The Genetics of Odontogenesis: Implications in Dental Anthropology and Palæo-Odontology

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ABSTRACT Palaeoanthropology and forensic odontology rely significantly upon detailed dental morphology that is ultimately the phenotypic expression of the underlying genotype and developmental phenomena. Odontogenesis is the consequence of a complex series of molecular interactions controlled by epigenetic signals acting on embryonic epithelial-mesenchymal tissues of ectodermal, neural crest and mesodermal origin. Of the estimated 24,847 genes of the human genome (Pearson, 2003) some 200 or more genes have been directly or indirectly involved in tooth development (http://bite-it.helsinki.fi). The loci of these genes on the 22 pairs of autosomes and the pair of sex chromosomes are being identified by their mutations that give rise to phenotypic dental abnormalities. The sequential cascades of stages from initiation through the bud, cap, bell, mineralization, root formation and eruption of teeth are all under genetic control but subject to environmental influences. Identification of specific genes with clinical phenotypes provides invaluable clues to familial, racial and evolutionary affinities, all of jurisprudential, heredity and evolutionary significance to odontologists. Combining the genetics of odontogenesis with forensic evidence and palaeoanthropological fossil data provides an unparalled source of information on heredity, environmental and evolutionary events through teeth, the most durable of all biological structures after death. It is paradoxical that teeth are most susceptible to decay during life, but postmortem are the last structures to disintegrate. Teeth truly tell tales of the living and the dead. *Dental Anthropology 2004;17(1):1-7.*

EVOLUTIONARY GENETICS

> "The crown of the human tooth even in its minute details represents little that is fortuitous. It is the resultant of inherited ancestral conditions, modifying further by evolution and involution."
>
> A. Hrdlička, 1924

Dental characters predominate in the identification of most species and genera, both of fossil and extant varieties. In this respect, teeth are unique among organs in enabling direct comparisons to be made between fresh specimens formed a few months previously and fossils excavated from sediments formed millions of years ago. Teeth depict their genetically inherited patterns, and thus their evolutionary history, more accurately than all other organs. This precision of genetic expression is due to their highly protected developmental environment, ensconced as they are in their submerged dental follicles until their full morphological maturity, before emerging into the potentially damaging environment.

By casting their primeval and delicate genotypic templates into the enduringly fossilized form of highly mineralized phenotypic morphology, teeth are the ultimate and amongst the most perfect extrinsic expressors of the intrinsic units of evolutionary change, the mutations of genes.

The intricate morphology of the crowns of human teeth reflects both a long and complex phylogenetic archival record and a brief but extraordinarily elaborate ontogenetic formulation. This combination of long hereditary and short embryologic developments lies within the genes determining tooth shapes. The influence of phylogenetic factors upon the ontogeny of teeth is responsible for many of the factors peculiar to odontogenesis, making the study of dental development at the forefront of "evo-devo" exploration. The divergence of taxa heretofore based exclusively on fossil remnants may now be pursued by studying the selective action of genes during developmental processes (McCollum and Sharpe, 2001). New pathways of palaeoanthropological research are now being revealed by the genetic revolution.

The genetics underlying phenotypic dental characteristics that are directly observable has enabled rates and degrees of gene flow to be calculated and genetic drift to be estimated in divergent populations. Mutations may be traced in this manner, and the

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selective advantages of particular dental conformations might account for dental micro-evolution. The development of cusps, ridges and fissures that enhance the predatory and masticatory capability of teeth are evolutionary advancements that correlate with different diets and environmental niches.

DEVELOPMENTAL GENETICS

The complexity of contributions of over 200 genes to odontogenesis makes the elucidation of each genes' individual responsibility for each stage of development a daunting task. Most of these genes encode signals as well as their receptors, both in the cytoplasm and in transcription factors regulating gene expression in the nucleus (Thesleff, 2000). It is the mutation or deletion of these genes, by phenotypically expressing dental malformations or anodontia, or by experimental "knock outs" of specific genes, that some of the responsibilities of each gene is revealed. The intricacies of RNA editing, complex regulatory networks and criss-crossing molecular pathways makes meaningless the exact identification of genetic units. Moreover, the overlapping and redundancy of genetic expression patterns during development make the unravelling of the skein of influences particularly difficult.

Teeth initially developed in primitive fishes from the adaption of placoid scales overlying their jaws to form dermal denticles (Smith and Johanson, 2003). With the pending identification of genes responsible for the development of ectodermally-derived hard tissues, the revelation of the evolution of teeth becomes a possibility in the newly emerging discipline of phylogenomics (Eisen and Fraser, 2003). The synteny of conserved genes across species will account for the identification of "dental" genes in human odontogenesis having initially evolved in piscine species. This phylogenetic dermal origin of teeth is reflected in the embryonic development of human teeth, which although they develop submerged beneath the oral gingival epithelium, originate in part from ectodermal tissue. Teeth are derived from two of the primary germ layers, ectoderm and mesoderm, with a neural crest contribution. The enamel of teeth is derived from oral ectoderm, and neural crest mesenchyme provides material for the dentine, pulp and cementum. The periodontium is of both neural crest and mesodermal origin.

The morphogenesis of the maxillary and mandibular teeth is under the control of two different genetic programs, accounting for variation between upper and lower dentitions that provide for taxonomic distinctions. Combinations of different sized teeth within individuals reflect mosaic evolutionary derivations (McCollum and Sharpe, 2001).

An early signally event in tooth development at 6 weeks postconception is the induction of odontogenic mesenchyme by bone morphogenetic proteins (BMPs) and fibroblast growth factors (FGFs) from the oral ectoderm. These initial odontogenic epithelial signals induce in the mesenchyme the expression of reciprocal signal molecules to the epithelium that results in the formation of the dental placode. The placodal signals, expressed as Sonic hedgehog (SHH), Wingless (Wnt) and tumor necrosis factor (TNF) molecules regulate the budding of the epithelium and condensation of the mesenchyme, effectively creating tooth buds (Thesleff and Mikkola, 2002). The number of tooth buds developing in each jaw is genetically determined, with an initial identicality that is later altered by their location. The differential odontogenic patterning creating a variety of tooth shapes (incisors, canines, molars) is organized by a homeodomain code of transcription factors expressed in restricted regions during development (Sharpe, 1995; Tucker and Sharpe, 1999; Cobourne and Sharpe, 2003). These factors include the Msx genes, Dlx family members, Pax 9, Lhx genes and Barx1 (Francis-West *et al*., 1998, Maas and Bei, 1997; Jung *et al*., 2003). The precise role of many of these signaling molecules during early budding is still under investigation. Barx1 expression is restricted to the presumptive proximal (posterior) region of the first pharyngeal arch, influencing the tooth buds to a molarization pattern (Tucker *et al*., 1999). The LIM homeodomain protein Islet 1 (ISL1) that is exclusively expressed in the presumptive incisor epithelium coincides with expression of Bmp4 that induces MSX1 expression in the underlying mesenchyme (Mitsiadis *et al*., 2003). The mesenchyme of the presumptive distal (anterior) region of the first arch expresses both Msx1 and Alx3 homeobox genes that determine incisiform shapes to the developing tooth buds (ten Berge *et al*., 1993). The region of overlap between Msx and Dlx genes codes for canines and premolars (Fig. 1).

The transcription factor Runx 2 and the signal Fgf 3 regulate epithelial morphogenesis from bud to cap stages. A primary enamel knot forms at the tip of the tooth bud, consequent to BMP 4 induction. The exit of enamel knot cells marks the onset of development of the tooth crown to form a cap-like structure that surrounds the underlying mesenchyme, referred to as the dental papilla. A SHH signal from the enamel knot is required for the growth of the epithelial cervical loops flanking the enamel knots and encompassing the dental papilla (Thesleff, 2003). Primary enamel knots initiate secondary enamel knots, thereby regulating the patterning of the tooth crown.. The arrangements and intercuspal dimensions of molar teeth are determined by the enamel knots (Townsend *et al*., 2003). Enamel knots are transient signaling centers that disappear by apoptosis (Vaahtokari *et al*., 1996). The consequent epithelial sheet folds in an exact sequence to produce undulating peaks and valleys, adumbrating cusps and fissures in the future crowns. This folding must involve

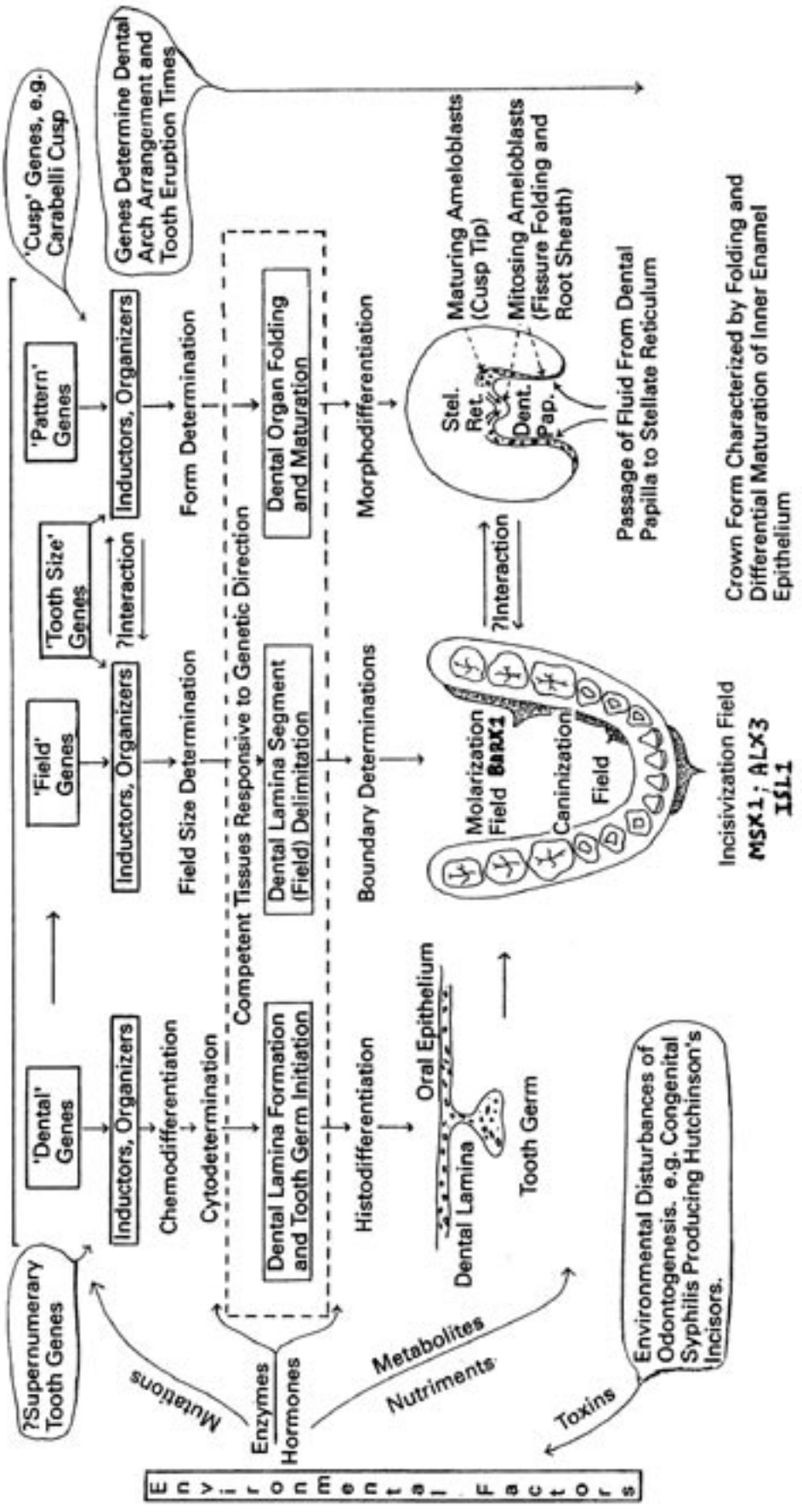

Fig 1. Schematic depiction of factors operating in odontogenesis.

differential mitotic activity by inhibition and activation determined by gene expression patterns to produce different tooth shapes (Salazar-Ciudad and Jernvall, 2002).

ENAMEL FORMATION

The secretion of the proteins unique to the enamel matrix, ameloblastin, amelogenin, enamelin and tuftelin by ameloblasts precedes the most intense mineralization of any tissue in the body (Dong *et al*., 2000). The ameloblast, the heralder of the hardest of human tissues, lays down a matrix that by mineralization becomes petrified, providing fossilized, immortal remains within the living jaws. Enamelin, the largest enamel extracellular matrix protein is a uniquely ameloblastic secretion, and is involved in the nucleation of apatite crystals (Gibson, 1999). Enamelin persists in mature enamel, whereas ameloblastin and amelogenin occur only temporarily in immature enamel (Robinson *et al*., 1989; Deutsch 1989). Moreover, there is an evolutionary sequence to the appearance of these proteins, with enamelins appearing earlier in phylogenetic history than amelogenins, and differing in their distribution among species (Herold *et al*., 1989), emphasizing the relationship of molecular biology to phylogeny. The tuftelin gene (TUFT1) has been mapped to chromosome 1q (Deutsch *et al*., 1994). The gene for the ameloblastin protein, AMBN, is located on chromosome 4q, and is a single copy gene containing 13 exons (Toyosawa *et al*., 2000).

ENAMEL THICKNESS

The speed and direction of migration of the ameloblasts in laying down enamel matrix, again under genetic control, determines the ultimate thickness of the enamel cap of the dental crown. The limited life of postmitotic ameloblasts, determined by their programmed early cell death, varies in different locations on the dental crown surface. This accounts for the varying ultimate thickness of enamel, from minimal along the cervical margins and in fissure depth, to maximal over the cusp peaks. This variation of enamel thickness not only reflects the longevity of ameloblasts, but also the speed of their migration. This combination of ameloblastic activities varies phylogenetically, accounting for the different maximal thicknesses of enamel found among hominoids and hominins (Beynon and Wood, 1986; Grine and Martin, 1989). The thin enamel of the gorilla, chimpanzee and orangutan contrasts strongly with the thick enamel of Homo sapiens and the australopithecines. The folivorous diet of the great apes, relatively free of abrasive grit, is not as wearing on dental enamel as the gritty omnivorous diet of hominins. Enamel thickness is correlated with longevity, as hominins long outlive pongids. The periodicity of incremental deposition of the enamel matrix leading to the striae of Retzius, allows for age assessment at the time of death or exfoliation of extant and fossil teeth (Boyde 1963; FitzGerald 1996; Shellis 1998). During the year or two that a tooth develops and erupts, it accumulates isotopes of carbon and oxygen. Variations in the ratios of C^{13} to C^{12} and O^{18} to O^{16} provide evidence of the ambient diets of fossilized teeth. This isotopic evidence, in turn, may provide information on the provenance of recovered remains, even to the extent of tracing habitats and migrations during a lifetime, as revealed by the peregrinations of the Alpine Iceman (Müller *et al*., 2003).

Ameloblasts are extremely sensitive to metabolic, dietary and drug influences during enamel matrix deposition. The mechanisms of mineralized tissue deposition during amelogenesis provide a kymographic record of the state of metabolism and nutrition of the individual that is permanently entombed in the hard dental tissues.

Accordingly, illnesses and drug therapy during amelogenesis may be recorded as hypoplasias, hypomineralization or distinctive marks in matured enamel. Such examples as tetracyline staining or the neonatal line reflecting the change from intrauterine to extrauterine nutrition are ineradicably imprinted on enamel.

Incremental enamel apposition produces surface perikymata that allows determination of variations in their spacing, reflecting chronological deposition rates (Guatelli-Steinberg 2003). These rates have been determined to differ between apes, hominids and hominins (Dean *et al*., 2001). Amelogenesis can provide insights into cladistic relationships of the different species of hominoids, and their different rates of body maturation (Beynon and Dean, 1998; Smith, Martin and Leakey, 2003). The rapid growth of the Neanderthals has been based upon incremental dental data (Rozzi and de Castro, 2004).

The direct association of the sex chromosome genes that influences enamel development with the thickness of this tissue and with taurodontism indicates the ontogenetic link of dental morphology with evolutionary changes and phylogenetic influences. The aneuploid presence of extra sex chromosomes (47, XXX females, 47, XYY males) manifest thicker than normal enamel (Alvesalo *et al*., 1985; Alvesalo *et al*. 1987). Taurodontism, a trait carrying strong Neandertaloid associations is linked with aberrant sex-chromosome syndromes (Gage, 1978; Varrela *et al*., 1990).

ODONTOGENESIS

Each tooth germ consists of an enamel organ and a dental papilla surrounded by a dental follicle or sac. The dental papilla, of neural crest origin, and dental follicle of mesodermal origin, are the anlagen of the dental pulp and part of the periodontal apparatus

respectively.

Each enamel organ during its development changes from its initial small bud shape, enlarging by rapid mitosis of the basal cells into a cap shape, and later cupping into a large bell shape, by which shapes the three stages of enamel organ development are designated. Concomitant with these morphological alterations, histodifferentiation occurs within the enamel organ. Its external layer forms the outer enamel epithelium, a layer of cuboidal cells subjacent to the developing follicle. The stellate reticulum, composed of stellate cells set in a fluid matrix, constitutes the central bulk of the early enamel organ. The indented inner layer, lining the dental papilla, forms the inner enamel epithelium, part of which differentiates into the transient secretory columnar ameloblasts that form enamel. Lining a portion of the stellate reticular surface of the inner enamel epithelium is a squamous cellular condensation, the stratum intermedium, that probably assists the ameloblasts in forming enamel. The inner and outer enamel epithelia form the cervical loop, elongating into Hertwig's epithelial root sheath, that, by enclosing more and more of the dental papilla, outlines the root(s) of the tooth. The number of roots of a tooth is determined by the subdivision, or lack thereof, of the root sheath into one, two or three compartments. The regulation of root development is dependent upon genes encoding nuclear factor I (NFI) transcription-replication proteins (Steele-Perkins *et al*., 2003). Aneuploid variation of the X chromosome's "dental genes" appears to influence the mitotic activity of odontoblasts to produce taurodontic teeth (Varrela and Alvesalo, 1988; Varrela *et al*., 1990).

The inner enamel epithelium interacts with the ectomesenchymal cells of the dental papilla, whose peripheral cells differentiate into odontoblasts. The formation of dentine by the odontoblasts precedes, and is necessary for, the induction of premeloblasts into ameloblasts to produce enamel. The inner enamel epithelium of the root sheath induces odontoblast differentiation but, lacking a stratum intermedium, fails to differentiate itself into enamel-forming ameloblasts, accounting for the absence of enamel from the roots. Cementum forms on dentine adjacent to the sites of disintegration of the outer enamel epithelium of the root sheath. The fragmentation of the root sheath, due to programmed cell death (apoptosis) leaves clusters of cells, the epithelial rests of Malassez, in the periodontal ligament. These rests are the source of potential periodontal cysts. The fibers in the initial cementum derive solely from fibers of the pre-existing dental follicle that form the first principal fibers of the periodontal ligament.

The ameloblasts of the inner enamel epithelium and the adjacent odontoblasts together form a bilaminar membrane, which spreads by mitosis under genetic control and varies among the tooth germs in different areas as previously described. The ameloblasts secrete a protein matrix of amelogenins and enamelins that later mineralize as enamel rods or prisms as they retreat from the membrane. Concomitantly, the odontoblasts secrete the collagen matrix of predentine, which later calcifies to dentine. Dentine deposition is a continuous process throughout life. The dental papilla differentiates into the dental pulp, the peripheral cells into odontoblasts, and the remaining cells into fibroblasts. Enamel formation is restricted to the pre-eruptive phase of odontogenesis and ends with the deposition of an organic layer, the enamel cuticle. The enamel organ collapses after deposition of this cuticle. The inner and outer enamel epithelia together with the remains of the stratum intermedium form the reduced enamel epithelium, which later fuses with the overlying oral mucous membrane to initiate the pathway for eruption.

The tissues of the dental pulp, the only unmineralized dental tissues, are confined within the enclosed pulp chamber, protected by the surrounding mineralized tissues. This protection provides the possibility of preservation of pulp tissues beyond death, enabling both forensic and palaeo-odontological investigations to be performed on tissues that may reveal DNA formulations (Komuro *et al*., 1998). Moreover, dental pulp tissues may contain stem cells of highly proliferative clonogenic capability, with the potentiality to differentiate into a variety of cell types (Gronthos *et al*., 2002; Miura *et al*., 2003). The possibility of clinical application of this stem cell source for therapies and tissue engineering remains to be explored, but the cloning of a whole individual from a dental pulp cell is still a fictional absurdity. Nonetheless, dental pulp cells have been shown to provide neurotrophic support for dopaminergic neurons as a treatment modality for Parkinson's disease (Nosrat *et al*., 2004). Moreover, the cultivation of stem cells to produce teeth has been successfully achieved in experiments with mice, and portends the future therapeutic replacement of teeth in humans (Ohazama *et al*., 2004).

CONCLUSIONS

Odontogenesis and phylogenesis are inextric-ably interlinked through genetics in a combination that accounts for the complex functional morphology of the total dentition and its individual units, the teeth. The dental components-the crowns and their cusps, the roots, the pulp chambers and their tissues and the periodontal apparatus-are moulded by the twin forces of evolution and embryonic development. Thus, a synthesis of the features of comparative anatomy and developmental biology with the systematics of evolution is necessary for an understanding of the morphologic diversity and intricate structure of the dentition.

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