The Baboon Model for Dental Development

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1 Introduction

The dental research implications of the physiological, immunological, and morphological similarities between baboons and humans have long been recognized (Virgadamo et al., 1972; Aufdemorte et al., 1993). Applied dentistry has widely employed the baboon as a model upon which to develop procedures and techniques and to test material biocompatibility prior to introduction into general practice on humans. For example, baboons have been used for the tests of procedures to mechanically modify jaw bone growth (Bell et al., 1999), tests of responses to allograft mixtures for bony reconstructions (Kohles et al., 2000), development for therapeutic osteogenesis and functional and morphological bone repair techniques (Ripamonti, 1992), tests of gene products (such as BMP proteins) to induce periodontal regeneration (Ripamonti et al., 2001), protocols for stabilizing jaws for treating fractures (Fisher et al., 1990), assessments of bone response to prosthetic fit (Carr et al., 1996), and tests of responses to orthodontic apparatus (Woods and Nanda, 1991). Comparisons of different types of implants (Hamner, 1973; Foti et al., 1999), implant protocols (Dortbudak et al., 2002), and long-term implant effects (Whittaker et al., 1990) have been conducted using the baboon model. A variety of treatments have been assessed in the baboon model including cavity treatment protocols (Fuks et al., 1990), effectiveness of restorative and implant alloys and amalgams (Gettleman et al., 1980), capping procedures and agents (Pameijer and Stanley, 1998), biocompatibility of endodontic materials (Pascon et al., 1991), root canal sealers (Perlmutter et al., 1987), procedures for apicoectomies, pulp wounds, and furcation perforations (Oguntebi et al., 1988; Das et al., 1997; Rafter et al., 2002), and instrumented prostheses (Hohl and Tucek, 1982). Digital imaging technologies for pretreatment planning (Rajnay et al., 1996) and protocols for and effects of segmental osteotomies (Lownie et al., 1996) have been tested in baboons. Baboons have also served as models for oral diseases and infections (McMahon et al., 1990; Miller et al., 1995), including carcinogenesis (Hamner, 1973).

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In addition to these many practical applications, dental growth and development in the baboon have proven to be a highly informative model for understanding human odontogenesis. This chapter focuses on the current knowledge of dental development and how the baboon model has contributed to it. We also discuss how the baboon model may shape the future of this research.

The study of dental development has expanded rapidly over the past 15 years. What was once a field of inquiry dominated by comparative studies of eruption, mineralization sequence, and timing has been transformed during the past three decades into one of the most intriguing subjects in developmental biology and genetics. Fueled by the revolutionary technological and scientific advances in molecular biology and genetics, this transformation has somewhat diminished the overall impact that baboon research has on the field in general. In other ways, these advances provide new opportunities and directions for baboon dental research. Currently, research in dental development is focused primarily on four salient processes: those responsible for establishing the overall dental formula, development of specific crown morphology, crown mineralization, and crown eruption scheduling. These processes are interrelated and probably share genetic and non-genetic determinants, but for ease of discussion we address each of them separately. We first review what is known about each issue and then discuss the historical involvement, and future, of the baboon model in each.

2 Development of the Dental Formula

Advances toward understanding the processes and patterning mechanisms that result in the dental formula have been made primarily through gene expression and knockout studies of mice (Maas and Bei, 1997; Stock et al., 1997; Weiss et al., 1998; Jernvall and Thesleff, 2000; Stock, 2001; Tucker and Sharpe, 2004). Researchers are interested in knowing, for example, how incisors are produced in one region of the mouth and molars in another and how the number of teeth is established. This overall dental patterning may be the result of a combinatorial code of gene expression, much like that seen for *Hox* genes and the vertebral column (Kessel and Gruss, 1991; Condie and Capecchi, 1993). Because *Hox* genes are not expressed in the tissues from which the dentition develops, several other homeobox genes from the *Barx*, *Dlx*, and *Msx* families have been implicated in an odontogenetic code model (Sharpe, 1995; Thomas and Sharpe, 1998). Another model, based on the concept of reaction-diffusion or Bateson-Turing processes, also has been proposed. In this model morphogens interact in differential wave-like patterns to produce spatial variation in chemical reactions, such as inhibition, production, and autocatalysis (Turing, 1952; Kieser, 1984; Jernvall, 1995; and Jernvall et al., 1998; Weiss et al., 1998). Cells respond to these spatial morphogenetic variations and produce spatially patterned morphology, such as in pigmentation, mineralization, or location of scales or feathers. Current experimental and syndromic evidence can be interpreted to

support both models (Vastardis et al., 1996; Thomas et al., 1997; Ferguson et al., 1998; van den Boogaard et al., 2000).

Morphologically different tooth classes are determined, differentiate, grow, and develop within the maxilla and mandible; therefore, an explanation for their ultimate patterning may be found in the development of these bony tissues. Early in development the first arch of the embryo gives rise to the right and left mandibular arches that grow distally from the body and join at midline to form the mandibular symphysis. The maxillary arch forms from both the first arch and the frontonasal mass. The maxillary incisors derive from the frontonasal tissue whereas the maxillary canines, premolars, and molars derive from the first arch processes. Several feasible processes have been proposed to determine maxillary versus mandibular concerted patterning (Zhao et al., 2000a; Weiss et al., 1998), but gene expression studies to date have been unable to provide clear evidence as to which, if any, of these models is correct.

Morphological studies of development show considerable correlation between maxillary and mandibular tooth shape, suggesting that the growth and development of teeth in both arches may be influenced by common genetic and/or environmental factors (Marshall and Butler, 1966; Butler, 1992; Jernvall and Jung, 2000). Olson and Miller (1958) studied the morphological integration in the postcanine dentition of the South American monkey *Aotus trivirgatus* and found differences in the patterns of correlation between linear size measures of upper and lower teeth. Their results also can be interpreted to imply shared effects of genes, environmental factors, or both to the growth and to the development of the upper and lower jaws. Cheverud and colleagues (Cheverud, 1996; Leamy et al., 1999; Workman et al., 2002) have used quantitative genetic analyses to detect morphological integration resulting from the shared effects of genes (or pleiotropy) and ultimately correlate morphologically integrated units with quantitative trait loci (QTL) effects. Our own quantitative genetic analyses of dental variation in the captive, pedigreed breeding colony at the Southwest National Primate Research Center (SNRPC) in San Antonio, Texas, have yielded evidence for a genetic basis for morphological integration between maxillary and mandibular dental patterning (Hlusko and Mahaney, 2003).

The mechanisms that determine the number and position of teeth do not always result in a normal human dentition, causing numerous problems for affected individuals (Mossey, 1999; Vastardis, 2000). Missing teeth, or agenesis, is quite common in humans, with most patients missing just one or two of their permanent teeth [hypodontia (Matsumoto et al., 2001)]. Though these do result in spacing problems that often necessitate orthodontic treatment, the affected phenotypes are relatively mild. Agenesis is also associated with several more severe genetic syndromes, such as infantile osteopetrosis (Jälevik et al., 2002), segmental odontomaxillary dysplasia [SOD (Prusack et al., 2000)], and incontinentia pigmenti [Block-Sulzberger syndrome (Macey-Dare and Goodman, 1999)]. The affected phenotypes associated with infantile osteopetrosis can be reduced through bone marrow transplants soon after birth (Jälevik et al., 2002). Though this will induce development of some of the teeth, not all of them ultimately form and those that do are malformed. Incontinentia

pigmenti is an X-linked disorder affecting skin, teeth, eyes, hair, the central nervous system, and skeletal structure (Macey-Dare and Goodman, 1999). Both of these syndromes indicate significant pleiotropy between tooth patterning and many other systems. From what is known from the gene expression and knock-out studies, dental patterning is established quite early during development, as shown by the studies of segmental odontomaxillary dysplasia in humans. This is a non-progressive unilateral expansion of the maxillary bone limited to the premolar region. One or more premolars are typically missing in the affected region. It appears as though something early in development has been disrupted though the phenotype does not present until the age of nine or so (Prusack et al., 2000).

The presence of supernumerary teeth is also fairly common. Frequent manifestations of these are relatively underdeveloped teeth that occur in the maxillary palatal midline (mesiodens) which do not usually erupt but cause a diastema between the upper central incisors (Kurol, 2002). Supernumerary teeth can result in more serious problems when they fuse with other teeth (Kobayashi et al., 1999), erupt ectopically (Ericson and Kurol, 1987), or are associated with more severe phenotypes such as cleft palate (Aslan et al., 2000). There are even more severe syndromes such as cleidocranial dysplasia, an autosomal dominant disorder that hinders osteoblast differentiation which commonly results in supernumerary teeth and serious malocclusion (Cooper et al., 2001).

There is considerable evidence that many occurrences of missing and supernumerary teeth are heritable (Mossey, 1999). There is significant interpopulational variation in the prevalence of hypo- and hyperdontia; population prevalence estimates for congenitally missing teeth range from 1.6% in a survey of a non-inbred United States population to 36.5% in an inbred North American genetic isolate (Mahaney et al., 1990). Family studies of human subjects have demonstrated the linkage between agenesis and two homeodomain genes. Vastardis et al. (1996) find that a missense mutation in homeobox gene *MSX1* is present in all family members affected with some form of cleft palate and/or cleft lip. This gene is located on chromosome 4p and the mutation results in a haploinsufficiency (Hu et al., 1998). Similarly, Stockton et al. (2000) report a *PAX9* frameshift mutation that is present in all members of a family missing their permanent maxillary and mandibular molars, but otherwise having normal dental phenotypes. Vastardis (2000) advocates the use of such "family study" methods, suggesting that they will not only contribute to elucidating the genetic mechanisms that determine dental patterning but also possibly enable preclinical diagnosis, improving orthodontic treatment.

The baboon model promises to contribute significantly to our understanding of the mechanisms that determine the number and positioning of teeth. Agenesis and supernumerary teeth in baboons have yet to be studied, although there is anecdotal evidence from the SNPRC colony suggesting that such an investigation would be informative. Four of six individuals with erupted fourth molars are half-siblings with a common father (L. J. Hlusko, unpublished data).

3 Development of Tooth Crown Morphology

The next step in dental development involves the processes that determine number, size, shape, and placement of cusps on individual teeth (Jernvall and Thesleff, 2000; Stock, 2001). Most of our understanding of the events in these processes is derived from the mouse model or from human genetic syndromes that affect them. By mouse embryonic day 12 (E12) tooth buds have formed as outgrowths of a thickened band of epithelial tissue (the dental lamina), possibly specified by antagonistic FGF and BMP signaling. As the tooth bud invaginates into the mesenchyme, the inductive potential shifts from the epithelial tissue to the mesenchyme, initiating what is known as the cap stage. A condensation of non-proliferating epithelial cells then forms at the tip of the tooth bud. This condensation, known as an enamel knot, does not proliferate, expresses many of the same signaling molecules as other embryonic signaling centers, and is surrounded by fast-reproducing epithelial cells (Jernvall et al., 1998). The enamel knot grows distally from the mesial aspect of the tooth bud into a bullet-shaped structure (Jernvall et al., 1994); this structure then undergoes apoptosis in reverse order from its original growth, i.e., the most distal region dies off first (Vaahtokari et al., 1996).

This primary enamel knot gives rise to secondary enamel knots (E15-E16), circular condensations located at what becomes the tip of each cusp. The secondary enamel knots express virtually all the same known regulatory genes as the primary enamel knot (Jernvall, 2000), and no differences in homeobox gene expression have been found between the various cusps (Zhao et al., 2000b). However, species-specific cusp arrangements first appear with the development of the secondary enamel knots and are closely correlated with immediately preceding *Fgf4*, *Shh*, *Lef1*, and *p21* spatial expression patterns (Jernvall and Thesleff, 2000; Keränen et al., 1998; Jernvall et al., 2000).

Humans with anhidrotic ectodermal dysplasia have a genetic mutation that causes buccal and lingual molar cusps to be compressed or fused (Ferguson et al., 1997; Srivastava et al., 1997). *Tabby* mice have the same genetic mutation and a similar phenotype. When these affected mouse molars are cultured in vitro with FGF4 and –10, they have partially corrected cusp development (Pispa et al., 1999). Other genetic syndromes also result in abnormal tooth morphology, such as infantile osteopetrosis that causes agenesis or peg-shaped tooth crowns (Jälevik et al., 2002). Osteogenesis imperfecta is sometimes associated with bulbous crowns (O'Connell and Marini, 1999). Dyskeratosis congenital is an ectodermal disorder that results in diminutive maxillary lateral incisors and short roots (Brown, 2000). A wider phenotypic spectrum results from *22q11* deletion syndrome including cleft palate, enamel hypoplasia, hypomineralization, agenesis, and some abnormal tooth morphology in association with heart and immune problems, making these patients difficult to treat. Rieger syndrome also has a fairly wide phenotypic spectrum in which missing, small, and/or malformed teeth are associated with mild craniofacial dysmorphism, ocular anomalies, and umbilical stump abnormalities associated with a *PITX2* mutation (Amendt et al., 2000).

To date, the development of tooth crown morphology in the baboon has been investigated only to a limited degree by a few researchers. Baume and Lapin (1983) studied 500 baboon dentitions and found that inbred baboons have larger teeth than outbred baboons, although other morphological traits do not appear to be affected by inbreeding. Byrd (1977) studied non-metric traits across a range of Old World monkeys and found that second molars significantly exceeded first molars in presence and degree of expression of all traits studied, lending support to the interpretation of the action of morphogens.

In our analyses of molar crown variation, we are studying size and shape phenotypes. We have employed analytical approaches designed to detect and estimate independent and shared genetic and non-genetic effects (Almasy and Blangero, 1998) on complex traits like these. Patterns of shared effects are informative of the underlying patterning mechanism and may indicate the levels of hierarchical patterning previously unidentified. These analyses show that variations in specific dental crown size phenotypes in baboons are largely determined by the genes and environmental factors, which also contribute to variation in overall tooth size, body size, as well as by sex of the animal (Hlusko, 2000; Hlusko et al., 2002). In contrast, dental crown shape phenotypes appear to be more independent, not sharing common genetic or environmental underpinnings with these other factors [(Hlusko et al., 2004a) see Table 10.1]. A baboon whole genome linkage map exists (Rogers et al., 2000), making possible the genome screens for QTLs responsible for all or part of the detected genetic effects on these and other dental phenotypes. Our preliminary whole genome search for QTLs influencing variation in one of the shape

Table 10.1 Quantitative genetic analytical results for two baboon dental traits[a]

	Cingular remnant		Enamel thickness	
	RM^2	RM_2	LM_2	RM_2
N	310	303	336	332
Total h^2	0.50	0.53	0.40	0.32
Total c^2	0.03	0.10	0.04	0.00
Total e^2	0.47	0.37	0.56	0.68
Residual h^2	0.52±0.15	0.58±0.16	0.32±0.16	0.44 ±0.12
β length	↑↑	↑↑↑		
β width				
β age	↑	↑↑↑	↓	
β sex				
β age^2	↑			
β age∗sex	↓	↓		

[a] Direction of arrow indicates the direction of covariate effect; ↑ = sig $p < 0.10$; ↑ ↑ = sig $p < 0.01$; ↑↑↑ = sig $p < 0.001$; Total h^2: proportion of total phenotypic variance due to additive effects of genes; Total c^2: proportion of total phenotypic variance due to effects of significant covariates; Total e^2: proportion of total phenotypic variance due to random, unmeasured effects; Residual h^2: proportion of residual phenotypic variance (i.e., remaining after accounting for proportion due to significant covariate effects) due to additive genetic effects ± the standard error.

phenotypes has yielded suggestive evidence for a locus on baboon chromosome 5 that maps to a region of human chromosome 4q. This region is known to harbor the Casein gene cluster (Kawasaki and Weiss, 2003) and the genetic mutation underlying dentinogenesis imperfecta described below.

4 Tooth Crown Mineralization

During the bell stage (E16) of mouse odontogenesis, the enamel-forming ameloblasts derive from the epithelium and the mesenchyme gives rise to odontoblasts that form dentine. It is at this point in the mouse model that mineralization of the crown begins (for review see Simmer and Hu, 2001). Enamel comprises 96–97% calcium hydroxyapatite, having one of the highest mineral contents of all biological tissues. This tissue is secreted in daily increments as the ameloblast cells progress linearly from the dentino-enamel junction toward the occlusal surface of the tooth forming prism cross-striations that are preserved in the enamel structure. These daily increments are marked by circaseptan incremental markers (striae of Retzius), whose underlying biological cause is unknown. Simultaneously, odontoblasts are progressing inward from the dentino-enamel junction, depositing dentine in a similar rhythmic fashion. The enamel-forming cells are external to the crown and are consequently shed at eruption, resulting in a "locked" morphology alterable only through wear and breakage.

Enamel mineralization is a heterogeneous process involving proteins from at least six different genes (including amelogenin, enamelin, and ameloblastin) (Robinson et al., 1998). Though many enamel defects are caused by non-genetic factors involved in mineralization (Weerheijm et al., 2001), many others such as amelogenesis imperfecta demonstrate the important role that genes such as those listed above play in enamel mineralization (Robinson et al., 1998). Approximately 90% of the amelogenin expressed, the most abundant of the enamel proteins expressed during early mineralization, derives from genes on the sex chromosomes (Simmer and Hu, 2001). In contrast, human enamelin and ameloblastin are located on chromosome 4q and are associated with autosomal forms of amelogenesis imperfecta (Simmer and Hu, 2001). Dentinogenesis imperfecta is characterized by opalescent and discolored enamel, bulbous crowns, small narrow roots, and reduced pulp chambers and root canals (OMIM, 2001). This is sometimes associated with osteogenesis imperfecta, or brittle bone disease (O'Connell and Marini, 1999), but is known to be caused by a mutation in the *DSPP* gene encoding dentin phosphoprotein and dentin sialoprotein, also found on chromosome 4q (OMIM, 2001).

Enamel defects can also arise as epiphenomenona from genetic disorders and non-genetic trauma. For example, daily increments are halted and enamel hypoplasias form when the individual undergoes stress from birth and serious illness or malnutrition during childhood (Simmer and Hu, 2001). Similarly, hypoplasia is associated with the *22q11* deletion syndrome. Individuals with these enamel defects most commonly suffer from diffuse conditions like frequent infections. Therefore, the enamel defects themselves are probably not caused by the *22q11* deletion but

result as a side effect from the other affected phenotypes that result in stress to the individual during odontogenesis.

Swindler et al. (1968) looked at the calcification of baboon deciduous molars and compared them with the rhesus macaque and humans. They found that the cusp calcification sequence is the same for all three, but that the pattern of coalescence between the cusps differed between the Old World monkeys and humans. Swindler and Meekins (1991) studied the mineralization of the permanent baboon dentition and found that human molars take almost three times as long to mineralize as do baboon molars, though relative timing was effectively the same.

Variation in tooth crown mineralization in humans has been shown to have a significant heritable component. While a number of researchers have inferred genetic influences from observed sex differences and interpopulational differences in the timing of tooth mineralization in boys and girls (Maki et al., 1999), others have obtained direct estimates of the proportion of the phenotypic variance in the measures of enamelization in the studies of human twins (Townsend et al., 2003) and families (Brook and Smith, 1998).

The process and pattern of enamel mineralization appears to be highly conserved across mammalian orders in general, and among our anthropoid primate relatives in particular. It is likely that some of the genetic bases underlying these patterns and processes are also conserved. Therefore, the baboon presents a good model for studies to uncover the factors contributing to both normal and pathological dental crown mineralization. We have conducted statistical genetic analyses of variation in enamel thickness in the mandibular molars of pedigreed baboons (Hlusko et al., 2004b). Our initial analyses indicate that enamel thickness is highly variable in this population; and while genes are responsible for a significant proportion of the variance in this trait in baboons, sex and overall tooth size do not (Table 10.1). Planned QTL searches using the baboon linkage map may provide added confirmation for the roles of some of the genes already known to be involved in tooth mineralization and may point to other genes, hitherto not known to be involved in this process.

5 Dental Eruption Schedule

While significant progress has been made recently in deciphering the biology of dental eruption, the specific relationships between the required signaling molecules are not yet known (for review see Wise et al., 2002). Tooth eruption results from the interactions between osteoblasts, osteoclasts, and dental follicles via several known and possibly many unknown regulatory genes. All evidence to date indicates that each tooth erupts as a localized event, such that overall eruption does not appear to be systemic.

There has been considerable interest in the dental eruption patterns and schedules of animals, especially primates, because it is indicative of age and overall life history strategies (Schultz, 1935; Smith et al., 1994). Anomalies in normal eruption patterns may signify physiological problems, which is perhaps why neonatal and natal teeth have been a documented concern to humans since at least 59 BC (Cunha et al., 2001).

The timing of tooth eruption in many human populations (Loevy and Goldberg, 1999; Wake et al., 2000; Nyström et al., 2001) and other animals (Slaughter et al., 1974; Conroy and Mahoney, 1991; He et al., 2002), including baboons (Kuksova, 1958; Reed, 1973; Siegel and Sciulli, 1973; Schwendeman et al., 1980; Swindler, 1985; Swindler and Meekins, 1991; Phillips-Conroy and Jolly, 1988; Kahumbu and Eley, 1991), has been documented. For both baboons and humans, the teeth of females tend to erupt earlier than those of males. In general, the absolute rate of tooth eruption in baboons is approximately twice that in humans (Smith et al., 1994). However, because the overall rate of somatic development, growth, and maturation in the baboon is two to three times that of humans, tooth eruption probably occurs at roughly comparable developmental stages (Fig. 10.1). Comparisons of wild baboon populations show considerable similarity in eruption times, whereas dental eruption in captive populations occurs 1.5 years earlier than in wild populations (Phillips-Conroy and Jolly, 1988). The timing of dental eruption results from a complex set of environmental factors superimposed on a complex set of genetic factors.

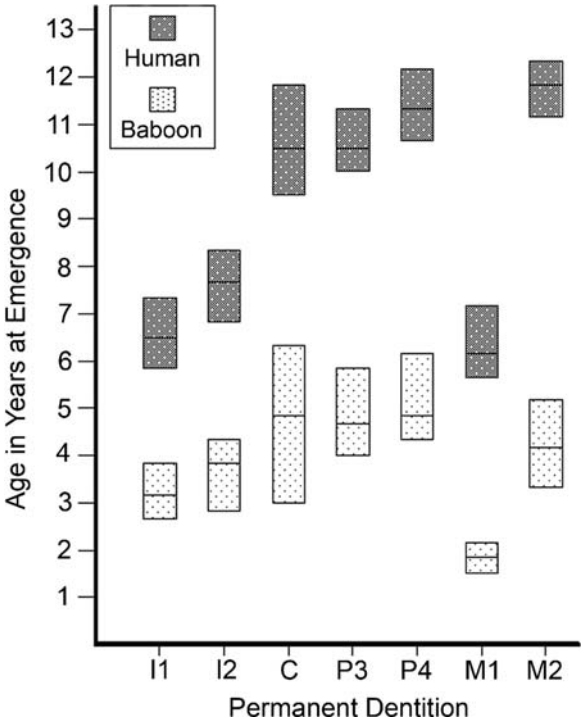

Fig. 10.1 Human and baboon emergence times for the permanent dentition. The middle line within each bar represents the average age at tooth eruption and the box represents the range of reported ages. Data compiled from Reed (1973), Phillips-Conroy and Jolly (1988), Kahumbu and Eley (1991), Eskeli et al. (1999), and Nystrom et al. (2001).

Abnormal dental development is associated with many syndromes (Wise et al., 2002). Delay in dental development can be caused by either a delay in the overall development, mineralization, and eruption of the dentition, or from obstacles that delay the eruption of teeth that formed in a normal time frame. The latter is the most common cause, and results from mechanical hindrances that include abnormality in the surrounding bony structures, such as sclerosteosis (Stephen et al., 2001), prolonged retention of or failure to shed primary teeth (Kurol, 2002), or supernumerary teeth or cysts (Flaitz and Hicks, 2001).

Syndromes that result in disruption to the overall timing of dental development are less common, and typically result from insult to hormonal regulation, such as growth hormone disorders [delay in eruption: GH disorders (Kjellberg et al., 2000); pituitary dwarfism (Kosowicz and Ryzmski, 1977); Laron-type dwarfism (Sarnat et al., 1988); and 21-hydroxylase-deficient non-classic congenital adrenal hyperplasia, or premature eruption (Singer et al., 2001)]. One of the classic and most confounding syndromes is the primary failure of eruption in which the permanent posterior teeth form normally but fail to erupt with no other associated systemic involvement, clearly a failure specifically of the eruption mechanism (Piattelli and Eleuterio, 1991).

6 Conclusions

Like other model organisms, the baboon offers a number of practical advantages over humans for studies of dental biology. For example, its environment can be monitored and/or controlled, allowing for the assessment of the effects of experimental manipulation, select environmental exposures, and genes in relatively large numbers of animals. However, perhaps the most important criterion in the evaluation of an animal model is its fidelity to the modeled species. Higher fidelity models facilitate extrapolation or generalization of research results to the modeled species. The high fidelity of the baboon as a model organism for the study of human dental variation is an obvious function of its phylogenetic proximity and consequent genetic, anatomical, morphological, and physiological similarities to humans.

A baboon is not a furry, smaller, shorter-lived version of a human with human dentition. Its dentition is readily distinguishable from that of our own species by the casual observer, and most of the syndromes and disorders that negatively affect human dental development, morphology, etc. have not been described in baboons. These observations initially may appear to lessen the value of the baboon as a model organism for dental studies. However, we take the position that the baboon is an excellent animal model for studies seeking to understand the contributors to normal variation in dental size, morphology, development, and function. We view pathology – whether evidenced as delayed, accelerated, or otherwise deficient mineralization; morphologically aberrant crown morphology; small, missing, or supernumerary teeth; or premature or delayed eruption and emergence – as the

extreme manifestation of normal variation. We posit that many of the genes and environmental factors that influence normal variation in dental development, morphology, and function are likely to contribute also to abnormal variation and/or disease under certain circumstances. The study of normal variation to gain insight into the processes, mechanisms, and/or factors that contribute to risk for a pathological outcome has proven a valuable adjunct to more common disease-focused studies using the data from humans and nonhuman animals alike.

The baboon is not the only nonhuman primate model for human dental variation, development, and/or disease. Indeed, humans and all their primate relatives share many dental characteristics – a number of which also are shared with non-primate mammals. However, owing to their phylogenetic proximity, odontological concordance is greatest between the members of the primate sub-order Haplorrhini, which includes the hominids (i.e., humans and the great apes) and the cercopithecids, or Old World monkeys (135 species, including macaques and baboons). As Swindler observed more than two decades ago (1985: 91), the degree of inter-specific correspondence in tooth formation likely "demonstrates the great similarities in basic mechanisms governing these processes. Whether in man, Great Ape, or monkey . . . [t]he major difference is time, the events are the same. As the yardstick moves from New World to Old World monkeys and . . . finally to humans, there is a noticeable trend for longer development. However, relative to the entire period of dental development for each group, the individual events appear to take about the same amount of time. It would seem, therefore, that any of these taxa could be used for understanding the processes of tooth formation in the other as long as the sliding time scale is considered." With this in mind, because it is one of the more thoroughly genetically characterized, nonhuman primate species available in suitable numbers for research *at this time*, we suggest that the baboon is perhaps the best animal model in which to dissect the *genetic* underpinnings of dental variation, development, and disease.

As we indicated at the outset of this chapter, following the advent of the molecular revolution in experimental biology, dental developmental biology and genetics by-passed the baboon and other nonhuman primates for smaller, shorter-lived animals like the mouse. This technological shift gave investigators substantial experimental power to dissect dental developmental processes at the cellular and molecular levels. However, generalizing the results of much of this work to humans has been difficult due to the extreme differences between humans and rodent model species. Concurrently, developments in primate genetics and genomics have resulted in increased utility of the baboon for research into dental developmental variation, including large, pedigreed families of baboons; computerized methods for management and analyses of phenotypic and genetic data from these large pedigrees; and a framework whole genome linkage map for the species. While all are essential for the effective use of this nonhuman primate as a model for dental developmental variation, the recently constructed baboon whole genome linkage map has proven the most important key to date. The landmarks on this baboon map are highly polymorphic human microsatellite loci (Rogers et al., 2000). Comparative genomic analyses have confirmed the homology of syntenic groups of these markers in baboons to

those in humans so that localization of a QTL contributing to variation in dental traits in baboons immediately identifies the human chromosomal region in which the gene or genes responsible for the QTL may also reside. These newly developed baboon genomics resources, combined with the species demonstrated value as a model organism for dental developmental variation in humans, should make the baboon an obvious choice for new studies in this and other oral biology-related lines of inquiry, e.g., studies of osteoporosis, oral bone loss, and periodontal disease (Aufdemorte et al., 1993); effects of genes, maternal nutrition, and/or infectious disease status on variation in craniofacial and dental growth and development; and development of "molecular orthodontic" procedures (Wise et al., 2002).

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