midfacial skeleton in an infant monkey (*Colobus*, left) and human (right). Related osteology is indicated. A premaxillary suture remnant is indicated (from Schwartz, 2005; reprinted with permission of the author).

primate tissues for this study was reviewed and approved by the Slippery Rock University Institutional Animal Care and Use Committee (IACUC). Prior to histologic processing, two neonatal specimens (*Saguinus geoffroyi, Eulemur macaco*) were CT scanned. One-half of bisected heads (seven specimens) or whole viscerocranial regions (two specimens) were decalcified in a formic acid–sodium citrate solution. Each specimen was processed for paraffin embedding and sectioned coronally at 10 μm to 12 μm. Every 10th section was mounted on glass slides with serial numbers and was stained alternately with hematoxylin and eosin, Gomori trichrome, or alcian blue-periodic acid-Schiff procedures. Intervening sections were saved for other procedures.

Using gross, CT, or histologic observations, all specimens were examined to establish the location of the anterior deciduous dentition relative to the PS (Fig. 1). Whether the suture intersected the deciduous upper lateral incisor (i^2) and canine (c), or passed between these teeth was noted.

Bone cell distribution along borders of the Pmx was described based on observations from all stained sections and was tabulated in two parts of the bone: the more rostral part in which the Pmx had no articulating surfaces and the more caudal part where the Pmx articulated with the maxillary and nasal bones (Fig. 2). In each of these regions, sections of the Pmx were examined for the presence and location of osteoblasts or osteoclasts along osseous boundaries (Tables 2 and 3). One neonatal specimen of each species was selected for 3D computer reconstruction using Scion Image software (NIH). Using a Leica DMLB photomicroscope, each section containing the Pmx bone was photographed and saved as a bitmap (BMP) file. Then, each section was opened using Adobe Photoshop 8.0 (Adobe, San Jose, CA) and was manually aligned as follows. Two adjacent sections were opened and the transparency was increased in the posterior-most section. The section was manually rotated until alignment was visually verified based on the use of fiducial landmarks such as the nasal septum, and teeth (also see Smith et al., 1997). The base section was then deleted and the aligned section was saved under a new file name. This aligned section became the new base section to align the next more

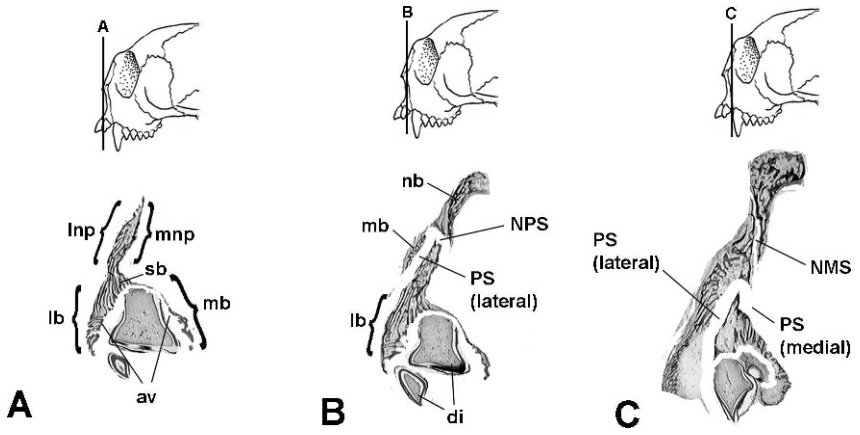

FIGURE 2 Morphological aspects of the Pmx in the anterior (nonarticulating) part of the Pmx (A; Table 1) and the more posterior portion (B, C; Table 2) that articulates with the nasal (nb) and maxillary bones (mb). Pmx processes and sutures that were analyzed included: the lateral and medial surface of the nasal process (lnp, mnp); alveolar margins (av); lateral, medial, and superior surfaces of the body (lb, mb, sb); and sutural surfaces of the Pmx at the nasopremaxillary suture (NPS) as well as the PS; di: deciduous incisor. The approximate position of the coronal plane is indicated on the top row of images.

TABLE 2 Summary of the Presence of Osteoclasts (−) and Osteoblasts (+) in the Rostral (Nonarticulating) Portion of the Premaxillary Bone. Regions of No Osteoblastic/Osteoclastic Cell Distribution Are Indicated by Ø and Some Data Were Not Available (N/A)

	SG3	*SG4*	*SG5*	*MM105*	*LR1*	*LR2*	*LR4*	*EM1*	*P6778*
Body									
Lateral	+	+	+	+	+	+	+	+	+
Medial*	−	+	+	+	+	+	+	+	+‖
Superior	+	+	+	+	+	+	+	+	+
Alveolar margin	− (+†)	−	−	− (+†§)	− (+†§)	− (+†§)	−	−	− (+†§)
Nasal process									
Lateral	+(−‡)	+	N/A	+	+	+	Ø	+	+(−‡)
Medial	− (+†)	−	N/A	−	−	Ø	−	+	+

* includes interpremaxillary suture.
† limited numbers of osteoblasts seen inferolaterally.
‡ limited numbers of osteoclasts seen laterally.
§ limited numbers of osteoblasts seen inferomedially.
‖ limited numbers of osteoclasts seen midmedial body.

TABLE 3 Summary of the Presence of Osteoclasts (−) and Osteoblasts (+) in the Rostral (Articulating) Portion of the Premaxillary Bone. Regions of No Osteoblastic/Osteoclastic Cell Distribution Are Indicated by Ø and Some Data Were Not Available (N/A)

	SG3	*SG4*	*SG5*	*MM105*	*LR1*	*LR2*	*LR4*	*EM1*	*P6778*
Body									
Lateral	+	+	+	− (+‡)	+	+	+	+	+
Medial*	−	+(−§)	+	+(−§)	+	+(−††)	+(−††)	+	+(−§)
Superior	+	+	+	+	+	+	+	+(−††)	+
Alveolar margin	−	− (+‖¶)	−**	−	−	−	−	−**	−(+‖¶)
Premaxillomaxillary suture									
Superolateral	+(−†)	+	+	+(−†)	+	+(−†)	+	+	+(−†)
Superomedial	+	+	+	+	Ø#	+	Ø	+(−**)	+
Nasopremaxillary suture	−	Ø	N/A	+	Ø	Ø	Ø	N/A	N/A

* includes interpremaxillary suture.
† limited numbers of osteoclasts seen at level of dc.
‡ limited numbers of osteoblasts seen superiorly.
§ limited numbers of osteoclasts seen inferiorly.
‖ limited numbers of osteoblasts seen inferolaterally.
¶ limited numbers of osteoblasts seen inferomedially.
# limited numbers of osteoclasts seen superiorly.
** limited numbers of osteoblasts seen superolaterally along alveolar margins in posterior sections.
†† limited numbers of osteoclasts seen superomedially.

posterior section. This process was repeated throughout the entire length of the Pmx bone.

To record the osteoblastic and osteoclastic distribution, the BMP file of each section was opened on a computer monitor using Adobe Photoshop 8.0, while simultaneously enlarging the same section on a Sony monitor connected to a camera system. Sequentially, osseous boundaries of the Pmx bone of each section were labeled as having osteoblastic (+), osteoclastic (−), or lack of (area with no bone cells) activity by using the type tool. Scion Image was used to project a 3D reconstruction of the isolated Pmx bone, with bone cells marked along osseous boundaries. The predominant cell type, or lack of bone cells, was recorded and tabulated according to rostrocaudal level (articulating, nonarticulating) and part (body, processes) of the Pmx (Tables 1 and 2).

Since the motile osteoclasts are not necessarily present on every segment of cross-sectioned bone undergoing resorption, osteopontin (OPN) immunohistochemistry was used to augment our information. Osteopontin is necessary for osteoclastic binding to bone (Reinholt et al., 1990; Heinegard et al., 1995). Therefore, when the outer margins of bone are OPN+, this marker indicates resorptive surfaces in the absence of the motile osteoclasts. Sections of seven cadaveric specimens were chosen for observations of bone cells and reactivity of OPN on the osseous boundaries of the premaxillary bone (Pmx). At least one of each genus studied for bone cell distribution was selected. Sections from these species were deparaffinized in xylenes and rehydrated through serial alcohols. Next, endogenous peroxidase activity was blocked by incubating slides in 3% H_2O_2 in methanol for 30 minutes at room temperature (RT). Slides were then blocked using 2% donkey serum (Santa Cruz Biotech, Santa Cruz, CA) for 30 minutes at RT. Labeling of osteopontin was achieved by incubating the slides with OPN antibody (Santa Cruz Biotech) at a 1:250 dilution in 2% donkey serum for 30 minutes at RT, with a subsequent incubation with donkey antigoat biotinylated secondary antibody (1:250 in PBS) for 30 minutes at RT. Staining was performed with a Vector ABC kit (Vector Laboratories, Burlingame, CA) according to the manufacturer's instructions using diaminobenzidine (DAB) as chromogen. Following treatment with DAB, slides were counterstained with Harris' hematoxylin (Surgipath, Richmond, IL) and dehydrated through serial alcohols into xylene, then coverslipped using Permount (Fischer Scientific, Pittsburgh, PA). OPN staining was considered positive if staining was more intense than that

found in comparable tissue on negative control slides that were incubated in the absence of primary antibody.

Results

The PS was consistently found between di2 and dc in all strepsirrhines regardless of observational method or age. Among haplorhine primates, the PS was variable and sometimes asymmetric (Fig. 3A). The PS was grossly observed to intersect di2 in perinatal *Saguinus geoffroyi, Leontopithecus rosalia*, and *Colobus guereza* (Fig. 3B). In other subadults, the PS variably passed more closely to either dc or di2 (rather than precisely between these teeth). Histologic sections and CT scans supported gross observations.

In all species, the alveolar margins of the Pmx appear osteoclastic in both rostral and caudal sections (Tables 2 and 3). Generally, the more anterior (nonarticulating) part of the body was osteoblastic in all species. More posteriorly, the lateral and superior surfaces of the body were osteoblastic. Some osteoclasts were observed along the medial surface of the body, among the more numerous osteoblasts (Table 2). The nasal process of tamarins (of all species) followed this trend with the lateral surface being osteoblastic and the medial surface being osteoclastic (Tables 2 and 3; Figs. 4 and 5).

Superolaterally, the PS is osteoblastic. However, half of the specimens have some osteoclasts at the level of the deciduous canine (Table 3). Superomedially, the PS is most often osteoblastic (Table 3). In tamarins the nasopremaxillary suture is generally devoid of bone cells. This suture does not exist in the lemurs (Tables 1 and 2; Figs. 4 and 5).

Results from OPN immunohistochemistry support the findings on bone cell distribution (Fig. 6). For example, the alveolar margins of the Pmx were OPN (+) and "scalloped." In addition, the contours of the nasal cavity (i.e., the medial surfaces of the body and nasal process of the premaxilla) were OPN (+).

Discussion

Since humans uniquely lose a discrete Pmx during fetal development, an understanding of the significance of this bone to orofacial growth has been elusive. The early incorporation of the premaxilla into the (aggregate) adult human maxilla has clouded issues regarding facial clefting and criteria for identification of teeth. Nonetheless, some authors regard this bone as an autonomous element during the early fetal period (Mauser et al., 1975; Mooney et al., 1991).

This study of nonhuman primates suggests that the PS usually courses between i^2 and c. Positional variability in the PS was typical of the perinatal haplorhines in our sample. These results suggest an ontogenetic decoupling of growth rates between dentition and facial bones in some species. In particular, the premaxillary bone and the dentition that forms within it may grow in an asynchronous manner. Our observations are in keeping with those of Wei et al. (2000) on developing macaques, who found that the gap between adult upper canine and the lateral incisor forms as the premaxilla overgrows the deciduous incisors. The authors suggested that growth at the PS is a major mechanism that maintains the gap which accommodates the size difference between deciduous and adult dentition.

The implied differences in Pmx growth patterns among nonhuman primates provide a new context for a description

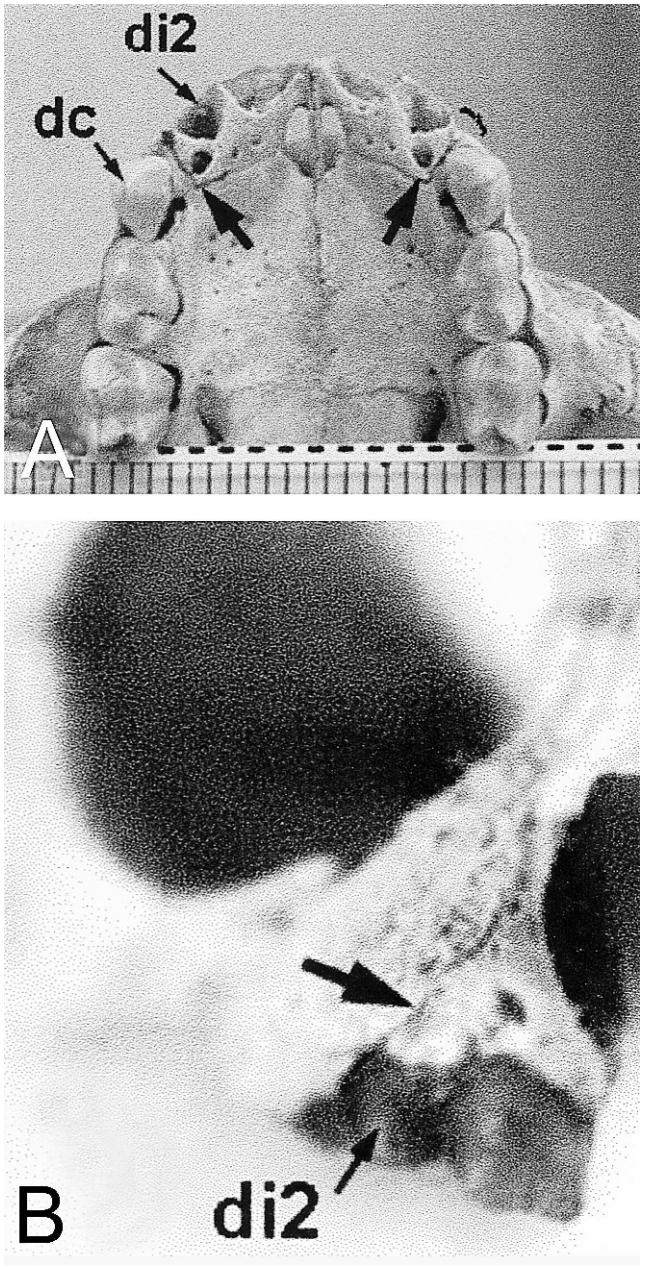

FIGURE 3 Gross, skeletal variations of the premaxillomaxillary suture (PS) in the anthropoids. A: Cercopithecus pygerythrus, juvenile, showing the PS (large arrows) at the palatal surface. Note the slight asymmetry. On the right side, the PS passes through the middle of the canine diastema (indicated by a bracket on the opposite side), between deciduous lateral incisor (di2) and canine (dc). On the left side, the PS passes more closely to the dc. B: The PS viewed from the facial aspect. In some neonatal anthropoids (*Colobus guereza*) the PS intersects the di2 at birth.

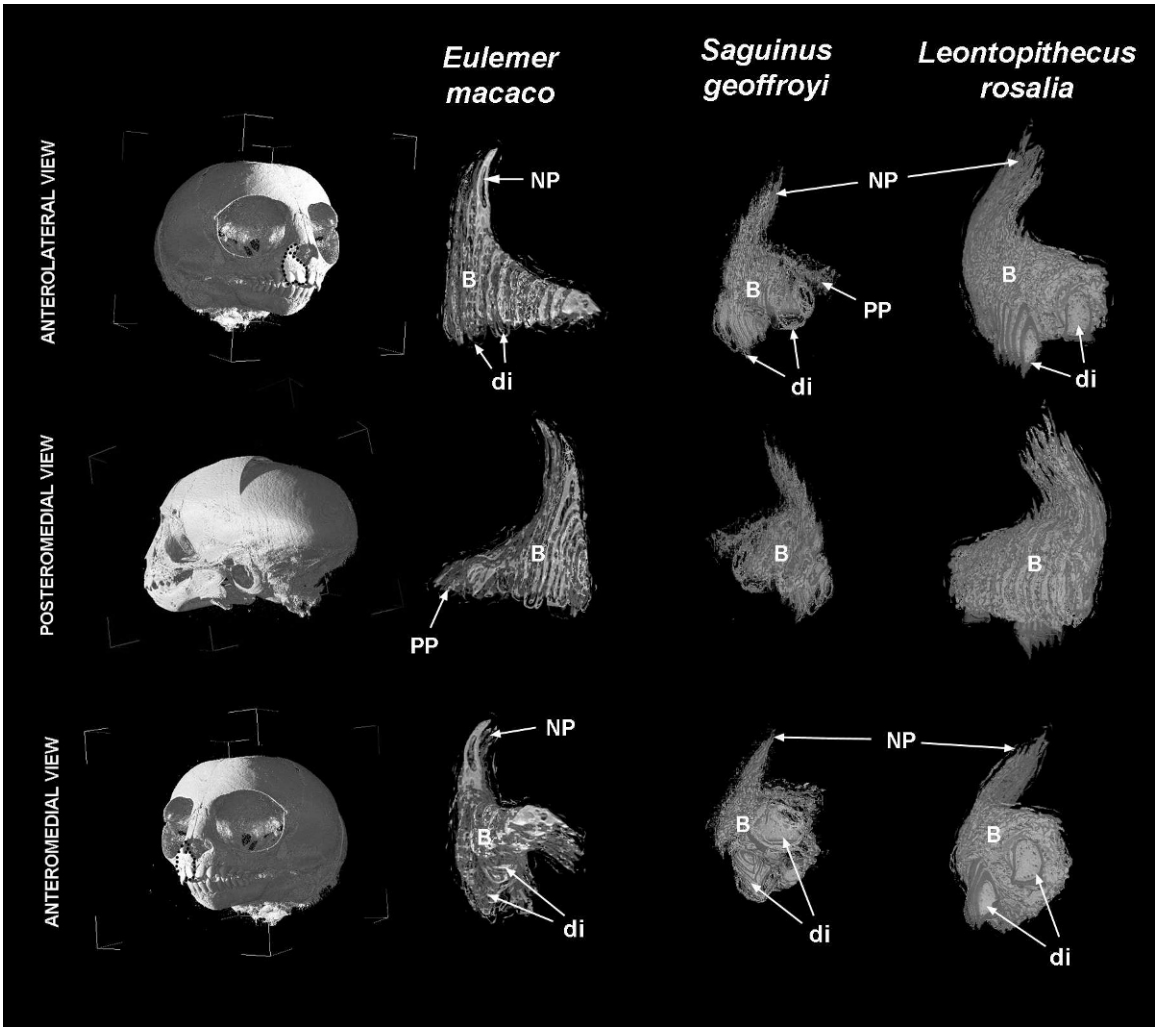

FIGURE 4 Three views of the isolated premaxilla in neonatal primates including a lemur (*Eulemur*) and two species of tamarins (*Saguinus*, *Leontopithecus*) to show features of the bone. To demonstrate orientation of the isolated bones relative to the skull, see the rotated images of a primate skull (3-dimensionally reconstructed from a marmoset) on the far left. Reconstruction from cross-sections was done using Scion Image software. Osteoblast distribution is visible in some views. See Tables 2 and 3 for more details. NP: nasal process; B: body; di: deciduous incisor; PP: palatal process.

of human Pmx development. Mooney et al. (1991) showed that the Pmx increases in volume during the second trimester, in keeping with growth rates of other craniofacial elements (Siegel et al., 1987). These authors also showed that the Pmx is of relatively reduced size in human fetuses with cleft lip and palate.

Mauser et al. (1975) tracked the distribution of bone cells along the surfaces of the Pmx during human fetal development. Until the formation of tooth crypts, the premaxilla is osteoblastic at all surfaces. Subsequently, the alveolar margins are resorptive for the duration of development. Osteoclastic activity is also seen at the posterior sutural surface and nasal surface of the Pmx. Labial and oral palatine surfaces are osteoblastic during fetal development. These findings are generally consistent with (1) downward growth of the midface and increased height of the nasal fossae and (2) growth of the deciduous incisors. After the fourth fetal month of human development, the premaxilla is partially fused with the maxilla, and the facial surface often shows no suture by birth (Ashley-Montagu, 1935; Mooney and Siegel, 1986). However, the palatal aspect of this suture is often patent throughout early infancy (Woo, 1949; Sejrsen et al., 1993). During prenatal development, the PS is variable in its position relative to the lateral incisor and canine (Ferenczy, 1958; Lisson and Kjaer, 1997). However, the partial union of the Pmx and maxilla makes the underlying basis for this variation difficult to understand.

Because these data are derived from nonhuman primates, the results relate to bone deposition and resorption in the Pmx as an individual bone. Observations on bone cell distribution were remarkably consistent among species. The general similarities reflect themes common to all primates, i.e., expansion of the nasal cavity, growth of incisors, and overall size increase of the Pmx. In addition, it may be considered that growth of the various craniofacial elements cannot be considered in autonomy. Expansion of

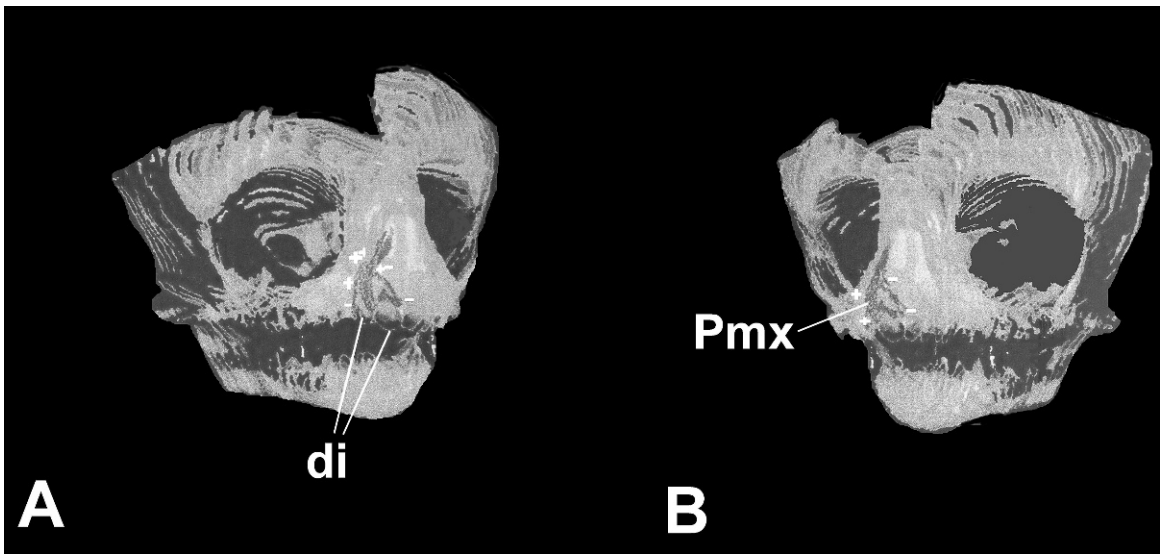

FIGURE 5 CT scan reconstruction with the Pmx highlighted and the osteoblastic (+) and osteoclastic (−) borders indicated. Anterolateral (A) and anteromedial views (B) of the Pmx of a neonatal *Saguinus geoffroyi* are shown. Note the osteoclastic surfaces at the inferolateral surface (adjacent to the maxillary bone), the interpremaxillary suture, and the medial margin of the nasal process (adjacent to the nasal cavity).

alveolar sockets via osteoclastic activity likely affects the osseous boundaries of adjacent elements, such as the maxillary sinus (Smith et al., 2005). Similarly, the osteoclastic activity along the lateral margin of the Pmx was coincidental with the osteoclasts distributed along the alveolar surface of the adjacent maxillary bone (see Fig. 6C). Thus, the Pmx may be constrained from appositional growth in its borders that are adjacent to the maxillary bone that houses the deciduous canine. This would explain the observation of osteoclasts along the outer margin of the Pmx in these regions.

Some parallels to the human fetal Pmx clearly exist, such as indications of resorption along the contour of the nasal cavity and alveoli. In this respect, the osseous development of this bone is similar among all primates, perhaps reflecting a regional trend related to dental growth and nasal fossa size increase. A noteworthy finding is that little distinction exists between primate suborders. The only exception may be that the medial aspect of the Pmx nasal process is resorptive in haplorhines but not in the lemurs. This implies that the Pmx broadens the anterior nasal fossa in the former group, but not in the longer-snouted lemurs.

Such basic similarities during the perinatal period appear to belie the fact that adult primates have substantial variation of dentition associated with the Pmx. Among adult primates, incisor teeth vary in morphology from small pegs to flat blades to ''caninoform'' daggers (Swindler, 2005; Ankel-Simons, 2007). Incisors also vary in arrangement. The Pmx portion of the dental arch varied in anterior

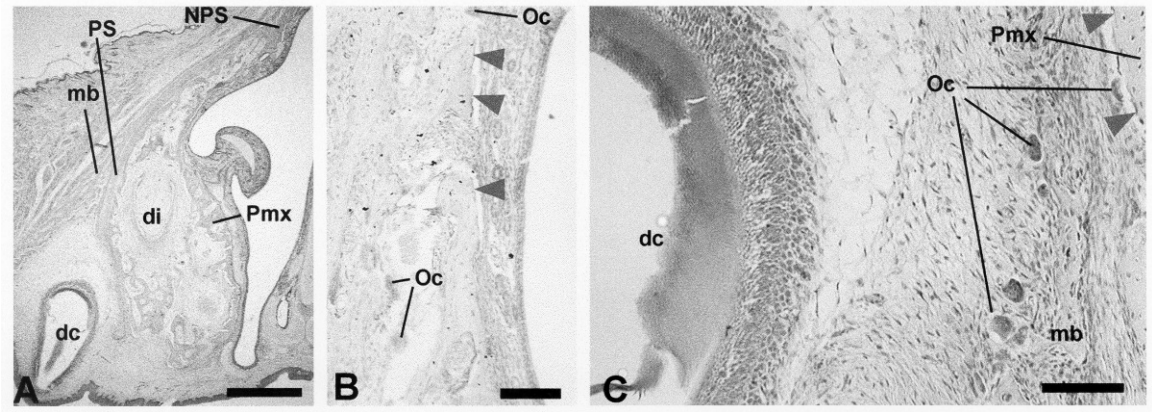

FIGURE 6 Micrographs of coronal sections through the Pmx of *Leontopithecus rosalia*, prepared with hematoxylin-eosin (6A) and osteopontin immunohistochemistry (6B, C). 6A shows the relationship of the Pmx to adjacent bones at the PS and NPS. Immunostaining for osteopontin is shown in closely adjacent sections in 6B (nasal process) and 6C (PS). Note the labeled surfaces of the nasal process (arrowheads) with an osteoclast (Oc) nearby. Osteoclasts are also within the spongy bone matrix. At the level of the deciduous canine (dc), the alveolar surface of the maxilla and the adjacent Pmx was labeled (arrowheads) and osteoclasts were seen. di, deciduous incisor; mb, maxillary bone. Scale bars: A, 1 mm; B, C, 0.1 mm.

contour, from flattened to convex (Ankel-Simons, 2007). Thus, development of the Pmx subsequent to infancy may well differ among primates. At a minimum, future studies may find differences in magnitude if not pattern of growth.

The adult variation notwithstanding, the present study suggests that nonhuman primates may provide valuable information concerning the development of the PS in relation to upper deciduous dentition. The human pattern of fetal Pmx growth seems entirely comparable to nonhuman primates at later stages of development. This implies a common trajectory of Pmx enlargement among primates. Thus, development of the premaxillary bone in nonhuman primates may reveal subtle distinctions in regional rates of growth. Future studies might consider quantitative differences in bone growth or associated cytokines among nonhuman primates in explaining positional variability of the PS.

Acknowledgments. We thank S. Mclaren and J. Wible of the Carnegie Museum for access to the sheletal sample. This is DLC publication #1118.

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