Developmental Disorders of the Dentition: An Update

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Dental anomalies are common congenital malformations that can occur either as isolated findings or as part of a syndrome. This review focuses on genetic causes of abnormal tooth development and the implications of these abnormalities for clinical care. As an introduction, we describe general insights into the genetics of tooth development obtained from mouse and zebrafish models. This is followed by a discussion of isolated as well as syndromic tooth agenesis, including Van der Woude syndrome (VWS), ectodermal dysplasias (EDs), oral-facial-digital (OFD) syndrome type I, Rieger syndrome, holoprosencephaly, and tooth anomalies associated with cleft lip and palate. Next, we review delayed formation and eruption of teeth, as well as abnormalities in tooth size, shape, and form. Finally, isolated and syndromic causes of supernumerary teeth are considered, including cleidocranial dysplasia and Gardner syndrome. © 2013 Wiley Periodicals, Inc.

KEY WORDS: mouse; zebrafish; teeth; hypodontia; supernumerary teeth; craniofacial; syndrome

INTRODUCTION

Genetic causes have been identified for both isolated tooth malformations and for the dental anomalies seen in patients with craniofacial developmental abnormalities. Congenitally missing teeth are seen in a host of syndromes, and supernumerary teeth are also central diagnostic findings in a number of syndromes. Additionally, mutations in several genes have been associated with both hypodontia and orofacial clefing.

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in humans and mice, indicating that tooth anomalies and orofacial clefting may share common developmental pathways. Because the study of tooth development is central to understanding the pathogenesis of dental anomalies, this review begins with an overview of recent studies in vertebrate animal models, which is followed by a survey of dental anomalies with known or suspected genetic causes.

LESSONS FROM ANIMAL MODELS

Mouse Dentition: the Major Model System

Most of our knowledge regarding the cellular and genetic basis of mammalian tooth development has come from mouse studies. Although mouse dentition is simpler than that of humans, the developmental mechanisms are thought to be highly conserved between the two. Both humans and rodents have fewer teeth than the unreduced pattern of their mammalian ancestors, in which up to three incisors, one canine, four premolars, and three molars may occur in each dental quadrant. A few species, such as some insectivores, have retained the full pattern of dentition. Humans have two incisors, one canine, two premolars and three molars in the permanent dentition.

The adult mouse dentition is much more reduced than in the human, consisting of three molars at the back of the mouth and one incisor at the front, separated by a toothless region called a diastema, in each quadrant (Fig. 1). Another major difference between mouse and human dentition is that mice have only a single set of teeth, whereas in humans the first set of teeth (primary or deciduous teeth) is replaced by a permanent set during childhood. The mouse therefore provides a simplified model for tooth formation in humans.

Beyond serving as a model for understanding mammalian tooth development in general, studying the development of the reduced dentition in mouse provides two advantages. First, the permanently renewing incisor serves as a model to study the role of stem cells in organ regeneration [Harada et al., 1999; Seidel et al., 2010; Feng et al., 2011; Juuri et al., 2012; Lapthanasupkul et al., 2012; Biehs et al., 2013]. Second, the mouse embryonic jaws contain rudimentary tooth primordia of teeth that were suppressed during evolution [Peterkova et al., 2002b; Hovorakova et al., 2011] (Fig. 1). In the majority of the diastemal tooth primordia, development is arrested [Peterkova et al., 2003], such that the development of the mouse diastema represents a model to study hypodontia [Peterkova et al., 1995]. Some of these rudimentary tooth primordia may be rescued and can give rise to supernumerary teeth [Peterkova et al., 2002a, 2006; Klein et al., 2006], which can model controlled tooth regeneration [Peterkova et al., 2006, 2009; Cobourne and Sharpe, 2010].

Teeth form through a series of reciprocal interactions between epithelium (derived from oral ectoderm) and mesenchyme (derived from cranial neural crest), which begin at mid-gestation.
in mouse embryos [Tucker and Sharpe, 2004]. The interactions between oral epithelium and underlying neural‐crest derived mesenchyme are mediated by secreted signaling molecules from the major signaling families (FGF, TGF‐β, WNT, and HH), which lead to various intracellular events, including expression of transcription factors (e.g., members of the Msx, Pax, and Runx families, discussed below) [Jussila and Thesleff, 2012; Jheon et al., 2013].

As the epithelium and mesenchyme interact, the developing tooth (tooth germ) progresses through several stages (Fig. 2). The first morphological sign of tooth development is a localized thickening of the oral epithelium. Next, the thickened (dental) epithelium invaginates into the underlying mesenchyme, forming a dental lamina and tooth buds, while the adjacent dental mesenchyme condenses around the forming tooth buds. Subsequently, the epithelium around the bud tip extends farther into the mesenchyme, forming a cap and then a bell stage tooth germ. The dental epithelium (enamel organ) is surrounded by a layer of dental mesenchyme (dental sac), and the enamel organ encloses the mesenchymal papilla. The dental papilla arises from a small population of highly proliferative mesenchymal cells in close proximity to the inner dental epithelium and the primary enamel knot [Rothova et al., 2012]. Further epithelial morphogenesis and expansion of the dental mesenchyme results in the formation of cusps. During the bell stage, cusp morphogenesis continues and cytodifferentiation begins, as the epithelial cells closest to the dental mesenchyme become enamel‐producing ameloblasts, and the adjacent mesenchymal cells become dentin‐producing odontoblasts [Ruch, 1995].

Epithelial morphogenesis and growth of the dental mesenchyme during the cap and bell stages are thought to be controlled and coordinated by signals produced by the enamel knot, a morphologically distinct region of the epithelium containing densely‐packed, non‐proliferating cells. The primary enamel knot forms at the center of the tooth germ at the onset of the cap stage [Jernvall et al., 1994] and is subsequently eliminated by apoptosis [Lesot et al., 1996; Vaahtokari et al., 1996]. Secondary enamel knots form at the cusp tips, and signals from them control later aspects of cusp morphogenesis [Jernvall et al., 1998].

In mouse and human, the upper incisors arise largely from the medial nasal process with a minor contribution of the maxillary facial process [Peterkova et al., 1995; Howorakova et al., 2006]. The upper and lower molars arise from the first pharyngeal arch, which appears to be molecularly patterned in terms of tooth location and identity before any morphological signs of tooth development are evident. The mesenchyme of the first pharyngeal arch initially has ubiquitous odontogenic potential, and the odontogenic mesenchyme is specified by its proximity to the oral epithelium, which is the source of the inductive signal. It is thought that FGF8 from the lateral oral epithelium and BMP4 from the medial oral epithelium differentially regulate the expression of transcription factors (e.g., Dlx1, Dlx2, and Barx1 are expressed laterally, whereas Msx1 and Msx2 are expressed medially) [Neubuser et al., 1997; Bei and Maas, 1998; Keranen et al., 1999; St Amand et al., 2000; Thomas et al., 2000]. These expression patterns have been proposed to represent an “odontogenic homebox code” that specifies tooth identity, analogous to homeobox codes found in other developmental systems [Sharpe, 1995].

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The earliest marker for the location of presumptive teeth is expression of Pax9, which results from antagonistic interactions of FGF and BMP signaling. Fgf8 induces Pax9 expression in first pharyngeal arch mesenchyme, whereas Bmp2 and Bmp4 inhibit this induction [Neubuser et al., 1997]. Therefore, Pax9 is expressed only in regions where Fgf8 is present but Bmp2 and Bmp4 are absent. Interestingly, although Pax9 marks the sites of future tooth development, in mouse studies Pax9 itself appears not to be necessary to position teeth or initiate odontogenesis. Thus, in the mouse Pax9 mutant, teeth

![Figure 2](image-url)
develop normally up to the bud stage (E13.5) before arresting, indicating that this gene is critical for bud development but not for tooth initiation [Peters et al., 1998]. The role of Pax9 in human hypodontia is discussed below.

The expression of other genes indicates that, at the earliest stages of tooth development, the instructive information resides in the epithelium. Sonic hedgehog (Shh) expression is restricted to the emerging tooth primordia. The restriction of Shh appears to be due to repression by Wnt7b in the non-dental epithelium [Sarkar et al., 2000]. At the bud stage, the instructive role shifts from the epithelium to the mesenchyme; transcription factors such as Msx1, Pax9, and Runx2 are expressed in the condensed dental mesenchyme [Thesleff, 2006]. These factors, all of which are important in human tooth development as well, promote the expression of secreted signaling molecules including Bmp4, Fgf3, and Wnt5a, which act upon the epithelium and induce the enamel knot.

**Zebrafish Dentition: An Up-and-Coming Model**

In recent years, animal models other than the mouse have emerged for the investigation of early development, organogenesis, and regeneration. Zebrafish in particular have become a favorite laboratory animal, as they are inexpensive to maintain, reproduce easily and abundantly, and have the vertebrate body plan. A vast array of genetic and molecular tools has been developed for zebrafish, which have now been used to model nearly every class of human disease.

The zebrafish has no teeth on its oral jaws, but it has maintained sets of teeth on the rearmost pharyngeal arch as a remnant of the once widespread oral tooth coverage in its remote ancestors. These pharyngeal teeth are continuously replaced throughout life and have been well characterized in terms of patterning, structure and morphodifferentiation [Huysseune et al., 1998; Van der heyden and Huysseune, 2000; Van der heyden et al., 2000] (Fig. 3). A number of studies have addressed the genetic and molecular underpinnings of tooth development and replacement [reviewed by Stock (2007)]. Tooth formation and replacement start early, well before many mutations become lethal (at 48 and 80 hr post-fertilization, resp.) [Borday-Birraux et al., 2006]. This circumvents the lethality encountered when modeling craniofacial anomalies and dental diseases in mouse models. Additionally, because mice do not replace their dentition, dissecting the mechanism of natural lifelong replacement in zebrafish represents a strategy for understanding tooth replacement in mammals that is not possible with the mouse model.

While some developmental genes that are expressed early in mammalian tooth development, such as pax9, are not expressed during zebrafish tooth development [Jackman et al., 2004], many parallels with mammalian teeth exist. The importance of Fgf signaling is similar to that in the mouse. Overexpression of Fgf ligands in zebrafish

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**Figure 3.** Zebrafish tooth development. **A,B:** Schematic representation of the pharyngeal dentition of a zebrafish at 6 days post-fertilization (dpf) (A) and 1-month old (B). Ventral tooth row, yellow; mediodorsal tooth row, ochre; dorsal tooth row, green; replacement teeth not shown in (B). At 6 dpf, primary teeth $3V^1$, $4V^1$, and $5V^1$ are attached, and the first replacement tooth ($4V^2$) is mineralizing. **C:** Alizarin stained and cleared preparation of the dentition of an 8 dpf zebrafish. Tooth $4V^2$ (arrowhead) is more advanced compared to the scheme shown in (A). Note keratinized pad (asterisk) opposing the teeth. **D:** SEM view of ventral teeth $2V$–$5V$ in a juvenile zebrafish (anterior to left). **E,F:** One micrometer plastic cross-sections through the pharyngeal dentition of a 5 dpf wild-type (WT) zebrafish (E) and 5 dpf $edar^{-/-}$ mutant (F). Teeth $3V$, $4V$, $5V$, and replacement tooth $4V^2$ are present in the WT; only $4V^1$ is present in the mutant. **G:** One micrometer plastic cross-section through an attaching tooth in a one month zebrafish; note odontoblasts (od) sending processes (arrowhead) into the dentin (d). Scale bars C,E,F = 25 μm, D = 100 μm, G = 50 μm.
engineered endonucleases such as ZFNs (zinc finger nucleases) and TALENs (transcription activator-like effector nucleases) (reviewed in Huang et al. [2012]). These techniques of reverse genetics hold great promise and will continue to increase the relevance of zebrafish as a model for craniofacial and dental diseases.

HUMAN TOOTH DEVELOPMENTAL ANOMALIES

Genetic tooth anomalies can be divided in three main ways. First, the type of anomaly, whether of number, shape, or both, must be determined. These anomalies can include too many teeth (hyperdontia), too few teeth (tooth agenesis), or abnormalities of shape such as taurodontism (enlargement of the body and pulp of the tooth). Second, it is important to know if the anomaly is syndromic, that is, part of a condition associated with other features, or whether it is isolated. Third, the mode of inheritance must be determined. Sporadic occurrences of genetic anomalies are presumed to be caused by recessive or multifactorial inheritance, by new mutations, or by stochastic occurrences. For the remainder of this review, we will focus on genetic causes of abnormal tooth development and the manifestations of these abnormalities in terms of clinical care; disorders of tooth mineralization are not discussed in this review.

Tooth Agenesis: Hypodontia, Oligodontia, and Anodontia

Hypodontia refers to the absence of one to six teeth, excluding third molars, whereas oligodontia refers to the absence of more than six teeth, excluding third molars. Third molars are excluded, as these are missing in up to 20% of patients, making this a very common finding. Anodontia is the complete absence of teeth in one or both dentitions. Together, these are referred to as tooth agenesis.

Hypodontia can occur as a sporadic finding, as part of a syndrome, or as a non-syndromic familial form. There are over 80 syndromes that include hypodontia (see Online Mendelian Inheritance in Man, http://www.ncbi.nlm.nih.gov/omim), and some representative syndromes are discussed below. Non-syndromic familial hypodontia may be inherited as an autosomal dominant [Alvesalo and Portin, 1969; Vastardis et al., 1996; Goldenberg et al., 2000], autosomal recessive [Ahmad et al., 1998; Pirinen et al., 2001], or sex-linked trait [Erpenstein and Pfeiffer, 1967; De Coster et al., 2009].

Missing teeth are more common in the permanent dentition than in the primary dentition, but there is a strong correlation between hypodontia in the primary and permanent dentition [Matalova et al., 2008]. In the primary dentition, the prevalence varies from 0.4% to 0.9% in Europe [Ravn, 1971; Jarvinen and Lehtinen, 1981] and is 2.4% in Japan [Yonezu et al., 1997]. In the permanent dentition, the most commonly missing teeth in Caucasians are the mandibular second premolars (4.2%), maxillary lateral incisors (2.3%), and maxillary second premolars (2.2%) [Polder et al., 2004]. Several researchers have reported a higher prevalence of hypodontia among females, with a female to male ratio of 3:2 [Brook, 1975], but the reasons for this are not known.

In individuals with congenitally missing teeth in one region but crowding in another, autotransplantation has good long-term prognosis if the transplanted tooth has completed half of its root formation [Paulsen et al., 1995]. Endosseous implant replacement of the missing teeth is another popular and viable option.
Sporadic hypodontia
Sporadic anodontia and oligodontia are rare, but sporadic hypodontia is a relatively common finding. As a general rule, if only one or a few teeth are missing, the missing tooth will be the most distal tooth of any given type. For example, if a molar is missing it is usually the third molar, if an incisor it is the lateral incisor and if a premolar it is usually the second premolar.

Both genetic and environmental factors may contribute to sporadic hypodontia [Schalk-Van Der Weide et al., 1993; Vastardis, 2000]. In terms of environmental influences, development of the permanent teeth may be affected by various factors such as trauma to the jaws, surgical procedures on the jaws, early extraction of the primary teeth, chemotherapy and radiation therapy [Schalk-Van Der Weide et al., 1993; Nasman et al., 1997]. Currently, little is known about the genetic etiologies of sporadic hypodontia, although these may be similar to those that cause familial non-syndromic hypodontia.

Mutation in PAX9 has been associated with both sporadic (or low-penetration familial) hypodontia and oligodontia [Pawlowska et al., 2010].

Familial, non-syndromic hypodontia
In familial hypodontia, the inheritance in the majority of families is autosomal dominant with incomplete penetrance and variable expressivity. Mutations in several genes have been found to cause familial hypodontia. It is also thought that many cases of familial hypodontia may represent a complex, multifactorial condition.

A missense mutation in MSX1 on chromosome 4 was the first mutation found to be associated with non-syndromic hypodontia. The mutation was found in all affected members of a family with missing second premolars and third molars. Some also had missing maxillary first premolars, mandibular first molars, one or both upper lateral incisors or a single lower central incisor. All had normal primary dentitions [Vastardis et al., 1996].

Subsequently, a second gene—PAX9 on chromosome 14—was found to be involved in hypodontia. A frame shift mutation in PAX9 was identified in a family with autosomal dominant hypodontia that had missing permanent molars [Stockton et al., 2000]. Some individuals were missing the maxillary and/or mandibular second premolars as well as central incisors. Since then a number of mutations and polymorphisms have been identified in the human PAX9 region with variable forms of oligodontia that mainly affect the molars [Niemenen et al., 2001; Frazier-Bowers et al., 2002; Das et al., 2003; Mostowska et al., 2003a,b, 2006].

More recently, hypodontia associated with AXIN2 mutations has been identified to affect a wider range of tooth types. In a four-generation Finnish family, 11 members were found to be missing at least 8 permanent teeth along with an increased risk of developing colorectal neoplasia [Lammi et al., 2004]. AXIN2 is a component of the WNT signaling pathway.

Mutations in two genes that can cause ED, EDA and WNT10A, can also cause isolated hypodontia; the syndromic effects of mutations in these genes are discussed later in this review. EDA mutations have recently been linked to non-syndromic hypodontia, which typically includes missing mandibular and/or upper incisors and canine [Yang et al., 2013]. A recent study found that 56% of the patients with isolated hypodontia had a mutation in WNT10A, which is strongly expressed in the dental epithelium at the tooth initiation stage and is required for normal tooth development beyond the bud stage.

Syndromic hypodontia
Van der Woude syndrome. VWS (OMIM #119300) is characterized by paramedian lip pits and sinuses, conical elevations of the lower lip, cleft lip and/or cleft palate (CP), and hypodontia. Adhesions between maxilla and mandible (syngnathia) have been reported [Leck and Aird, 1984]. At times, VWS can be identified solely based on lip pits [Soni et al., 2012]. VWS is the most common clefting syndrome and occurs in approximately 2% of the population with facial clefts [Rintala and Ranta, 1981; Schutte et al., 1996]. The prevalence of VWS is up to 1 in 40,000 still born or live births [Burdick, 1986].

VWS is inherited in an autosomal dominant fashion and is caused by mutations in the interferon regulatory factor 6 (IRF6) gene [Kondo et al., 2002]. However, there is some genetic heterogeneity in VWS [Wong et al., 2001]. IRF6 mutations also cause popliteal pterygium syndrome (PPS), which in addition to the craniofacial findings of VWS consists of genital abnormalities, webbing of fingers, toes, and behind knees, and other occasional features [Lees et al., 1999].

Lip pits are the most common manifestation of VWS. The occurrence has been reported in up to 88% of the affected individuals [Janku et al., 1980].
VWS is underdiagnosed because lower lip pits are often missed, leading to undetected submucous CP [Lam et al., 2010]. In CP patients with lower lip sinuses, the incidence of hypodontia was 77.8% [Ranta and Rintala, 1982].

Hypodontia is frequently seen in VWS, and a close association between VWS and congenital absence of second premolars has been shown [Schneider, 1973; Calzavara Pinton et al., 1989; Oberoi and Vargervik, 2005a]. There is a tendency toward greater maxillary hypoplasia in VWS, particularly in the most severe cleft type (bilateral CLP). In addition, the highest incidence of missing teeth is also seen in VWS with the more severe cleft type [Oberoi and Vargervik, 2005a].

Ectodermal dysplasia. There are more than 150 clinically distinct inherited syndromes in which ED is present. ED consists of variable defects in the morphogenesis of ectodermal derivatives including skin, sweat glands, hair, nails, and teeth. Many of the ED syndromes have non-ectodermal manifestations, which are not discussed here in detail. Patients with ED can have hypodontia or anodontia, with the anterior teeth usually conical or peg-shaped (Fig. 4); the alveolar ridge is deficient and patients tend to have hypoplastic maxillae with anterior crossbite and low face height with overclosure.

The ED syndromes can be inherited in an autosomal dominant, autosomal recessive, or X-linked form. The most common form of ED is X-linked hypohidrotic ED, or XLHED (OMIM 257980) and is caused by mutations in the gene encoding ectodysplasin-A (EDA), which is a member of the TNF signaling pathway. TNF signaling through EDA activates NFκB1, which is known to play an important role in odontogenesis [Ohazama and Sharpe, 2004]. Affected males show severe oligodontia or anodontia in both primary and permanent dentition. An average of nine permanent teeth develop in individuals with classic XLHED, typically the canines and first molars [Lexner et al., 2007]. Teeth are often smaller than average and have an altered morphology. Anterior teeth tend to be conical in shape. Dental radiographs are helpful in determining the extent of hypodontia. Taurodontism is more common in the molars of individuals with XLHED.

Female carriers have variable, milder phenotypic expressions resulting from X chromosome inactivation. They may have hypodontia or anodontia and abnormally shaped teeth. Sixty to eighty percent of carriers have some degree of hypodontia [Cambiagli et al., 2000]. In XLHED, both primary and permanent dentitions are affected [Clauss et al., 2008].

Odonto-onycho-dermal dysplasia (OMIM 257980) is an autosomal recessive ED syndrome caused by mutations in WNT10A [Adaimey et al., 2007]. These patients present with dry hair, severe hypodontia, smooth tongue, nail dysplasia, hyperhidrosis of palms and soles, and hyperkeratosis. As mentioned above, WNT10A mutations are also a common cause of isolated hypodontia.

Oral-facial-digital syndrome type I. OFD syndrome type I (OMIM 311200) is a developmental disorder characterized by malformations of the face, oral cavity, digits, central nervous system, and kidneys. The prevalence of OFD1 is 1 in 50,000 to 1 in 250,000 live births. OFD1 is an X-linked disorder caused by mutations in the gene OFD1. This gene is important for formation of a fetal organelle known as the primary cilium. OFD1 affects only females, as this condition is lethal in males. Although clinical features overlap with other types of OFD (of which there are at least 9), X-linked dominant inheritance and poly cystic kidney disease are specific to OFD1.

The typical oral manifestations of OFD1 are seen in the tongue, palate, and teeth. The tongue is lobed and is bifid or trifid with nodules (hamartomas or lipomas); this is seen in at least a third of patients with OFD1. Ankyloglossia due to a short lingual frenulum is common. Cleft hard or soft palate, submucous CP, or highly arched palate occur in more than 50% of affected patients. Alveolar clefts and accessory gingival frenulae are common. These fibrous bands are hyperplastic frenulae extending from the buccal mucous membrane to the alveolar ridge, resulting in notching of the alveolar ridges. Dental abnormalities include missing teeth, extra teeth, enamel dysplasia, and malocclusion [Al-Qattan, 1998; Toriello and Franco, 2007]. The lower lateral incisors are missing in 50% of individuals, and this is associated with fibrous bands in the region.

Rieger syndrome. Rieger syndrome (OMIM 601542) is an autosomal dominant disorder characterized by malformations in the anterior chamber of the eye, umbilical anomalies, and hypodontia. Its prevalence is 1 in 200,000. When the ocular abnormality is combined with other craniofacial, dental, and developmental somatic anomalies, it is given the name Axenfeld-Rieger syndrome (ARS; OMIM 180500). Glaucoma is found in 50% of the cases [Shields et al., 1985]. Craniofacial, dental, and umbilical anomalies are also regularly reported in connection with ARS [Childers and Wright, 1986; Dressler and Gramer, 2006]. Characteristic craniofacial features are maxillary hypoplasia, hypertelorism, and telecanthus. Other systemic features like anomalies of the pituitary gland, middle ear deafness, heart defects, hypoplasias, short stature, and mental retardation were diagnosed in several ARS patients [Shields et al., 1985; Ozeki et al., 1999].

Three genetic loci have been associated with ARS so far. FOXC1 and PITX2 encode transcription factors and are located on chromosomes 6p25 and 4q25, respectively [Tumer and
Bach-Holm, 2009]. A third locus for ARS was mapped to chromosome 13q14 but the gene has not yet been identified. Therefore ARS is considered as a morphologically and genetically heterogeneous disorder.

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Dental features include hypodontia/oligodontia of primary and permanent dentition. The most commonly missing teeth are lower second premolars and subsequently the central incisors and upper second premolars [Dressler et al., 2010]. The missing teeth in the anterior maxilla are thought to cause underdevelopment of the premaxilla. Other dental abnormalities include hyperplastic upper labial frenulum, peg-shaped front teeth, and small teeth, enamel hypoplasia, conical-shaped teeth, shortened roots, taurodontism, and delayed eruption.

**Holoprosencephaly.** Holoprosencephaly (HPE; OMIM # 236100), which occurs with a frequency of 1 in 16,000 live births and 1 in every 200 spontaneous abortions, is an etiologically heterogeneous condition with teratogenic and genetic factors [Hall et al., 1997]. HPE is caused by impaired midline cleavage of the embryonic forebrain. HPE is the most common defect of the forebrain and mid-face in human [Wallis and Muenke, 2000]. The most severe form is cyclopia, and the mildest phenotype is a single upper central incisor. Several loci for HPE have been mapped. HPE3 is caused by mutations in the Sonic hedgehog (SHH) gene, which was described above in the context of tooth development [Lami et al., 2013]. Both recessive and dominant inheritance of HPE has been reported [Cohen and Gorlin, 1969].

The HPE spectrum is commonly associated with solitary median maxillary control incisor (SMMCI), a rare dental anomaly that can occur in either a primary or permanent dentition. It can be an isolated dental finding or occur in association with other recognized syndromes or specific chromosomal abnormalities [Nanni et al., 2001]. The spectrum of defects is extremely variable, as some individuals can present with the full HPE spectrum, some may have only mild symptoms such as SMMCI, and others may have no symptoms at all [El-Jaick et al., 2007]. Sometimes SMMCI is the most easily recognizable anomaly associated with HPE [Hall et al., 1997]. All HPE patients have SMMCI, but not all SMMCI patients have been diagnosed with HPE [Kopp, 1967]. Several syndromes have been associated with SMMCI, including ED, Duane retraction syndrome, velocardiofacial syndrome, CHARGE syndrome, VACTERL association, and HPE [Oberoi and Vargervik, 2005b].

**Tooth anomalies associated with cleft lip and palate.** It has long been recognized that hypodontia is associated with clefts of the lip and palate. Studies have found that hypodontia is present in approximately 80% of children with non-syndromic clefts [Shapira et al., 1999], and the prevalence of hypodontia increases markedly with the severity of the cleft [Ranta, 1986]. The teeth most frequently missing on the cleft side were the upper permanent lateral incisors; these were absent in 74% of all cleft patients, followed by maxillary and mandibular second premolars. The teeth most often missing on the non-cleft side were the maxillary second premolars, followed by the maxillary lateral incisors and mandibular second premolars. Interestingly, congenital absence of both the maxillary lateral incisors and second premolars was found more frequently in siblings of patients with clefts as well [Eerens et al., 2001].

Hypodontia outside the cleft region is more frequent in cleft individuals than in non-cleft individuals [Shapira et al., 1999], and, in general, hypodontia occurs about 10 times more frequently on the cleft side, with left predominance. This is consistent with the side preference for unilateral cleft lip and palate. Additionally, the prevalence of hypodontia (excluding third molars) has been reported as 50% in Pierre Robin sequence, which comprises a triad of micrognathia, glossoptosis, and CP. In these cases, there is an increased frequency of hypodontia in the lower jaw compared to individuals with isolated cleft lip and palate [Ranta, 1986].

In addition, these individuals can have other anomalies related to the shape and size of individual teeth, or the presence of additional teeth. A recent meta-analysis concluded that patients with cleft lip and palate experience not only more tooth agenesis, but also supernumerary teeth and anomalous tooth morphology in comparison to non-cleft patients [Tannure et al., 2012]. The most frequently undersized teeth are upper lateral incisors, and while there is evidence that other teeth in cleft patients have higher levels of agenesis and dysmorphology than in non-cleft patients, the data are conflicting. In cleft patients, a high occurrence of a supernumerary lateral incisor (40–73%) has been detected in the primary dentition [Bohn, 1950; Hansen and Mehedinia, 2002].

From an embryological point of view, it has been shown using 3D reconstructions that the location of the fusion of the medial nasal and maxillary facial outgrowths transiently appears as a furrow on the mesenchymal aspect of the developing lateral incisor germ in humans until prenatal week 8. This implies that the upper incisor germ takes its origin partially from the maxillary outgrowth (Fig. 5) [Hovorakova et al., 2006]. This complex origin at a critical place of fusion of facial processes can explain the developmental vulnerability and resulting anomalies of the upper lateral incisor [Hovorakova et al., 2006]. Complete orofacial clefts of the lip and
alveolus result from the failure of the fusion of the medial nasal and maxillary processes. Consequently, the fusion of the dental epithelia is also absent and the two incisor subcomponents remain separate, such that a duplication of the lateral incisor occurs in the cleft area (Fig. 5). It has been proposed that the number of lateral incisors, even in normal individuals, depends on whether both, one, or no incisor subcomponent is able to give rise to a functional tooth [Hovorakova et al., 2006].

Delayed Formation and Eruption of Teeth

The permanent teeth usually replace the primary teeth between the ages of 6–12 years. However, eruption times for the permanent teeth can vary considerably. The lower incisor shows the least variability and the lower second premolar the greatest in timing of eruption. When two primary teeth are fused, it is linked with the absence of permanent teeth.

Several syndromes have delayed formation and eruption of teeth, including Apert syndrome [Kaloust et al., 1997], cleidocranial dysplasia, Dubowitz syndrome, Goltz syndrome, progeria, Menke syndrome and oculofaciocardiocidental (OFCD) syndrome [Oberoi et al., 2005]. Two of these syndromes are discussed below as examples.

In Apert syndrome, there are delays in both development and eruption, and there can also be ectopic eruption and abnormalities in incisor and molar shape [Kaloust et al., 1997]. Erupting teeth remain buried in thickened gingival tissues for long periods of time. The alveolar swellings of the maxillary arch are characteristic of the syndrome and have been shown to contain excessive mucopolysaccharides, predominantly hyaluronic acid [Peterson and Pruzansky, 1974]. Activating mutations in genes encoding receptors for Fibroblast Growth Factors, which were discussed above in the context of tooth development, cause Apert syndrome. However, it is not clear how these mutations contribute to the characteristic dental and gingival findings in Apert syndrome [Kaloust et al., 1997].

OFCD syndrome (OMIM 300166) is an X-linked condition with characteristic ocular, facial, cardiac, and dental findings in affected females and presumed lethality in affected males. The most typical dental anomaly is canine radiculomegaly (enlarged roots). Other findings include delayed dental development and eruption, oligodontia, retained primary teeth and variable root length. Mutations in the BCOR gene have been found in this condition [Ng et al., 2004].

Delayed tooth eruption has also been found in the upper jaw of patients with orofacial clefts. Eruption of the permanent upper lateral incisor, which is also sometimes absent in patients with cleft lip and palate, and the permanent second molar is retarded in patients with cleft lip and palate. In contrast, earlier eruption has been found in the permanent and deciduous maxillary canine, first and second premolars. The delay or acceleration of tooth eruption in cleft patients might be a consequence of the affected bones and teeth [Peterka et al., 1996].

Abnormalities in Tooth Size, Shape, and Form

Abnormalities in tooth size and shape are thought to result from disturbances in the morphodifferentiation (cap-bell) stage of development. About 5% of the population has a significant “tooth size discrepancy” due to disproportion in the size of upper and lower teeth. The most common abnormality is a variation in size of the upper lateral incisors and second premolars. In patients with
hypodontia, the most common abnormality is a peg-shaped upper lateral incisor.

There is very often a discrepancy between tooth size and jaw size. The combination of microdontia and normal jaw size is accompanied by the presence of tremata (free spaces between teeth). Similarly, a shorter jaw in the mesiodistal direction with teeth of normal size results in orthodontic anomalies. This disproportion is most pronounced in the upper jaw of cleft patients, where the permanent teeth have normal mesiodistal dimension, while the upper jaw arch is significantly shorter [Peterka et al., 1996].

Sometimes, tooth germs may fuse or germinate during development [Gutta et al., 2010], resulting in teeth with separate pulp chambers joined at the cementoenamel junction, thus elongating the pulp chambers vertically creating an apically displaced pulp. There is significant variation among modern day populations. The prevalence has been reported as 0.5% in Japanese [Daito, 1971], 0.57–3.2% in white Americans [Blumberg et al., 1971; Witkop, 1976], 4.5% in African Americans [Jorgenson et al., 1982], 8% in Jordanians [Darwazeh et al., 1998], 33–41% in certain African populations [Shaw, 1928], and 46.4% in young adult Chinese [Macdonald-Jankowski and Li, 1993]. Taurodontism is thought to be a polygenic trait, and both autosomal dominant and recessive inheritance have been suggested.

A taurodontic tooth is thought to result from a disturbance in growth of Hertwig’s epithelial root sheath. Based on this hypothesis, there may be an association between taurodontism and hypodontia, as both conditions may be attributed to defects in the growth of dental epithelium [Hu and Simmer, 2007]. Taurodontism has been described together with isolated [Stenvik et al., 1972; Seow and Lai, 1989; Schalk-Van Der Weide et al., 1993] and syndromic hypodontia in many syndromes, including 18p11.3 deletion [Kantaputra et al., 2006], Smith–Magenis syndrome [Tomona et al., 2006], tricho–dento–osseous syndrome [Hart et al., 1997; Wright et al., 1997; Price et al., 1999; Islam et al., 2005], Klinefelter’s syndrome [Komatz et al., 1978; Hillebrand et al., 1990; Yeh and Hsu, 1999], Williams syndrome [Axelson et al., 2003], McCune–Albright syndrome [Akintoye et al., 2003], Down syndrome [Alpoz and Eraton, 1997] and Ellis van Creveld syndrome [Hunter and Roberts, 1998]. It has also been described in individuals with cleft lip and palate. An autosomal dominant hypoplastic/hypomaturation amelogenesis imperfecta (AI) associated with taurodontism (OMIM 104510) has been mapped to the distal-less homeobox (DLX3) locus [Dong et al., 2005]. More recently, taurodontism has been linked with Laurence–Moon/Bardet–Biedl syndrome (LM/BBS) and therefore should be included as a minor criterion in diagnosing LM/BSS [Andersson et al., 2013]. Lastly, there may be a common genetic etiology between VWS, hypodontia, and taurodontism [Nawa et al., 2008]. The frequency of taurodontism in VWS subjects was almost 50% [Nawa et al., 2008].

Supernumerary Teeth

A supernumerary tooth is an additional tooth that can be found in any region of the dental arch. Supernumerary teeth result from disturbances during the initiation and proliferation stages of dental development. The most common supernumerary tooth that appears is in the maxillary midline and is called mesiodens. The prevalence of supernumerary teeth is between 0.3% and 0.8% in primary dentition and 1.5% and 3.5% in permanent dentition [Brook, 1974]. A male to female ratio of 2:1 is found in populations with single supernumerary teeth [Kantor et al., 1988] which increases to 3:1 for multiple supernumerary teeth [Gibson, 1979]. Although inherited forms are rare, a familial inheritance has been reported that can be autosomal dominant with incomplete penetrance, autosomal recessive [Cassia et al., 2004] or sex-linked pattern of inheritance [Burzynski and Escobar, 1983].

Greater than 90% of supernumeraries will occur in the upper jaw, and approximately 25% of the maxillary anterior supernumerary teeth erupt, but more commonly they are impacted and require extraction. Supernumerary teeth may be unilateral or bilateral, single or multiple, and may be found in one or both jaws. Multiple supernumerary teeth are rare in non-syndromic individuals, so such a finding should prompt a referral to a medical geneticist. An increased prevalence of supernumerary teeth can be found in cleft lip and palate patients, and there are over 20 syndromes with supernumerary teeth, the most common being cleidocranial dysplasia and Gardner syndrome [Moore et al., 2002]. The frequency of supernumerary teeth in individuals with unilateral cleft lip and/or palate was found to be 22.2% [Scheiner and Sampson, 1997], with males affected twice as often as females in the permanent dentition.

There are various hypotheses regarding the etiology of supernumerary teeth. According to one, a supernumerary tooth is created as a result of dichotomy of the tooth bud [Liu, 1995]. Another theory is that supernumeraries are formed as a result of local, independent conditioned hyperactivity of the dental lamina [Liu, 1995; Scheiner and Sampson, 1997]. Sometimes, supernumerary teeth can be interpreted as atavisms, if they appear at locations where teeth were suppressed during evolution [Smith, 1969; Peterkova et al., 2006]. The diagnosis of a supernumerary tooth is confirmed by radiographic examination if abnormal clinical signs are found. Periapical and occlusal radiographs are commonly used in the incisor
region. Three-dimensional cone beam CT is valuable as it shows the position of the supernumerary in all three dimensions, thereby enabling the correct buccal or palatal approach during removal and direction of force application for orthodontic alignment [Liu et al., 2007].

Some of the problems associated with supernumerary teeth include failure of eruption, displacement [Howard, 1967], crowding, and formation of dentigerous cysts [Awang and Siar, 1989]. Root resorption of adjacent teeth is a rare occurrence as well [Hogstrom and Andersson, 1987].

**Cleidocranial dysplasia**

The best-known syndrome associated with supernumerary teeth is cleidocranial dysplasia (CCD). CCD (OMIM #119600) is an autosomal dominant skeletal dysplasia associated with clavicle hypoplasia and dental abnormalities and has a prevalence of 1 in 1,000,000. It is caused by mutations in RUNX2, which encodes a transcription factor that activates osteoblast differentiation. One third of CCD cases are sporadic and represent new mutations [Otto et al., 2002].

Individuals with CCD have growth retardation with moderate short stature, delayed fontanelle closure with parietal and frontal bossing, midface hypoplasia, hypertelorism, low nasal bridge, brachydactyly and hearing loss. They may have CP or a narrow, high palate.

Dental manifestations are found in more than 90% of individuals with CCD and include delayed eruption of deciduous and permanent teeth, supernumerary teeth, retention cysts and enamel hypoplasia (Fig. 6) [Golan et al., 2003]. Formation and eruption of the deciduous teeth are usually normal. One suggested explanation for the delayed or non-eruption of many permanent and supernumerary teeth is the lack of cellular cementum in the apical region of impacted teeth [Manjunath et al., 2008]. While CCD patients at a younger age display relatively normal jaw proportions and morphology of the mandible, CCD patients at an older age display short lower face height, acute gonial angle, anterior inclination of the mandible, and mandibular prognathism; due to maxillary hypoplasia, individuals with CCD tend to have a Class III malocclusion [Ishii et al., 1998].

Because of challenges in dental management of these individuals with CCD, comprehensive orthodontic and surgical treatment is required. Additionally, there is a wide variation in supernumerary tooth development, including asymmetrical development of supernumerary teeth in the upper and lower jaw [Soni et al., 2012]. Delay of physiologic root resorption results in prolonged retention of the primary teeth, and the eruption of the permanent teeth is delayed and many fail to erupt [Shaikh and Shusterman, 1998]. The presence of supernumerary teeth is not pathognomonic for CCD; in fact, some patients may have no supernumerary teeth or even missing teeth [Richardson and Deussen, 1994].

Recent advances in dentistry, such as dental implants, allow better treatment options and outcomes for individuals with CCD. As an example, dental implants can be used not only for orthodontic tooth movement with reduced side effects, but also for replacing teeth that cannot be brought into the arch orthodontically. With the advancements in three-dimensional imaging, Cone Beam Computed Tomography (CBCT) is now routinely used in diagnosis and treatment planning [Liu et al., 2007].

**Gardner syndrome**

Gardner syndrome, a variant of familial adenomatous polyposis (FAP; OMIM #175100), is a rare autosomal dominant condition characterized by gastrointestinal polyps, multiple osteomas, and skin and soft tissue tumors including a characteristic retinal lesion. Approximately 10% of FAP individuals are affected by Gardner syndrome [Ramsaglia et al., 2007]. Gardner syndrome and FAP are caused by mutations in APC at 5q21 [Groden et al., 1991; Kinzler et al., 1991]. APC is a multidomain protein that plays a major role in tumor suppression by antagonizing the WNT signaling pathway [Barth et al., 1997].

Dental anomalies are present in 30–75% of patients with Gardner syndrome, and may include impacted or unerupted teeth, hypodontia, abnormal tooth morphology, supernumerary teeth, hypercementosis, compound odontomas, dentigerous cysts, fused molar roots, long and tapered molar roots, and multiple caries [Butler et al., 2005;
Madani and Madani, 2007; Basaran and Erkan, 2008). Osteomas occur in 68–82% and are generally located in the paranasal sinuses and mandible [Dawlatly et al., 1997; Madani and Madani, 2007]. They can also affect the skull and long bones [Cankaya et al., 2012]. In the mandible, central or lobulated osteomas can be observed; central osteomas are characteristically near the roots of the teeth, and lobulated types arise from the cortex and most commonly at the mandibular angle [Wesley et al., 1987]. Often the general dentists or orthodontists are the first health care professionals to suspect the diagnosis and refer to the oromaxillofacial surgeon [Cankaya et al., 2012].

CONCLUSION

Dental anomalies are seen as either isolated findings or in individuals with craniofacial developmental abnormalities, and in both cases they can profoundly affect the life of the affected individual. Studies of tooth development in animal models together with genetic studies of patients are improving our understanding of the causes of dental anomalies, and are laying the foundation for future biologically based treatments.

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