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REVIEW

Molecular Genetics of Supernumerary Tooth Formation

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Summary: Despite advances in the knowledge of tooth morphogenesis and differentiation, relatively little is known about the aetiology and molecular mechanisms underlying supernumerary tooth formation. A small number of supernumerary teeth may be a common developmental dental anomaly, while multiple supernumerary teeth usually have a genetic component and they are sometimes thought to represent a partial third dentition in humans. Mice, which are commonly used for studying tooth development, only exhibit one dentition, with very few mouse models exhibiting supernumerary teeth similar to those in humans. Inactivation of *Apc* or forced activation of Wnt/β(catenin signalling results in multiple supernumerary tooth formation in both humans and in mice, but the key genes in these pathways are not very clear. Analysis of other model systems with continuous tooth replacement or secondary tooth formation, such as fish, snake, lizard, and ferret, is providing insights into the molecular and cellular mechanisms underlying succesional tooth development, and will assist in the studies on supernumerary tooth formation in humans. This information, together with the advances in stem cell biology and tissue engineering, will pave ways for the tooth regeneration and tooth bioengineering. genesis 49:261–277, 2011. **© 2011 Wiley-Liss, Inc.**

Key words: supernumerary teeth; cleidocranial dysplasia; familiar adenomatous polyposis; Runx2; Apc; tooth development; tooth replacement; successional tooth

INTRODUCTION

Teeth are vertebrate specific organs that are mainly used for processing of food, defense, and in humans also for speech production. During tooth development, the dental epithelium and the underlying neural crest derived ectomesenchyme interact reciprocally and sequentially for the initiation, morphogenesis, and cell differentiation of the teeth (Bei, 2009; Jernvall and Salazar-Ciudad, 2007; Tummers and Thesleff, 2009). While some nonmammal species have multirowed dentition and replace their teeth regularly throughout the lifetime, mammalian vertebrates exhibit one row of teeth and only renew their teeth once, or in some rodents, without any replacement (Jarvinen *et al.*, 2009; Koussoulakou *et al.*, 2009; Mikkola, 2009; Tummers and Thesleff, 2009). Humans have two sets of dentitions. There are 20 teeth in the deciduous (primary) dentition, with one central incisor, one lateral incisor, one canine, and two premolars in each quadrant of the jaw. There are 32 teeth in the permanent dentition, with one central incisor, one lateral incisor, one canine, two premolars, and three molars in each quadrant of the jaw. Supernumerary teeth, or hyperdontia, refer to the teeth that form in addition to the normal dental formula (Cobourne and Sharpe, 2010; D'souza and Klein, 2007; Fleming *et al.*, 2010; Gunduz and Muglali, 2007; Yague-Garcia *et al.*, 2009). They may occur in any region of the dental arch, in the maxilla or in the mandible, singly or in multiples, unilaterally or bilaterally, erupted or unerupted. They can be associated with a syndrome or they can be found in non-syndromic patients (Diaz *et al.*, 2009; Ferres-Padro *et al.*, 2009; Garvey *et al.*, 1999; Leco Berrocal *et al.*, 2007; Liu *et al.*, 2007).

Prevalence and Types of Supernumerary Teeth in Humans

The reported prevalence of supernumerary teeth ranges from 0.2% to 0.8% in the deciduous dentition, and ranges from 0.5% to 5.3% in the permanent dentition with geographic variations (Brook, 1974; Fardi

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et al., 2010; Ferres-Padro *et al*., 2009; Leco Berrocal *et al*., 2007; Mckibben and Brearley, 1971; Rajab and Hamdan, 2002; Stellzig *et al*., 1997; Yague-Garcia *et al*., 2009; Yusof, 1990). The incidence of supernumerary teeth is usually higher in males than in females. The reported male to female ratio was between 1.18:1 to 4.5:1 (Brook, 1984; Fernandez Montenegro *et al*., 2006; Ferres-Padro *et al*., 2009; Leco Berrocal *et al*., 2007; Liu, D. G. *et al*., 2007; Patchett *et al*., 2001; Rajab and Hamdan, 2002; Salcido-Garcia *et al*., 2004; Yassin and Hamori, 2009; Yusof, 1990). Supernumerary teeth are usually found to be single and unilateral. The most common supernumerary teeth are mesiodens, which occur between the maxillary central incisors (Hyun *et al*., 2009). More rarely, they can be located in the premolar and distomolar regions, and appear as supernumerary premolars or supernumerary fourth and fifth molars (Bodin *et al*., 1978; Ersin *et al*., 2004; Fernandez Montenegro *et al*., 2006; Ferres-Padro *et al*., 2009; Grimanis *et al*., 1991; Kaya *et al*., 2010; Kokten *et al*., 2003; Leco Berrocal *et al*., 2007; Liu, 1995; Mason *et al*., 2000; Rajab and Hamdan, 2002; Saarenmaa, 1951; Salcido-Garcia *et al*., 2004; Yassin and Hamori, 2009). Supernumerary premolars constitute proximately 10% of the total supernumerary cases, and almost 75% of those are in the mandible (Hyun *et al*., 2008; Kawashita and Saito, 2010). It was reported that 76%–86% non-syndromic cases have only one supernumerary tooth, and 12%–23% cases have two supernumerary teeth (Diaz *et al*., 2009; Fernandez Montenegro *et al*., 2006; Rajab and Hamdan, 2002). Only 1% of non-syndromic cases have multiple supernumerary teeth, which occur most frequently in the mandibular premolar area, followed by the molar and the anterior regions, respectively (Batra *et al*., 2005; Diaz *et al*., 2009; Hyun *et al*., 2008; Inchingolo *et al*., 2010; Orhan *et al*., 2006; Yague-Garcia *et al*., 2009; Yusof, 1990).

Supernumerary teeth in the deciduous dentition are usually normal or conical shaped, whereas supernumerary teeth in the permanent dentition can exhibit various shapes. They may have normal morphology or may be rudimentary and miniature with little or no resemblance to the other teeth (Batra *et al*., 2005). Based on their morphology, supernumerary teeth are classified into four types, including conical type, tuberculate type, supplemental teeth, and odontomas (Garvey *et al*., 1999). The most common supernumerary teeth are small conical peg-shaped with root development at the similar stage or ahead of that of adjacent teeth. They usually develop in the anterior maxilla as mesiodens. Tuberculate supernumerary teeth are large barrel-shaped with multiple cusps or tubercles. Their root development is delayed compared to that of adjacent teeth. They are mostly found unerupted in the palatal aspect of the maxillary central incisors, and this can cause the impaction of permanent maxillary incisors (Backman and Wahlin, 2001; Foster and Taylor, 1969; Liu, 1995; Mitchell and Bennett, 1992; Rajab and Hamdan, 2002; Yassin and Hamori, 2009). Supplemental teeth are duplications of teeth in the normal dentition with essentially normal size and shape, and they are usually found at the end of a tooth series. The most common supplemental tooth is the permanent maxillary lateral incisor, but supplemental premolars and molars were also reported. The majority of supernumerary teeth found in the primary dentition are of the supplemental type. They usually erupt with normal morphology and alignment, and often appear as a supplemental lateral upper incisor (Ferres-Padro *et al*., 2009; Garvey *et al*., 1999). This may cause underreported and low prevalence of supernumerary teeth in the primary dentition (Fleming *et al*., 2010). There are special cases exhibiting permanent supernumerary teeth developing as supplemental teeth and forming after the permanent teeth. These are thought to represent a third dentition, best known as manifestations of cleidocranial dysplasia (see later). Odontoma was listed as the fourth category of supernumerary teeth (Garvey *et al*., 1999; Howard, 1967). Odontoma contains a mass of dental tissues (enamel, dentin, cementum, pulp tissue), and is usually considered to be a hamartomatous (benign and local with disorganized mass) malformation rather than a neoplasm. There is no gender predilection in the occurrence of odontomas. On the basis of their gross and radiographic features, odontomas are further sub-classified into compound and complex types (Ferres-Padro *et al*., 2009; Rajab and Hamdan, 2002; Yassin and Hamori, 2009). Compound odontomas contain some rudimentary tooth-like structures and are commonly found in the anterior maxilla, whereas complex odontomas contain totally disorganized mass of dental tissues and are often found in the premolar and molar regions (Garvey *et al*., 1999; Tozoglu *et al*., 2010). Rarely, an odontoma can erupt into the oral cavity (Serra-Serra *et al*., 2009; Tozoglu *et al*., 2010).

Some supernumerary teeth are just impacted in the jaw with no obvious adverse effects. They were usually identified incidentally during radiographic examinations for some other reasons (Inchingolo *et al*., 2010; Kawashita and Saito, 2010; Rajab and Hamdan, 2002; Yague-Garcia *et al*., 2009). However, the development of some supernumerary teeth can cause a broad range of complications, including retained or delayed eruption of permanent teeth, diastemas, displacement, rotation, crowding, root resorption, periodontal lesions, or pulp necrosis of adjacent teeth. They can also cause dentigerous (odontogenic) cyst, and the presence of unerupted supernumerary teeth may compromise tooth implantation as well as alveolar bone grafting in patients with cleft palate (Diaz *et al*., 2009; Ferres-Padro *et al*., 2009; Garvey *et al*., 1999; Giancotti *et al*., 2002; Hyun *et al*., 2009; Yassin and Hamori, 2009).

Etiology of Supernumerary Teeth in Humans

Most supernumerary teeth are isolated cases, although some may be familial inherited and some may be syndrome associated events (Batra *et al*., 2005; Diaz *et al*., 2009). The etiology of supernumerary teeth is still uncertain. A number of theories have been postulated to try to explain their presence, including atavism (evolutionary throwback), tooth germ dichotomy, hyperactivity of the dental lamina, and genetic and environmental factors (Primosch, 1981; Saarenmaa, 1951).

The atavism or phylogenetic theory suggested that the occurrence of supernumerary teeth is a regression to the extinct ancestral tissues or anthropoids. This theory is based on the phenomena that ancestor mammals have more teeth with three incisors, one canine, four premolars, and three molars in each quadrant of the jaw (Babu *et al*., 1998; Osborne, 1978; Smith, 1969). The teeth of common modern mammals belong to these four tooth families. It is generally thought that during evolution, the total number of teeth per dentition decreased (from polyodonty to oligodonty) and the generations of teeth were also reduced (from polyphyodonty to diphyodonty or monophyodonty); whereas the morphology of teeth became more complex (from homodonty to heterodonty). Over the course of evolution, the teeth in placental mammals tend to disappear in an order that is opposite to the order of their eruption (Koussoulakou *et al*., 2009).

The tooth germ dichotomy theory proposed that during early tooth development, the dental lamina was divided into two parts of equal or different size, thus giving rise to two teeth with similar size, or one normal tooth and one dysmorphic tooth (Garvey *et al*., 1999; Liu, 1995; Taylor, 1972). Munne *et al*. analyzed in detail mouse incisor development and found that the large incisor placodes form through the fusion of multiple small placodes, and the balance between activator and inhibitor molecules regulates the size of the placodes. Small disturbances in the balance of these signals could cause disintegration or splitting of the placode and thus the formation of two or three small incisors (Munne *et al*., 2010). Hovorakova *et al*. analyzed the development of deciduous upper lateral incisor in human embryos using serial sections and computer-aided 3D reconstructions, and found that deciduous upper lateral incisors originate from the fusion of two dental epithelial thickenings, which were separated by a groove at the formal fusion site of the medial nasal and maxillary processes. Later, these two dental epithelial thickenings fused together and formed a continuous dental lamina, from which the deciduous upper lateral incisor develops (Hovorakova *et al*., 2006). Any disturbance causing cleft or incomplete fusion of the dental epithelial thickenings can result in the formation of supernumerary teeth. This may explain why the supernumerary upper lateral incisor often appears in the deciduous dentition, and in the conditions of cleft palate and cleft lip (Ferres-Padro *et al*., 2009).

Hyperactivity of the dental lamina is another widely accepted theory (Diaz *et al*., 2009; Foley and Del Rio, 1970; Garvey *et al*., 1999; Hattab *et al*., 1994; Liu, 1995; Primosch, 1981; Rajab and Hamdan, 2002; Saarenmaa, 1951; Zilberman *et al*., 1992). Primary dental lamina (odontogenic band) is the thickening of oral ectoderm forming during the initiation stage of deciduous teeth and it gives rise to the deciduous dentition. During the cap or bell stage of deciduous tooth development, successional dental lamina forms from the lingual or posterior aspect of deciduous tooth enamel organ. It later elongates under the oral epithelium and buds into the jaw mesenchyme forming the successional (permanent) tooth or the posterior molar teeth (Jarvinen *et al*., 2009 and references therein). Once the crown of the permanent tooth has formed, the dental lamina undergoes programmed cell death and degenerates. Residues of un-degenerated dental lamina epithelial cells may cause eruption cysts (Cohen, 1984), while over-proliferation or prolonged survival of dental lamina epithelial cells may cause supernumerary tooth formation (Cohen, 1984; Diaz *et al*., 2009; Jarvinen *et al*., 2009).

Heredity is also believed to be an important factor. Supernumerary teeth occur more commonly in the relatives of affected patients than in the general population (Babu *et al*., 1998; Becker *et al*., 1982; Gallas and Garcia, 2000; Mercuri and O'neill, 1980; Rubin *et al*., 1981; Winter, 1969). They can be transmitted as an autosomal recessive or autosomal dominant trait with incomplete penetrance, or may be associated with the X chromosome (Batra *et al*., 2005; Brook, 1984; Cadenat *et al*., 1977; Garvey *et al*., 1999; Primosch, 1981). There are also reports that supernumerary teeth are sometimes associated with polydactyly and extra nipples (Hyun *et al*., 2008; Kantor *et al*., 1988). The etiology of odontomas is still unknown. It is usually thought to be hereditary or due to a disturbance during tooth development triggered by trauma or infection (Tozoglu *et al*., 2010).

Human Syndromes Associated With Supernumerary Teeth

A small number of supernumerary teeth may be a common developmental dental anomaly (Acikgoz *et al*., 2006; Hyun *et al*., 2008). However, multiple supernumerary teeth are rare. Although there are some reports of multiple supernumerary teeth without any systemic conditions or associated syndromes (Diaz *et al*., 2009; Hyun *et al*., 2008; Inchingolo *et al*., 2010; Orhan *et al*., 2006; Yague-Garcia *et al*., 2009), in most cases, multiple supernumerary teeth are associated with other conditions or defects such as cleft palate and cleft lip, or with variable syndromes. Supernumerary teeth in cleft plate

and cleft lip may be caused by the splitting of tooth germs in the cleft regions. Syndromes exhibiting supernumerary teeth include cleidocranial dysplasia (Atasu *et al*., 1996; Cooper *et al*., 2001; Quack *et al*., 1999; Yoshida *et al*., 2002), familial adenomatous polyposis (including Gardner's syndrome)(Mcfarland *et al*., 1968), Ehlers-Danlos syndrome (Ferreira *et al*., 2008; Majorana and Facchetti, 1992; Melamed *et al.*, 1994; Premalatha *et al.*, 2010), Nance-Horan syndrome (Bixler *et al.*, 1984; Hibbert, 2005; Van Dorp and Delleman, 1979; Walpole *et al.*, 1990), Fabry syndrome (Brindley *et al.*, 1975; Regattieri and Parker, 1973), Chondroectodermal dysplasia (Ellis-van Creveld syndrome)(Garvey *et al.*, 1999; Prabhu *et al.*, 1978), Tricho-rhino phalangic syndrome (Giedion, 1966; Kantaputra *et al.*, 2008), and Robinow syndrome (Mazzeu *et al.*, 2007). The inheritance and genetics of these syndromes are summarized in Table 1. Here we will review in detail the supernumerary teeth in cleidocranial dysplasia and familial adenomatous polyposis.

Supernumerary Teeth in Cleidocranial Dysplasia

Cleidocranial dysplasia (CCD, MIM 119600) is a rare autosomal dominant disorder characterized by general bone dysplasia, patent cranial sutures and fontanelles, hypoplastic clavicles, short stature, and dental abnormalities, including retention of deciduous teeth, delayed or failure of eruption of permanent teeth, as well as variable numbers of supernumerary teeth along with dental crowding and malocclusion (Fig. 1; (Atasu *et al.*, 1996; Becker *et al.*, 1997a; Becker *et al.*, 1997b; Cooper *et al.*, 2001; D'alessandro *et al.*, 2010; Jensen and Kreiborg, 1990; Kreiborg *et al.*, 1999; Quack *et al.*, 1999; Suda *et al.*, 2010; Yoshida *et al.*, 2002). CCD is present at a frequency of one in one million individuals. It affects all ethnic groups, and males and females are affected equally. Genetic studies mapped CCD to chromosomal 6p21, and heterozygous mutations (haploinsufficiency) in *RUNX2* (*CBFA1*) gene has been identified to be responsible for the development of CCD in both humans and mice (Ducy *et al.*, 1997; *Komori et al.,* 1997; Mundlos *et al.*, 1997; Otto *et al.*, 1997). *RUNX2* is a key transcription factor involved in osteoblast differentiation and skeletal morphogenesis (Ducy *et al.,* 1997; Komori *et al.*, 1997). *RUNX2* spans a region over 220 kb on chromosome 6p21, and contains nine exons that can be alternatively spliced (Geoffroy *et al.,* 1998). *RUNX2* gene can be transcribed from two distantly located promoters leading to the production of two major mRNA transcripts with different 5′-UTR and 5′ coding sequences (Li and Xiao, 2007). Approximately 60–70% clinically confirmed CCD patients exhibit mutations in *RUNX2* gene, including insertion, deletion, nonsense, and missense variants. Most of them were located in the

Table 1
Human Syndromes Associated With Supernumerary Teeth

Syndrome	Genetics	Gene	References
Cleidocranial dysplasia (MIM 119600)	Chromosome 6p21, autosomal dominant	*RUNX2* (MIM 600211)	Jensen and Kreiborg, 1990; Komori *et al.*, 1997; Kreiborg *et al.*, 1999; Mundlos *et al.*, 1997; Quack *et al.*, 1999; Lee *et al.*, 1997.
Familial adenomatous polyposis, including Gardner syndrome (MIM 175100)	Chromosome 5q21-q22, autosomal dominant	*APC* (MIM 611731)	Fader *et al.*, 1962; Half *et al.*, 2009; Ida *et al.*, 1981; Mcfarland *et al.*, 1968.
Ehlers-Danlos syndrome, type III (MIM 130020)	Chromosome 6p21.3 and 2q31, autosomal dominant	*Tenascin-XB* (MIM 600985) or *COL3A1* (MIM 120180)	Ferreira *et al.*, 2008; Majorana and Facchetti, 1992; Melamed *et al.*, 1994; Premalatha *et al.*, 2010.
Nance-Horan syndrome (MIM 302350)	chromosome Xp22.13, X-linked dominant	*NHS* (MIM 300457)	Bixler *et al.*, 1984; Hibbert, 2005; Van Dorp and Delleman, 1979; Walpole *et al.*, 1990.
Fabry disease (MIM 301500)	Chromosome Xq22, X-linked	a-*alactosidase A* (MIM 300644)	Brindley *et al.*, 1975; Regattieri and Parker 1973.
Ellis-Van Creveld syndrome (MIM 225500)	Chromosome 4p16, autosomal recessive	*EVC* (MIM 604831) or *EVC2* (MIM 607261)	Garvey *et al.*, 1999; Prabhu *et al.*, 1978.
Tricho-Rhino-Phalangeal syndrome (MIM 190351)	Chromosome 8q24.12, autosomal dominant	*TRPS1* (MOM 604386)	Giedion, 1966; Kantaputra *et al.*, 2008.
Robinow syndrome (MIM 180700)	autosomal dominant or autosomal recessive	*ROR2* (MIM 602337)	Mazzeu *et al.*, 2007.

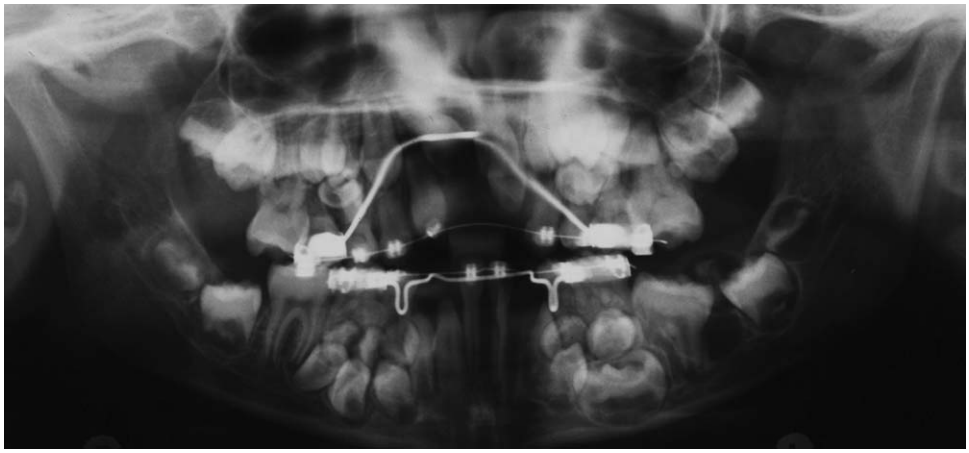

FIG. 1. Panoramic radiograph showing multiple impacted supernumerary teeth in the nine-year-old male with cleidocranial dysplasia. Orthodontic alignment is required to keep sufficient space in the dental arch for further treatment. (Courtesy of Bonnie L. Padwa, DMD, MD, Children's Hospital Boston, Harvard Medical School).

runt domain and were predicted to abolish DNA binding and alter the transactivation activity of *RUNX2* (*Lee et al.,* 1997; Mundlos *et al.*, 1997; Otto *et al.*, 2002; Otto *et al.*, 1997). Deletion of the entire *RUNX2* gene and/or its contiguous genes have also been described, and this accounts for ~13% of CCD individuals who have normal results on sequence analysis (El-Gharbawy *et al.,* 2010; Izumi *et al.*, 2006; Lee, M. T. *et al.*, 2008; Otto *et al.*, 2002; Quack *et al.*, 1999). *RUNX2* mutation is so far the only known molecular etiology for CCD. There are still many CCD patients without any detectable mutations in *RUNX2*, and this would indicate a genetic heterogeneity such as mutations in genes interacting with or regulating RUNX2, or due to some other unidentified mechanisms (Lee *et al.*, 2008).

Mutations in *RUNX2* have a high penetrance and extreme variability, ranging from isolated dental anomalies to fully manifesting disease with poorly ossified cranium and absence of clavicles (Golan *et al.*, 2000; Mendoza-Londono and Lee, 1993). The phenotype may vary greatly among individuals even in the same family with the same mutation. Haploinsufficiency for *RUNX2* gene is usually associated with classic CCD. There are some exceptions, including the 90insC and Thr200Ala mutations, which are associated with mild CCD, isolated dental anomalies, and significant intrafamilial variability, suggesting that haploinsufficiency of the gene product is quite sensitive to the modulation by other modifier genes, and hypomorphic/neomorphic effects and genetic modifiers may alter the clinical expressivity of these mutations (Bourdeau *et al.*, 2001; Zhou *et al.*, 1999).

Up to 94% of CCD patients exhibit dental anomalies including supernumerary teeth (Golan *et al.*, 2003). However, no clear genotype-phenotype correlation has been established (Otto *et al.*, 2002). Although Yoshida reported a significant correlation between the number of supernumerary teeth and the degree of short stature (Yoshida *et al.*, 2002), most other studies suggested that the correlation between the genotype and supernumerary tooth formation is very low. Individuals with CCD having identical *RUNX2* gene mutations showed a wide variation in the supernumerary tooth formation, and many of the supernumerary teeth occurred asymmetrically in the maxilla and the mandible, implying that the number and position of supernumerary teeth are not solely governed by *RUNX2* mutation. Other non-genetic factors, such as epigenetic factors, modifier genes, copy number variations, as well as environmental factors, may also be involved in the formation of supernumerary teeth in CCD (Ryoo *et al.,* 2010; Suda *et al.*, 2007; Suda *et al.*, 2010).

In CCD patients, the formation of primary and permanent teeth was normal (although with problems in shedding of primary teeth and eruption of permanent teeth), and the morphology of supernumerary teeth usually resembles their normal counterparts. However, the development of supernumerary teeth is delayed a couple of years compared to the normal permanent teeth. It was hypothesized that the dental lamina for both primary and permanent dentition is normal, but does not resolve completely thus resulting in the formation of supernumerary teeth (Jensen and Kreiborg, 1990; Lukinmaa *et al.*, 1995). Radiographic examination of tooth development in individual CCD patients over several years indicated that the supernumerary teeth in fact developed in sequence next to the corresponding permanent teeth. Therefore, supernumerary teeth in CCD are thought to arise from the permanent teeth, and they may represent a part of the third dentition (Jensen and Kreiborg, 1990).

Runx2 heterozygous mutant mice mostly phenocopied the skeletal defects of CCD in humans, but with no supernumerary tooth formation (Otto *et al.*, 1997). In

line with this, the *Runx2* homozygous null mutant mice have no bone. However, the tooth development in *Runx2* null mutants is arrested at the late bud stage (D'souza *et al.*, 1999). This may be because mice only have one dentition and they are not good model for studying successional or de novo supernumerary tooth formation. During mouse tooth development, *Runx2* is expressed in the dental mesenchyme mediating epithelial Fgf signals into the dental mesenchyme. Mesenchymal Fgf signaling then sends back to the dental epithelium, regulating the transition of tooth bud to cap stage (Aberg *et al.*, 2004). Notably, in *Runx2* homozygous and heterozygous mouse upper molars, a prominent epithelial bud regularly presents. This epithelial bud protrudes lingually with active Shh signaling, and it may represent the extension of dental lamina for the successional tooth formation in mice. Hence, although *Runx2* is required for primary tooth development, it prevents the growth of dental lamina and the successional tooth formation (Wang *et al.*, 2005).

Supernumerary Teeth in Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP, MIM 175100), also named as adenomatous polyposis of the colon (*APC*), is an autosomal dominant hereditary disorder characterized by the development of hundreds to thousands precancerous colorectal adenomatous polyps, some of which, without colectomy, will inevitably develop into cancer. In addition to colorectal neoplasm, these individuals can develop variable extracolonic lesions, including upper gastrointestinal polyposis, osteomas, congenital hypertrophy of the retinal pigment epithelium, soft tissue tumors, desmoids tumors, and dental anomalies (Boffano *et al.*, 2010; Chimenos-Kustner *et al.*, 2005; Fader *et al.*, 1962; Gardner and Richards, 1953; Half *et al.*, 2009; Mcfarland *et al.*, 1968; Ramaglia *et al.*, 2007; Wijn *et al.*, 2007). Dental abnormalities include impacted teeth, congenital absence of one or more teeth, supernumerary teeth, dentigerous cysts associated with the crown of unerupted tooth, and odontomas (Chimenos-Kustner *et al.*, 2005; Half *et al.*, 2009; Wijn *et al.*, 2007). Tooth extraction may be difficult due to root anomalies and almost complete absence of periodontal space caused by the extensive hypercementosis (excessive cementum formation on the roots)(Ramaglia *et al.*, 2007). Gardner syndrome is a variant of FAP characterized by multiple adenomas of the colon and rectum typical of FAP together with osteomas and soft tissue tumors (epidermoid cysts, fibromas, desmoids tumors)(Gardner and Richards, 1953; Ramaglia *et al.*, 2007). Supernumerary teeth and odontomas were originally described as a part of Gardner syndrome, but they can also occur in FAP patients with or without other extracolonic lesions (Fonseca *et al.*, 2007; Ramaglia *et al.*, 2007; Wijn *et al.*, 2007). The oral and maxillofacial manifestations can show up many years before the occurrence of intestinal polyposis, and these may lead to the early diagnosis of FAP (Boffano *et al.*, 2010; Fonseca *et al.*, 2007).

FAP and Gardner syndrome are caused by germline mutations in the *APC* gene (Cruz-Correa and Giardiello, 2002; Okamoto *et al.*, 1990; Wijn *et al.*, 2007). *APC* is located on chromosome 5q21-q22 and it can be alternatively spliced in multiple coding and noncoding regions. The main transcript has 15 exons with 8532 base pairs that code for 2843 amino acids resulting in a 311.8 kd protein. The exon 15 is largest coding region (6,500 bp) and comprises over three-quarters of the coding region of the gene (Groden *et al.*, 1991; Kinzler *et al.*, 1991). *APC* is a tumor suppressor gene involved in the downregulation of free intracellular β-catenin, the major signal transducer of canonical Wnt signaling pathway, as well as a central component of the E-cadherin adhesion complex (Groden *et al.*, 1991; Heinen, 2010). In addition, the *APC* protein may also play roles in chromosomal stability, regulation of cell migration up the colonic crypt and cell adhesion through association with E-cadherin, regulation of cell polarity through association with GSK3β, and other functions associated with microtubule bundles (Clevers, 2006; Heinen, 2010; Phelps *et al.*, 2009). Inactivation of *APC* would lead to stabilization and accumulation of the proto-oncogene β-catenin, dysregulation of the cell cycle, and chromosomal instability (Wijn *et al.*, 2007).

A large number of germline mutations have been identified in the *APC* gene. Most of the mutations are located in the 5′ region of the gene and cause a premature truncation of the APC protein, usually through single amino-acid substitutions or frameshifts (Friedl *et al.*, 2001; Heinen, 2010). Mutation analysis in large samples of FAP patients has revealed consistent correlations between the site of *APC* mutation and clinical manifestations encompassing both colonic lesions and some extracolonic features (Caspari *et al.*, 1994; Caspari *et al.*, 1995; Friedl *et al.*, 2001; Heinen, 2010; Nieuwenhuis and Vasen, 2007; Ramaglia *et al.*, 2007; Wallis *et al.*, 1999). Approximately 11%–27% patients have supernumerary teeth, but so far no specific codon mutation of the *APC* gene was found to correlate with supernumerary teeth and/or odontomas. There are wide familial and regional variations in oral manifestations in patients with FAP (Sondergaard *et al.*, 1987; Wijn *et al.*, 2007). It was reported that in pedigrees with mutations 3′ of codon 1444, the mean number of abnormalities on dental panoramic radiographs is three to five times higher than in those with mutations between codon 1 and 1444 (Davies *et al.*, 1995). Correlations seems to exist between dental abnormalities and the number and type of osteomas, with the highest incidence of supernumerary teeth and odontomas is found

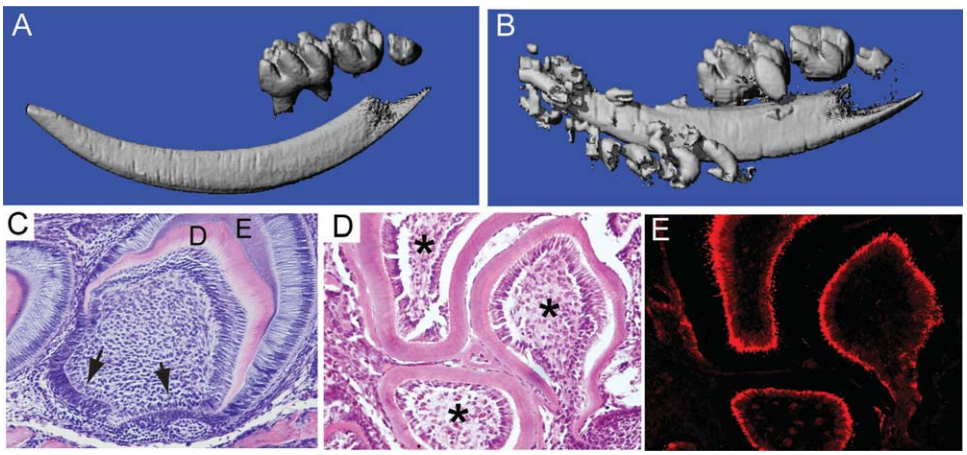

FIG. 2. K14-Cre^{8Brn};Apc$^{cko/cko}$ mice exhibit multiple mineralized supernumerary teeth. **A, B:** 3D reconstruction of Micro-CT pictures in P13 mice. Wild type mice (A) have one incisor and three molars in each quadrant of the oral cavity, whereas *K14-Cre^{8Brn};Apc$^{cko/cko}$* mice (B) exhibit multiple mineralized supernumerary teeth around the incisor and molar teeth. **C**: Some of the supernumerary teeth have well differentiated ameloblasts and odontoblasts, and Hertwig's epithelial root sheath starting to form roots (arrows). D, dentin; E, enamel. **D**: Hematoxylin and eosin staining of supernumerary teeth (asterisk) in *K14-Cre^{8Brn};Apc$^{cko/cko}$* mice. **E**: Neurofilament staining shows neural innervations inside the dental pulp and protruding into the dentin tubules of these supernumerary teeth.

in FAP patients with three or more osteomas (Kubo *et al.*, 1989; Wijn *et al.*, 2007; Wolf *et al.*, 1986). No correlation was found between dental abnormalities and colonic adenomas (Takeuchi *et al.*, 1993). Supernumerary teeth in patients with FAP are often small peg shaped and are mainly located in the alveolar bone between the teeth or attached to follicle of an impacted tooth (Ida *et al.*, 1981; Chimenos-Kustner *et al.*, 2005; Davies *et al.*, 1995; Half *et al.*, 2009; Kubo *et al.*, 1989; Thakker *et al.*, 1995; Wijn *et al.*, 2007). Common sites of supernumerary unerupted teeth are in the anterior regions and around canines, similar to non-FAP populations (Ida *et al.*, 1981; Kubo *et al.*, 1989). The reported prevalence of odontomas in patients with FAP was between 9.4% and 83.3%, with similar distribution in the mandible and in the maxilla (Wijn *et al.*, 2007). They are often located in the incisal-premolar area and can be multiple (Chimenos-Kustner *et al.*, 2005; Half *et al.*, 2009; Ida *et al.*, 1981; Wijn *et al.*, 2007).

Some mouse strains with genetically modified *Apc* gene have been established, and heterozygous *Apc* mutant mice showed gastro-intestinal and other tumor predisposition phenotypes similar to human patients with FAP (Fodde *et al.*, 1994; Moser *et al.*, 1995; Oshima *et al.*, 1995; Smits *et al.*, 1997). *Apc* homozygous mutant mouse embryos died early before or during grastrulation stage (Ishikawa *et al.*, 2003; Oshima *et al.*, 1995). Conditional knockout of *Apc* gene (*Apc$^{cko/cko}$*) under the control of human keratin 14 (*K14*) promoter, which drives gene expression to the basal cells of epidermis and oral and dental epithelium, resulted in aberrant development of several epithelial derived organs, including hair follicle, thymus, and supernumerary teeth (Kuraguchi *et al.*, 2006). Most of the supernumerary teeth were simple unicuspid cones, while some multicuspid teeth were also observed in both molar and incisor regions. Some supernumerary teeth exhibit well-differentiated ameloblasts and odontoblasts with enamel and dentin matrix depositions, as well as blood supply and innervations (see Fig. 2). Some supernumerary teeth even start to form roots, indicating that these supernumerary teeth may function as natural teeth (Wang *et al.*, 2009).

Two different *K14-Cre* mouse lines were used to delineate the role of *Apc* in tooth development. The *K14-Cre^{1Amc}* mice exhibited uniform Cre recombinase activity throughout the oral and dental epithelium, whereas *K14-Cre^{8Brn}* mice showed a mosaic pattern of Cre activity in the oral and dental epithelial cells (Dassule *et al.*, 2000; *Jonkers et al.,* 2001; Wang *et al.*, 2009). The *K14-Cre^{1Amc};Apc$^{cko/cko}$* mice exhibit severe defects in ectodermal derived organs and died shortly after birth with numerous irregular epithelial buds protruding from the oral epithelium into the jaw mesenchyme. This phenotype is very similar to the mice with constitutive activation of β-catenin in embryonic oral epithelium under the *K14* promoter (*K14-Cre;* β*-catenin$^{\Delta ex3f/+}$*) (Jarvinen *et al.*, 2006; *Liu, F. et al.,* 2008). The *K14-Cre;* β*-catenin$^{\Delta ex3f/+}$* mice also died at birth and their irregular oral epithelial buddings, when transplanted under the kidney capsule of immune deficiency mice, can further develop into many small teeth. In the *K14-Cre^{1Amc};Apc$^{cko/cko}$* mice, the expression of both β-catenin transcripts (*Ctnnb1*) and β-catenin protein were dramatically upregulated in the oral epithelium. Genetic deletion of β-catenin (*Ctnnb1$^{cko/cko}$*) in the oral epithelium of *Apc* loss-of-function (*K14-Cre^{1Amc};Apc$^{cko/cko}$*) mice suppressed the formation of

supernumerary teeth. Although Apc may have other functions during development, these data formally proved that the induction of supernumerary teeth by *Apc* loss-of-function was through activation of Wnt/β(catenin signaling (Wang *et al.,* 2009).

The *K14-Cre*^{8Brn};*Apc*$^{cko/cko}$ mice with mosaic deletion of Apc in the epidermis and oral epithelium can survive after birth, though all mutant mice died before postnatal 19 days (Kuraguchi *et al.*, 2006). This anyway provided a longer time window for studying the development of supernumerary teeth (Wang *et al.*, 2009). In the *K14-Cre*^{8Brn};*Apc*$^{cko/cko}$ mice, a lot of supernumerary teeth formed from multiple regions of the jaw, on both labial and lingual aspects of the principle molar and incisor teeth, or directly derived from oral epithelium. Supernumerary tooth germs can even form on the Hertwig's epithelial root sheath in the developing root, as well as in the vestibular lamina, a temporal oral epithelial invagination that in wild type mice will eventually undergo apoptosis forming the space between the gingiva and the inner cheek.

Notably, adult oral tissues, especially young adult tissues, are still responsive to loss of *Apc* or activation of Wnt/β(catenin signaling, and are able to form new teeth (Wang *et al.,* 2009). In the old adult mice, supernumerary teeth can be induced on both labial and lingual sides of the incisors, which contain adult stem cells supporting the continuous growth of mouse incisors (Liu *et al.*, 2010; Wang *et al.*, 2009). In the young mice, supernumerary tooth germs were induced in multiple regions of the jaw in both incisor and molar regions. They can form directly from the oral epithelium, in the dental lamina connecting the developing molar or incisor tooth germs to the oral epithelium, in the tooth crown regions, as well as in the elongating and furcation area of the developing root (Wang *et al.*, 2009). These data indicate that young mice retain odontogenic potential in multiple regions of the jaw. In humans, the development of permanent teeth starts during the embryonic and fetal periods, and then continues for many years after birth into adolescence. In particular, the third molars start to develop after birth and it was reported that the onset of mandibular third molar formation ranges from 5.86 to 14.66 years old (Bolanos *et al.*, 2003). Children and adolescents thus retain dental lamina epithelial cells in their jaw, and this holds great promises for biological tooth regenerations and tooth repairs.

Interestingly, *Msx1*, which is required for endogenous tooth development, is dispensable for supernumerary tooth formation in mice with the loss of function of *Apc* in the oral and dental epithelium (Wang *et al.,* 2009). In the developing teeth of wild type mice, *Msx1* is expressed in the dental mesenchyme and forms a positive feedback loop with Bmp4 regulating the development of tooth bud into the cap stage (Bei *et al.,* 2000; Chen *et al.*, 1996; Maas and Bei, 1997). Synergistic interaction between Msx1 and Pax9 is also crucial for lower incisor development (Nakatomi *et al.*, 2010). In *Msx1* null mutant mice, tooth development is arrested at the bud stage (Chen *et al.,* 1996; Satokata and Maas, 1994). However, deletion of *Msx1* in *K14-Cre*^{8Brn};*Apc*$^{cko/cko}$ mice had no effect on the formation of supernumerary teeth. Both *Bmp4* and *Fgf3*, which are downregulated in *Msx1* deficient mouse tooth germs, were expressed in the mesenhcyme of supernumerary teeth in *K14-Cre*^{8Brn};*Apc*$^{cko/cko}$;*Msx1*$^{-/-}$ mice, and *Bmp4* was also expressed in the epithelium of these supernumerary teeth. These data indicate that *Apc* loss-of-function can bypass the mesenchymal Msx1-Bmp4 feedback loop that is normally required for endogenous tooth development (Wang *et al.,* 2009). Mutations in *MSX1* in humans cause tooth agenesis (Vastardis *et al.,* 1996). These results provide possibilities in the future to use the human *MSX1* deficient oral tissues to generate supernumerary teeth for the treatment of their missing teeth.

Another interesting finding was that only a small subset of *Apc* deficient cells was able to recruit surrounding wild type oral epithelial cells, and induce adjacent wild type mesenchymal cells to form new teeth. Some wild type epithelial cells adjacent to the *Apc* deficient cells can also be induced to express high levels of β-catenin protein in the nucleus, suggesting that *Apc* deficient cells can function in a non-cell autonomous manner, and both *Apc* deficient cells and surrounding wild type epithelial cells participate in the formation of enamel knot signaling center in supernumerary tooth germs as well as the whole supernumerary tooth formation (Wang *et al.,* 2009). *Fgf8* was shown to be a direct target gene of Wnt/β-catenin signaling, and Wnt/β-catenin signaling regulates and maintains *Fgf8* expression in the oral epithelium (Wang *et al.,* 2009). *Fgf8* is one of the earliest molecules expressed during the initiation stage of tooth development (Kettunen *et al.,* 1998). However, *Fgf8* itself cannot induce new tooth formation in vitro, suggesting that other Wnt target genes are also involved in the initiation of supernumerary tooth formation (Wang *et al.*, 2009).

Various Model Systems For Studying Supernumerary Tooth Formation

Mice have been used for a long time as the predominant model for studying tooth development. However, mouse dentition is highly reduced with only one incisor and three molars, separated by a toothless diastema region, in each quadrant of the jaw. In addition, mice have only a single primary dentition and their teeth are not replaced. Therefore, the mice may not be an optimal model for studying tooth replacement and supernumerary tooth formation (Huysseune and Thesleff, 2004). Most of reported mouse supernumerary teeth

are located in the diastema region in front of the first molars. This is not a de novo tooth formation but the rescue of vestigial tooth rudiments. During early stages of tooth development, many transient vestigial dental buds develop in the diastema area. Some of them can develop into bud stage, but later regress and disappear by apoptosis, or merge with the mesial crown of the first molar tooth (Peterkova *et al.,* 2002, 2005, 2009; Prochazka *et al.*, 2010; Viriot *et al.*, 2002; Witter *et al.*, 2005). Major signaling pathways regulating tooth development are also expressed in these vestigial dental buds. Modulation of these signals can rescue these vestigial tooth rudiments to develop into supernumerary diastema teeth (Tummers and Thesleff, 2009). A number of mutant mouse stains have been reported exhibiting supernumerary diastema teeth, including mice with overexpression of *Eda* or *Edar* (Kangas *et al.,* 2004; Mustonen *et al.*, 2003; Pispa *et al.*, 2004; Tucker *et al.*, 2004), *Tabby* mice with mutation of *Eda* (Charles *et al.,* 2009; Peterkova *et al.*, 2005), *Sprouty2* or *Sprouty4* null mutant mice affecting Fgf signaling(Klein *et al.,* 2006), hypomorphic Polaris mice and *Wnt1-Cre*; Polaris conditional mutant mice affecting Shh signaling (Ohazama *et al.*, 2009; Zhang *et al.*, 2003), *Pax6* mutant mice (Kaufman *et al.,* 1995), and *Gas1* null mutant mice (Ohazama *et al.,* 2009). *Sostdc1* (*Ectodin/Wise/* USAG-1) null mutant mice and *Lrp4* (a receptor that suppresses Wnt signaling) hypomorphic mice present supernumerary teeth in both incisors and molar regions (Ahn *et al.,* 2010; Kassai *et al.*, 2005; Murashima-Suginami *et al.*, 2007; Ohazama *et al.*, 2008). It was shown that Sostdc1 suppresses the survival of the diastema or incisor vestigial buds by serving as an inhibitor of Lrp5- and Lrp6-dependent Wnt signaling. Inactivation of Sostdc1 leads to elevated Wnt signaling and, increased proliferation and continuous development of vestigial tooth buds to form supernumerary teeth (Ahn *et al.*, 2010). Lrp4 was also shown to inhibit canonical Wnt signaling by binding to Sostdc1 and loss of function of *Lrp4* may lead to elevated Wnt signaling (Ohazama *et al.,* 2008).

Transgenic Mice With De Novo Supernumerary Tooth Formation

De novo supernumerary teeth arising directly from the primary tooth germs or dental lamina have been reported in *Apc* loss-of-function or β-catenin gain-of-function mice (as discussed in the previous section), and in the *Sp6 (Epiprofin*) deficient mice. *Sp6* is a zinc-finger transcription factor that is mainly expressed in epithelial cells in the developing teeth, hair follicles, limb buds, as well as in the adult lungs (Nakamura *et al.,* 2004; Talamillo *et al.*, 2010). The *Sp6* gene generates two different transcripts, termed *Sp6* and *Epiprofin*, which differ in the first exon but ultimately code for the same Sp6 protein (Hertveldt *et al.*, 2007). During mouse tooth development, *Sp6* is expressed in the dental epithelium during early stage of tooth development, and later in the inner dental epithelium of the enamel organ and also in the differentiated odontoblasts (Nakamura *et al.,* 2004). *Sp6* deficient mice initially had delayed tooth development, but later developed multiple supernumerary teeth in both incisor and molar regions. At early stage, *Sp6* mutant mouse dental epithelium showed reduced cell proliferation and differentiation, as well as compromised enamel knot signaling center. Starting from E16.5 bell stage, multiple non-proliferating enamel knot-like structures formed ectopically in the enamel organ of primary tooth germs, and then further grew and branches into the jaw mesenchyme, eventually developing into supernumerary teeth (Jimenez-Rojo *et al.,* 2010; Nakamura *et al.*, 2008). So far, no human supernumerary teeth have been reported to be associated with the *SP6* gene.

Mammals only have one row of teeth in each jaw. Interestingly, in *Osr2* null mutant mouse embryos, supernumerary tooth germs were found developing directly from the oral epithelium lingual to their molar tooth germs (Zhang *et al.*, 2009). This was, however, different from the successional (replacement) or supernumerary tooth formation in all the vertebrates reported, but may be similar to the formation of a second tooth row in multirowed fish (Mikkola, 2009; Zhang *et al.*, 2009). In the developing mouse tooth germs, *Osr2* is expressed in the molar mesenchyme in a lingual-to-buccal gradient that is complementary to the expression pattern of Bmp4. In *Osr2* null mutant embryos, expression of several odontogenic factors, including *Pitx2*, *Shh*, *Msx1*, and *Lef1*, was upregulated or expanded. Deletion of *Msx1*, a feedback activator of Bmp4, in the *Osr2* mutant mice prevented the formation of supernumerary teeth, suggesting that expansion of the odontogenic field in *Osr2* mutant embryos required *Msx1*, and antagonistic interactions between Osr2 and Msx1 pattern the tooth morphogenetic field (Zhang *et al.*, 2009).

Current Models for Studying Successional Tooth Formation

It has been suggested that in humans a "third dentition," with one or more supernumerary teeth, can occur in addition to the permanent dentition, and supernumerary teeth are sometimes thought to represent a partial post-permanent dentition (Jensen and Kreiborg, 1990; Murashima-Suginami *et al.*, 2007; Ooe, 1969). Analysis of successional tooth formation may help with understanding the molecular genetics of supernumerary tooth formation, and will also provide information of the behaviors and regulations of dental stem cells. As mice are not good model for studying tooth replace-

ment, some other models have been established to analyze successional tooth formation, including reptiles, fish, lizard, and snake, which replace their teeth continuously throughout life, as well as some mammals with secondary teeth, such as ferret (Berkovitz and Moore, 1975; Fraser *et al.*, 2004, 2006a,b; Handrigan *et al.*, 2010; Handrigan and Richman, 2010a,b; Jarvinen *et al.*, 2009; Osborn, 1978). Detailed histological analysis on the tooth replacement of these models indicate that the successional teeth are initiated from the dental lamina epithelium, which grows from the lingual side of the deciduous tooth enamel organ, and it later elongates and buds into the jaw mesenchyme forming the successional tooth. Jarvinen *et al.* showed that in ferret, *Sostdc1* is expressed in the elongating successional dental lamina at the interface between the lamina and the deciduous tooth, as well as the buccal side of the dental lamina, suggesting that Sostdc1 may play a role in defining the identity of the dental lamina (Jarvinen *et al.,* 2009). Handrigan *et al.* analyzed successional tooth formation in snake and in lizard, and proposed that dental epithelial stem cells are responsible for the formation of succcessional lamina, and Wnt signaling may regulate the stem cell fate in these cells (Handrigan *et al.*, 2010). Maintenance or reactivation of a competent dental lamina is thus pivotal for the replacement tooth and supernumerary formation (Jarvinen *et al.*, 2009; Tummers and Thesleff, 2009).

CONCLUDING REMARKS

Multiple supernumerary teeth may have genetic components in their etiology and represent partial of the third dentition in humans. Research in recent years has taught us much about the molecular mechanisms underlying tooth morphogenesis and differentiation. However, relatively little is known about the initiation of tooth formation, the genetic control of successional teeth, as well as the mechanisms underlying supernumerary tooth formation. The supernumerary teeth generated in *Apc* loss-of-function or β-catenion gain-of-function mice are in line with the tooth phenotypes observed in human FAP. These information, although exciting and informative, leave many critical questions concerning induction of supernumerary teeth unanswered. Since *Apc* is a tumor suppressor gene and β(catenion is a proto-oncogene, further studies are needed to identify the genes, cytokines, or small molecules, to activate Wnt/β-catenin signaling and to stimulate new tooth formation in vitro and/or in vivo. Better understanding of the role of Wnt/β-catenion, Apc, and *Runx2* in the formation of supernumerary teeth, together with detailed analysis of successional tooth formation in various model systems, will provide fundamental insights into the molecular genetics of supernumerary teeth in humans and will also assist in tooth regeneration and tooth engineering in the clinic.

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