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Evolution and development of teeth

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ABSTRACT

Teeth as a feeding mechanism in an oral cavity (mouth) are functionally and locationally linked with jaws. In fossils, teeth found in the oral cavity are usually linked with jaws, although mineralised structures with the same histology as teeth are known in fossils before jaws appeared. Denticles in the skin occur in both fossil and extant fish. Pharyngeal denticles also occur in both extant and fossil gnathostomes but in only a few fossil agnathans (thelodonts). Complex structures with dentine and enamel have been described in the earliest jawless vertebrates, conodonts. Such fossils have been used to suggest that teeth and jaws have evolved and developed independently. Our understanding of the developmental biology of mammalian tooth development has increased greatly in the last few years to a point where we now understand some of the basic genetic interactions controlling tooth initiation, morphogenesis and patterning. The aim of this review is to see what this developmental information can reveal about evolution of the dentition.

Key words: Tooth development; homeobox; signalling.

INTRODUCTION—WHY TEETH?

There are many things that make teeth special: they contain the hardest biological substance known (enamel); palaeontologists and anthropologists alike rely on their unique preservation within the fossil record, and thus much of our understanding of animal evolution is based on teeth; an individual's age can be accurately estimated from tooth sections; forensic science relies heavily on dental records for identification.

From an evolutionary-developmental perspective there are four important features that make teeth an attractive model system. (1) Cusp patterns, tooth shapes and their arrangement in a dental pattern are unique to each species and as indicative of a species as its DNA. (2) Because tooth pattern is intimately linked to feeding and hence survival, changes in tooth pattern in evolution provide a major basis for adaptations linked to exploitation of new feeding niches. (3) Tooth development is a simple process, involving just two embryonic cell types. (4) Embryonic tooth primordia can be easily cultured in vitro to completely recapitulate normal development. This enables many different types of experimental manipulation to be carried out, including recombinations between different species.

THE EVOLUTION OF TEETH AND JAWS—THE AGNATHAN TO GNATHOSTOME TRANSITION

Simplistically, the evolution of teeth is believed to have occurred by one of two different mechanisms: (1) teeth evolved independently from jaws from pharyngeal denticles, similar to those found in many extant species of fish such as zebrafish (Smith & Coates, 1998, 2001); (2) teeth evolved at the same time as, or after, jaws by internalisation of skin denticles (dermal armour) similar to those found on modern-day sharks (Reif 1982, reviewed by Smith & Coates, 2001). In common with many issues in vertebrate evolution, this can only be resolved by a rigorous test using cladistic analysis of a far more complete fossil record. It is interesting however to evaluate what developmental biology can contribute to our understanding of tooth and jaw evolution.

Analysis of gene expression patterns in the jaw primordia of mouse and bird embryos at times before overt cellular differentiation shows that most, if not

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all, genes are similarly expressed in the two species (Francis-West et al. 1994; Thesleff & Sharpe, 1997; Francis-West et al. 1998; Tucker et al. 1998; Barlow et al. 1999). Thus orofacial development in a species that has teeth, cartilage and bone involves the same genes as development of a species with cartilage and bone but no teeth. Functional data, principally from gene targeting (knockouts) in mice, show that although there are specific genetic pathways involved in tooth and jaw development, tooth morphogenesis shares many key genes with jaw skeletal morphogenesis. The latter suggests that these 2 tissues evolved independently but that the evolution of heterodonty (teeth with different shapes) from homodonty (teeth with one simple, conical shape) involved co-option of existing genetic pathways controlling jaw skeletal morphogenesis.

Disruptions that affect dental patterning also produce abnormal skeletal development of the jaws. Thus *Dlxl/Dlx2* double mutants and *activin βA* mutants have abnormal dental patterning with no development of maxillary molars and no development of incisors and mandibular molars respectively (Matsuk et al. 1995; Qiu et al. 1995, 1997; Thomas et al. 1997; Ferguson et al. 1998). There are, however, many examples of gene knockouts that affect jaw hard tissue development but where tooth development is normal. *Pitx1* is a homeobox gene expressed in jaw primordia mesenchyme from E9. *Pitx1* knockout mice have a very truncated mandible but despite this, teeth are present and appear normal (Lanctôt et al. 1997, 1999). *Goosecoid* (*Gsc*) is a homeobox gene expressed in jaw primordia mesenchyme from E10.5 (Gaunt et al. 1993; Tucker et al. 1999). *Gsc* null mice have abnormal mandibular bone development but teeth are normal and, in addition, formation of Meckel's cartilage, the template for mandible bone formation, is normal. *Gsc* is thus a gene required for mandibular bone development but not for tooth or Meckels cartilage development (Riverez-Pérez et al. 1995, 1999; Yamada et al. 1997).

There are also examples of genes such as *Lef1* and *Pax9* which are required for the early development of all mammalian teeth but which appear to have little effect on jaw skeletal development. *Pax9* is expressed in early odontogenic mesenchyme from E10 and marks the sites of future tooth formation (Neubüser et al. 1995). In *Pax9* knockout mice, in which all tooth development is arrested at the bud stage, the jaws develop fairly normally except that the coronoid process of the mandible and the alveolar ridges of both jaws are missing (Neubüser et al. 1997). *Lef-1* mutant mice have a very similar phenotype to *Pax9* mutants, where development of all teeth is arrested at the bud stage (van Genderen et al. 1994; Kratochwil et al. 1996). This indicates that there are genes required for early development of teeth that are not involved in jaw development and similarly there are genes required for jaw skeletal development that are not involved in early tooth development. This genetic independence of tooth from jaw development suggests they evolved independently. However, the fact that genes regulating dental patterning, i.e. the development of different shapes (types) of teeth, also regulate jaw skeletal morphogenesis implies that dental patterning, which is a later event in evolution, resulted from co-option of genes regulating jaw morphogenesis. The ability of developing teeth to adapt genetic pathways that were in place to regulate jaw morphogenesis may have thus represented an important step in the evolution of heterodonty.

In humans there are numerous examples of tooth patterning abnormalities that occur in the absence of skeletal abnormalities. Thus for example hypodontia (missing teeth) can occur in the absence of any obviously abnormal jaw phenotype. However, this is one example where the mouse, which develops only one set of teeth, is a poor model for humans in which deciduous and permanent teeth develop. Significantly, it is the replacement teeth in humans that are almost always affected in hypodontia, whereas the deciduous dentition develops normally. This suggests that there are important aspects of the development of permanent teeth, that involve different genetic control to deciduous tooth development or jaw skeleton formation.

SPECIFICATION OF DENTAL AND SKELETAL CELLS

During development of the mammalian mandible, different hard tissues, teeth (dentine and cementum), bone and cartilage develop from neural crest-derived ectomesenchyme cells. The mechanisms that determine which cells differentiate into these different tissues are beginning to be elucidated. It is now clear that the ectomesenchyme cells of the developing mandible, (and presumably other orofacial primordia), are capable of differentiating into any of these different hard tissue producing cell types, odontoblasts (dentine), osteoblasts (bone), and chondrocytes (cartilage) and the signals that direct differentiation come from the overlying epithelium. Cranial neural crest cells that populate each facial primordium do not appear to be prepatterned into specific odontogenic, osteogenic or chondrogenic populations

but rather are directed down the appropriate differentiation pathway under the influence of ectodermal signals.

Evidence for how the early specification of odontogenic from skeletogenic cells occurs in the developing mandible comes from expression of the Lim-domain homeobox genes *Lhx6* and *Lhx7* and *Gsc*. Expression of *Lhx6* and *Lhx7* is restricted to the ectomesenchyme closest to the oral epithelium (oral) that forms teeth whereas *Gsc* is expressed more posteriorly (aboral) in ectomesenchyme cells that do not form teeth but which do form skeletal cells (Grigoriou et al. 1998; Tucker et al. 1999). This early oral/aboral division of the mandibular primordium is regulated by FGF8 from the oral epithelium. FGF8 is required for expression of *Lhx6/7* and *Gsc* and *Lhx6/7* repress *Gsc* expression (Fig. 1). The mechanism that restricts *Lhx6/7* expression to oral ectomesenchyme is not known but does not involve *Gsc* since *Lhx6/7* expression is unaltered in *Gsc* mutant embryos. These interactions suggest that *Lhx6/7* fall into the category of essential odontogenic genes that are also required for jaw skeletal development, in this case indirectly via their influence on Gsc expression. Functional evidence for their role awaits the generation of *Lhx6/7* double mutants (Zhao et al. 1999).

CONTROL OF DENTAL PATTERNING

Tooth shape is indelibly linked to position in the jaws. Tooth shapes have evolved for particular functions. Incisors and canines are grasping/cutting teeth, premolars and molars are both grinding and cutting teeth. In heterodont dentitions there is little point in having grasping/cutting teeth at the rear of the mouth and grinding teeth at the front.

Although mice only possess only two types of teeth, incisors and molars, experiments in this model system have identified genes that have a role in the determination of tooth type (MacKenzie et al. 1991, 1992; Sharpe, 1995; Thomas et al. 1997; Tucker et al. 1998). The observations that a number of different homeobox genes are expressed in distinct spatial domains in early jaw primordia mesenchyme has led to the suggestion that determination of tooth type is regulated by these genes. The Odontogenic Homeobox Code model of tooth patterning (Fig. 2) that has been proposed states that in mice, genes such as *Barx1*, *Dlx1* and *Dlx2* have specific roles in directing mesenchyme cells to follow a multicuspid (molar) pathway of tooth morphogenesis (Sharpe, 1995; Thomas & Sharpe 1998; Tucker & Sharpe, 1998). Genes such as *Msxl* and members of the Alx family have roles in directing cells to follow a monocuspid (incisor) pathway. An additional key feature of this model is that it is not only the expression of these genes in particular mesenchymal cells that is important but also the absence of expression of other genes. Thus maxillary molar morphogenesis not only requires the presence of *Barx1*, *Dlx1* and *Dlx2* but also the absence of *Msx1* and Alx genes (McCollum & Sharpe, 2001).

Functional evidence for this model comes from both gain- and loss-of-function experiments in mice. Mice with null mutations in both *Dlx1* and *Dlx2* genes fail to develop maxillary molars but all other teeth are normal (Qiu et al. 1997; Thomas et al. 1997). The development of mandibular molars in these mice is believed to result from the expression *Dlx5* and *Dlx6* that are functionally redundant for *Dlx1* and *Dlx2*. Interestingly, each of these Dlx genes individually does have an essential role in jaw skeletal development but not in tooth development (Qiu et al. 1997; Acampora et al. 1999; Depew et al. 1999). Ectopic expression of *Barx1* in distal mandibular primordia mesenchyme, accompanied by loss of *Msx1* expression results in a transformation of incisor teeth into molars (Tucker et al. 1998). Significantly the *Dlx1/2* double mutant mice also have defects in maxillary proximal skeletal tissues and *Msx1* mutant mice have defects in distal jaw skeletal tissues (Satokata & Maas, 1994; Qiu et al. 1997). Thus genes that regulate molar morphogenesis also regulate proximal jaw skeletal development and genes that regulate incisor morphogenesis also regulate distal jaw development. The indication from these data is that jaw morphogenesis and tooth patterning are controlled by the same genes. Since heterodont dentitions (different tooth shapes in the same dentition) evolved after homodont dentitions (teeth of all one shape), this suggests that different tooth shapes evolved by co-opting genes that were already expressed in facial primordia development to regulate jaw skeletal morphogenesis.

The generation of tooth shapes other than incisors and molars is suggested to involve overlapping domains of homeobox genes. Thus for example the mesenchyme cells that express *Msx1*, *Dlx1* and *Dlx2* might correspond to development of canines or premolars.

MANDIBLES AND MAXILLAS

In many respects, tooth patterning is very similar to patterning of the axial skeleton. Vertebral bodies are

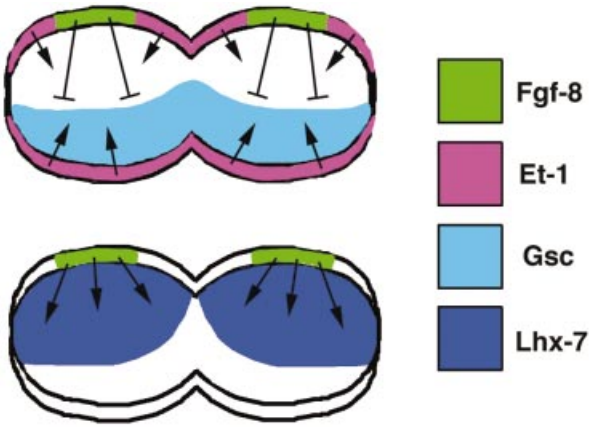

Fig. 1. Diagrammatic representation of signalling interactions that regulate the division of the mandibular arch primordium into dental and skeletal domains. The expression of *Lhx6/7* in presumptive oral mesenchyme and *Gsc* in the aboral mesenchyme are regulated by epithelial signals. Fgf8 induces both *Lhx6/7* and *Gsc* expression and *Lhx6/7* repress *Gsc* expression. Endothelin-1 (Et1) produced from the arch surface epithelium acts to maintain Gsc expression.

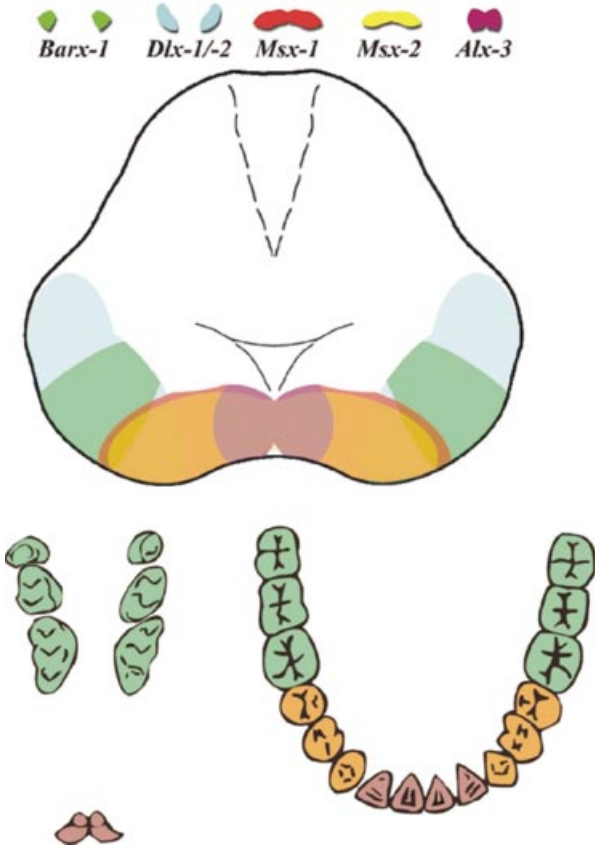

Fig. 2. Diagrammatic representation of the Odontogenic Homeobox Code model of dental patterning. An oral view of the mandibular arch primordium is shown with domains of several homeobox genes expressed in the mesenchyme. Expression of each homeobox gene is represented by a different colour shown in the key at the top of the figure. The key also illustrates the different shaped expression domains of each of the genes in mandibular primordium ectomesenchyme. Where expression domains overlap the colours are combined, thus for example, the domain where *Msx1* (red) and *Msx2* (yellow) overlap is shown in orange. These overlapping domains provide the positional information to direct tooth germ morphogenesis. In the mouse dentition (lower left) *Barx1* and *Dlx1/2* expressing cells, that are *Msx1/2* and *Alx3* negative, develop as molars whereas *Msx1/2* and *Alx3* expressing cells that are *Barx1* and *Dlx1/2* negative develop as incisors. In human dentition, (lower right), canines and premolars are proposed to develop from cells expressing *Msx1/2* that are negative for *Alx3*, *Barx1* but positive for *Dlx1/2*. Reproduced from McCollum & Sharpe (2001).

mineralised 'organs' with a basic structure that is modified according to rostro-caudal position. The morphogenesis of each individual vertebrae is fixed in any given species such that the relative order in the spine can easily be reconstructed from fossil remains. Similarly, arrangements of different shapes and sizes of teeth on the two jaws are fixed and dental patterns can be reconstructed even when teeth are isolated from the jaws. This is particularly evident for teeth that occlude. Mammalian molar teeth are designed to function by making specific contacts with each other on the upper and lower jaws. Molars cannot function without such occlusion. Thus in the same way that each vertebra precisely 'fits' with immediate neighbours, each tooth aligns precisely with its counterpart on the opposing jaw. In the absence of any conflicting constraints, the most logical developmental mechanism for ensuring tooth development on opposing jaws is coordinated, would be to use the same basic genetic mechanism that is subtly modified to produce slight differences in shape between opposing teeth. It is now clear that this is not the mechanism and morphogenesis of teeth on the different facial primordia is in fact regulated by different genetic pathways. The most striking demonstration of this involves the activin signalling pathway. Activin is a member of the TGFβ superfamily of signalling proteins that binds to membrane receptors and activates gene transcription via the Smad-mediated pathway (Attisano & Wrana, 1998). Mouse mutants in the *activin* βA gene have a tooth phenotype where all incisors and mandibular molars are arrested at the bud stage but maxillary molars develop normally (Matsuk et al. 1995; Ferguson et al. 1998). Significantly, loss of expression of downstream genes, such as *follistatin*, is evident in all tooth germs, including developing maxillary molars, in *activin* βA mutant embryos. This and other evidence (unpublished) clearly shows that the activin signalling pathway, although essential for incisor and mandibular molar tooth development, is not required for development of maxillary molars. Thus, molar specification on the mouse maxillary primordia involves a different genetic pathway to specification of molars on the mandible.

Transplantation of cells between the early mandibular and maxillary primordia has revealed that cells behave according to their donor genetic programme and not as the host cells. Thus mandibular cells that express *Dlx5* and *Dlx6* continue to express these genes when transplanted to the maxillary primordium, despite being surrounded by cells that do not express these genes. Similarly, maxillary primordium cells that do not express *Dlx5* or *Dlx6*, do not start to express these cells when transplanted to the mandible, despite being surrounded by *Dlx5* and *Dlx6*-expressing cells (Ferguson et al. 2000).

Many of the genetic mechanisms that control maxillary and mandibular molar (and indeed incisor) development are the same. It is the early responses of the mesenchyme cells to epithelial signals that establish cell position, and hence morphogenesis that are different. This probably reflects different origins of the mesenchymal cells in the neural tube. Thus the cranial neural crest cells that form the mandible originate from the rostral hindbrain and caudal midbrain whereas those that form the fronto-nasal process originate from the caudal forebrain and midbrain (Osumi-Yamashita et al. 1994). It is also possible that the cells that form the maxillary process have a different origin from those that form the mandibular process. If not a different origin they certainly have a different history.

The early genetic processes that influence jaw hard tissue morphogenesis thus reveal differences between the jaw primordia that are reflected in different mechanisms used to establish tooth morphogenesis. One evolutionary interpretation of this is that the different genetic pathways are related to the obviously different skeletal morphogenesis of the upper and lower jaws. Thus for example, *Dlx5* and *Dlx6* are required for producing the normal skeletal morphogenesis of the lower jaw. Morphogenesis of teeth on the jaws involves the same genes that control skeletal morphogenesis despite the fact that the functions of these genes are unique to one or other jaw primordium. Again, the simplest interpretation of this is that the evolution of heterdont dentitions used existing genetic pathways that were already in place to regulate jaw morphogenesis.

How therefore do these developmental data relate to the most recent evolutionary suggestions that teeth evolved before jaws? First it is important to realise that in this view of tooth evolution the first teeth to evolve were not oral (marginal) teeth but where embedded in the pharynx. Thus the 'teeth before jaw' hypothesis does not refer to oral teeth as we know them in mammals. This being the case it is not difficult

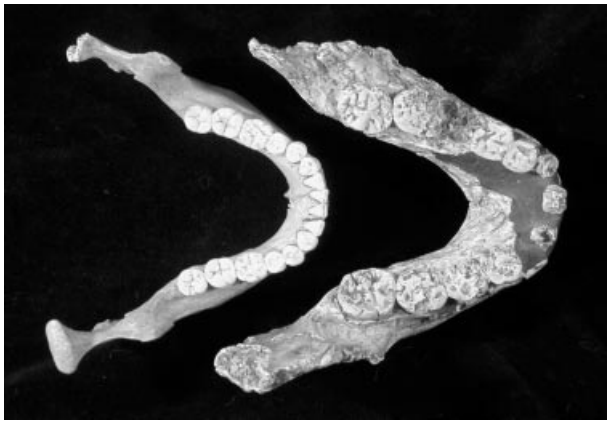

Fig. 3. Lower jaws of human (left) and *A. boisei* (right).

to reconcile the developmental data where pharyngeal teeth moved forwards towards the oral cavity at the time of or after the agnathan to gnathostome transition. Since the genetic pathways regulating jaw morphogenesis were already in place to produce the required skeletal morphogenesis of the jaws, the pharyngeal teeth developing in the oral cavity were exposed to this information which was deployed to produce different shapes of teeth, and thus heterodonty evolved. Perhaps significantly, the differences in tooth shapes vary greatly along the anteroposterior axis (incisor-molar) in heterdonts but far less so at equivalent positions on the upper and lower jaws. This is consistent with the concept of the agnathan to gnathostome transition involving the modification of anterior arches of the segmented pharyngeal skeleton into dorsal and ventral articulating portions that were initially morphologically similar. This was then followed by considerable elaboration of these dorsal and ventral jaws during gnathostome evolution, such that the anterior and posterior regions of each jaw evolved very different skeletal morphologies.

A UNIQUE POSITION IN HOMINID EVOLUTION

Because of the inherent hardness of enamel and dentine, teeth are often well preserved in the fossil record. Consequently, mammalian palaeontology relies heavily on fossil tooth remains to infer evolutionary processes and reconstruct phylogenetic relationships. There is little question that this is a fundamentally sound exercise. Once formed, teeth are incapable of modification or repair. Selection therefore favours those particular dental variants better able to resist functional attrition and thereby extend the reproductive abilities of their carriers. This variation in dental pattern and cusp morphology clearly derives from genetically determined variation in odontogenesis.

In recent years, the widespread application of quantitative cladistic methods has resulted in the reliance of an increased number of cranial characters to infer phylogenetic relationships. Such atomisation of cranial morphology, in which the independence of large numbers of cranial and dental traits is necessarily implied (usually between 50 and 100), as alien to a developmental biologist as it is at odds with our emerging knowledge of cranial morphogenesis. As discussed here, tooth morphogenesis shares many genes with jaw skeletal morphogenesis. Therefore selective change of the dentition may well be genetically correlated with other changes in the face and skull. From a different perspective, cranial features may be functionally correlated with the dentition as well. For example, postcanine tooth size varies considerably among mammalian taxa. Functionally, selective increase in the size of the postcanine dentition lowers the amount of occlusal pressure generated during chewing. It is therefore little surprise that taxa characterized by selective enlargement of postcanine occlusal areas also display evidence that the cross-sectional area of their masticatory musculature was enlarged as well.

The contribution of the dentition to the shaping of the mammalian face and skull is often overlooked in cladistic studies, leading to erroneous phylogenetic relationship interpretations. An excellent example of this comes from the field of palaeoanthropology, the study of hominid evolution. One of the most enigmatic aspects of the human fossil record is the origin and evolution of the robust australopithecines. These highly specialised, long-extinct side-branches of the human family tree are characterised by a dental pattern which combined absolutely large postcanine teeth (premolars and molars) with relatively and absolutely small canines and incisors. Three species of robust australopithecine are currently recognised: *A. aethiopicus* and *A. boisei* in East Africa (Lake Turkana region) and *A. robustus* in South Africa. The relatively intact fossil sequence of the Shungura formation of Ethiopia preserves the mosaic transition from early *A. aethiopicus* to later *A. boisei*. The relationship of *A. robustus* to the East African robust lineage is less clear.

Cladistic analyses of early hominid phylogeny virtually always identify *A. robustus* as the sister taxon of *A. aethiopicus*/*A. boisei* due to the large number of presumably independent craniofacial characters the South African species shares with its East African counterparts. However, a morphogenetic consideration of these characters, which includes such features as forward placement of the zygomatic bone within the face, large mandibular cross-sectional area, concave nasoalveolar process, heavily inflated mastoid process and a thick palate, indicates that they are all more reasonably interpreted as the correlated developmental by-products of the unusual dental proportions characteristic of the robust taxa (McCollum, 1999).

The inclusion of developmentally redundant cranial characters such as these in cladistic studies of early hominid phylogeny overshadows the far more phylogenetically relevant variation in dental morphology expressed by these taxa. For example, although *A. robustus* and *A. boisei* share the character of an extremely large postcanine dentition, they do not share identical postcanine tooth morphologies. Rather, *A. boisei* displays a number of non-size-related features of the postcanine dentition (e.g. distinctive morphology of the lower fourth premolar, distinct lower molar cusp proportions) not observed in *A. robustus*. In addition, the teeth of *A. robustus*, while large in comparison to those of most non-robust early hominid taxa, are nevertheless notably smaller than those of the East African forms (Fig. 3). This variation in tooth size implies either that a reduction in tooth size occurred during the evolution of *A. robustus* from an *A. aethiopicus* ancestor, or that the East and South African robust taxa evolved independently. In this particular case teeth give a very different perspective of robust australopithecine phylogeny.

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REFERENCES

ACAMPORA D, MERLO GR, PALEARI L, ZEREGA B, POSTIGLIONE MP, MANTERO S et al. (1999) Craniofacial, vestibular and bone defects in mice lacking the Distal-less-related gene Dlx5. *Development* **126**, 3795–3809.

ATTISANO L, WRANA JL (1998) Mads and Smads in TGFβ signalling. *Current Opinions in Cell Biology* **10**, 188–194.

BARLOW AJ, BOGARDI J-P, LADHER R, FRANCIS-WEST PH (1999) Expression of chick *Barx-1* and its differential regulation of FGF-8 and BMP signaling in the maxillary primordia. *Developmental Dynamics* **214**, 291–307.

DEPEW MJ, LIU JK, LONG JE, PRESLEY R, MENESES JJ, PEDERSEN RA et al. (1999) Dlx5 regulates regional development of the branchial arches and sensory capsules. *Development* **126**, 3831–46.

FERGUSON C, TUCKER AS, CHRISTENSEN L, LAU A, MATSUK MM, SHARPE PT (1998) Activin is an essential early mesenchymal signal in tool development that is required for patterning of the murine dentition. *Genes and Development* **12**, 2636–2649.

FERGUSON C, TUCKER AS, SHARPE PT (2000) Temporo-spatial cell interactions regulating mandibular and maxillary arch patterning. *Development* **127**, 403–412.

FRANCIS-WEST PH, TATLA T, BRICKELL P (1994) Expression patterns of bone morphogenetic proteins Bmp-4 and Bmp-2 in the developing chick face suggest a role in outgrowth of the primordia. *Developmental Dynamics* **201**, 168–178.

FRANCIS-WEST P, LADHER R, BARLOW A, GRAVESON A (1998) Signalling interactions during facial development. *Mechanisms of Development* **75**, 3–28.

GAUNT SJ, BLUM M, DE ROBERTIS EM (1993) Expression of the mouse goosecoid gene during mid-embryogenesis may mark mesenchymal cell lineages in the developing head, limbs and body wall. *Development* **117**, 769–778.

GRIGORIOU M, TUCKER AS, SHARPE PT, PACHNIS V (1998) Expression and regulation of Lhx6 and Lhx7, a novel subfamily of LIM homeodomain encoding genes, suggests a role in mammalian head development. *Development* **125**, 2063–2074.

KRATOCHWIL K, DULL M, FARINAS I, GALCERAN J, GROSSCHEDL R (1996) Lef1 expression is activated by BMP-4 and regulates inductive tissue interactions in tooth and hair development. *Genes and Development* **10**, 1382–1394.

LANCTÔT C, LAMOLET B, DROUIN J (1997) The bicoid-related homeoprotein Ptx1 defines the most anterior domain of the embryo and differentiates posterior from anterior lateral mesoderm. *Development* **124**, 2807–2817.

LANCTÔT C, MOREAU A, CHAMBERLAND M, TREMBLAY ML, DROUIN J (1999) Hindlimb patterning and mandible development require the Ptx1 gene. *Development* **126**, 1805–1810.

MACKENZIE A, LEEMING GL, JOWETT AK, FERGUSON MW, SHARPE PT (1991) The homeobox gene Hox 7.1 has specific regional and temporal expression patterns during early murine craniofacial embryogenesis, especially tooth development in vivo and in vitro. *Development* **111**, 269–285.

MACKENZIE AL, FERGUSON MWJ, SHARPE PT (1992) Expression patterns of the homeobox gene Hox-8 in the mouse embryo suggest a role in specifying tooth initiation and shape. *Development* **115**, 403–420.

MATZUK MM, KUMAR TR, VASSALLI A, BICKENBACH JR, ROOP DR, JAENISCH R et al. (1995) Functional analysis of activins during mammalian development. *Nature* **374**, 354–356.

MCCOLLUM MA (1999) The robust australopithecine face: a morphogenetic perspective. *Science* **284**, 301–305.

MCCOLLUM MA, SHARPE PT (2001) Developmental genetics and early hominid craniodental evolution *Bioessays*, in press.

NEUBÜSER A, PETERS H, BALLING R, MARTIN GR (1997) Antagonistic interactions between FGF and BMP signaling pathways: a mechanism for positioning the sites of tooth formation. *Cell* **90**, 247–255.

OSUMI-YAMASHITA N, NINOMIYA Y, DOI H, ETO K (1994) The contribution of both forebrain and midbrain crest cells to the mesenchyme in the frontonasal mass of mouse embryos. *Developmental Biology* **164**, 409–419.

QIU M, BULFONE A, GHATTAS I, MENESES JJ, CHRISTENSEN L, SHARPE PT et al. (1997) Role of the Dlx homeobox genes in proximodistal patterning of the branchial arches: mutations of Dlx-1, Dlx-2, and Dlx-1 and -2 alter morphogenesis of proximal skeletal and soft tissue structures derived from the first and second arches. *Developmental Biology* **185**, 165–184.

QIU M, BULFONE A, MARTINEZ S, MENESES JJ, SHIMAMURA K, PEDERSEN RA et al. (1995) Null mutation of Dlx-2 results in abnormal morphogenesis of proximal first and second branchial arch derivatives and abnormal differentiation in the forebrain. *Genes and Development* **9**, 2523–2538.

REIF W-E (1982) Evolution of dermal skeleton and dentition in vertebrates: odontode-regulation theory. *Evolutionary Biology* **15**, 287–368.

RIVERA-PÉREZ JA, MALLO M, GENDRON-MAGUIRE M, GRIDLEY T, BEHRINGER RR (1995) Goosecoid is not an essential component of the mouse gastrula organizer but is required for craniofacial and rib development. *Development* **121**, 3005–3012.

RIVERA-PÉREZ JA, WAKAMIYA M, BEHRINGER RR (1999) Goosecoid acts cell autonomously in mesenchyme-derived tissues during craniofacial development. *Development* **126**, 3811–3821.

SATOKATA I, MAAS R (1994) Msx1 deficient mice exhibit cleft palate and abnormalities of craniofacial and tooth development. *Nature Genetics* **6**, 348–356.

SHARPE PT (1995) Homeobox genes and orofacial development. *Connective Tissue Research* **32**, 17–25.

SMITH MM, COATES MI (1998) Evolutionary origins of the vertebrate dentition: phylogenetic patterns and developmental evolution. *Eur. J Oral Sci* **106**, 482–500.

SMITH MM, COATES MI (2001) The evolution of vertebrate dentitions: phylogenetic pattern and developmental models. In *Major Events in Early Vertebrate Evolution*. (ed. Ahlberg PE). London: Taylor & Francis.

THESLEFF I, SHARPE PT (1997) Signalling networks regulating dental development. *Mechanisms of Development* **67**, 111–23.

THOMAS BL, SHARPE PT (1998) Patterning of the murine dentition by homeobox genes. *Eur. J. Oral. Sci* **106** (Suppl. 1), 48–54.

THOMAS BL, TUCKER AS, QUI M, FERGUSON CA, HARDCASTLE Z, RUBENSTEIN JL et al. (1997) Role of Dlx-1 and Dlx-2 genes in patterning of the murine dentition. *Development* **124**, 4811–4818.

TUCKER AS, SHARPE PT (1998) Molecular genetics of tooth morphogenesis and patterning: the right shape in the right place. *Journal of Dental Research* **78**, 826–834.

TUCKER AS, MATTHEWS KL, SHARPE PT (1998) Transformation of tooth type induced by inhibition of BMP signaling. *Science* **282**, 1136–1138.

TUCKER AS, YAMADA G, GRIGORIUO M, PACHNIS V, SHARPE PT (1999) Fgf-8 determines rostral-caudal polarity in the first branchial arch. *Development* **126**, 51–61.

VAN GENDEREN C, OKAMURA RM, FARINAS I, QUO R, PARSLOW TG, BRUHN L et al. (1994) Development of several organs that require inductive epithelial-mesenchymal interactions is impaired in *LEF-1* deficient mice. *Genes and Development* **8**, 2691–2703.

YAMADA G, MANSOURI A, TORRES M, STUART ET, BLUM M, SCHULTZ M et al. (1995) Targeted mutation of the murine goosecoid gene results in craniofacial defects and neonatal death. *Development* **121**, 2917–2922.

ZHAO Y, GUO Y-J, TOMAC AC, TAYLOR NR, GRINBERG A, LEE EJ et al. (1999) Isolated cleft palate in mice with a targeted mutation of the LIM homeobox gene Lhx8. *Proceedings of the National Academy of Sciences of the USA* **96**, 15002–15006.