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REVIEW

The epidemiology of supernumerary teeth and the associated molecular mechanism

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ABSTRACT. Supernumerary teeth are common clinical dental anomalies. Although various studies have provided abundant information regarding genes and signaling pathways involved in tooth morphogenesis, which include Wnt, FGF, BMP, and Shh, the molecular mechanism of tooth formation, especially for supernumerary teeth, is still unclear. In the population, some cases of supernumerary teeth are sporadic, while others are syndrome-related with familial hereditary. The prompt and accurate diagnosis of syndrome related supernumerary teeth is quite important for some distinctive disorders. Mice are the most commonly used model system for investigating supernumerary teeth. The upregulation of Wnt and Shh signaling in the dental epithelium results in the formation of multiple supernumerary teeth in mice. Understanding the molecular mechanism of supernumerary teeth is also a component of understanding tooth formation in general and provides clinical guidance for early diagnosis and treatment in the future.

KEYWORDS. supernumerary teeth, signaling pathways, syndrome

INTRODUCTION

Supernumerary teeth are defined as "Teeth, or tooh-like structures that have either erupted or remain unerupted in addition to the 20 primary and 32 permanent teeth."[1] The morphology of supernumerary teeth can be similar to that of the normal teeth or quite different, they

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can be classified into following types: conical type, tuberculate type, supplemental teeth and odontomas. The extra teeth can occur as a single tooth or multiple teeth, in a unilateral or bilateral fashion[2] and in any region of the dentition, though they frequently occur in the premaxillary.[3-7] The most common region in which these teeth arise is in the middle of the maxillary between 2 middle incisors, and the most common form of mesiodens is the canine-like type, which comprises 60% of all mesiodens.[8]

Pippi[9] summarized the prevalence of supernumerary teeth of previous studies, the rates varied from 0.04% to 2.29%. That may due to the different evaluation of methods or samples. Recently, Japanese scientists report that the prevalence of supernumerary teeth in permanent dentition was 0.04%, which was lower than the other investigations.[10] It may because they only focus on the erupted ones but ignored the unerupted ones. Shilpa[11] reported that the prevalence of supernumerary teeth in the primary dentition is 0.21%, while in mixed dentition, the rate was 0.9%.[12] Additionally, the occurrence of supernumerary teeth varies depending on gender, as it appears to be more common in males than females.[10,11,13] Furthermore, supernumerary teeth occur in the midline region more often in males, while incisor region supernumerary teeth are more common in females.[14]

Supernumerary teeth in the permanent dentition are usually accompanied by various dental anomalies, such as odontoloxia, impaction, rotated permanent teeth adjacent to the supernumerary teeth, delayed eruption, ectopic eruption, overcrowding, periapical resorption of permanent teeth and the formation of follicular cysts.[15-18] Usually, supernumerary teeth are extracted because of their influence on normal dentition and aesthetics factors.

DIAGNOSIS AND MANAGEMENT

In most cases, erupted supernumerary teeth could be diagnosed by general oral examination, and imaging methods could be helped in diagnosis of unerupted extra teeth. More significantly, doctors should pay attention to the distinction between real supernumerary with uerupted prematurely deciduous teeth.

The management of supernumerary teeth depends on their type, position, and possible complications, as detected clinically and radiographically, and there is no clear consensus on when is the best time to remove unerupted supernumerary teeth.[16] Under the following circumstances an immediate elimination of the supernumerary teeth should be considered: inhibition or delay of eruption, displacement of the adjacent tooth, interference with orthodontic appliances, presence of a pathologic condition, or spontaneous eruption of the supernumerary teeth.[19]

THEORY REGARDING SUPERNUMERARY TEETH FORMATION

The factors driving the morphogenesis of supernumerary teeth have remained unclear until now. Sometimes extra teeth occur as a sporadic case, but usually occur with some syndromic disease and cluster within families. Anthonappa[2] et al. summarized the possible aetiologies for the initiation of supernumerary teeth, which included atavism, dichotomy, hyperactivity of the dental lamina, heredity, progress zone theory and unified etiology.

The theory regarding hyperactivity of the dental lamina is widely accepted, and it suggests that there is a localized, independent and conditional hyperactivity of the remaining epithelial cells of the dental lamina. Excessive activity of the dental lamina is associated with abnormal development of embryos caused by genetic factors.[20]

All the theories mentioned above have opened the door to research in the field of supernumerary teeth. Until now, each theory has had its own advantages, however, each one can only partially explain the phenomenon. Although hyperactivity of dental lamina is the most acceptable reason, we still do not know what cause this hyperactivity: genes or environmental factors? The etiology of supernumerary teeth is multifactorial, resulting from both

genetic and environmental factors. There is a long way to go if we want to gain clarity regarding supernumerary teeth and be able to manipulate the number and morphogenesis of teeth temporally and spatially.

SYNDROMES RELATED TO SUPERNUMERARY TEETH

Supernumerary teeth can occur as sporadic cases in some conditions but usually occur in association with some syndromic disease and familiar tendency. We list the syndromes associated with supernumerary teeth (Table. 1). Multiple supernumerary teeth with non-syndromic reasons are rarer and usually they are strongly associated with syndromic diseases, like cleidocranial dysplasia (CCD) and Gardner's syndrome. Runx2 and APC are the pathogenic genes of CCD and Gardner's syndrome, respectively. Clinical manifestations of some syndromes can be accompanied by supernumerary teeth, which have been identified are Enamel-Renal-Gingival syndrome,[21] craniosynostosis,[22] Crouzon syndrome,[23] Ehlers-Danlos syndrome[24] Incontinentia pigmenti,[25] Ellis-Van Creveld syndrome,[26] Hallerman-Streiff syndrome[27](Ahn considered they are uerupted prematurely deciduous teeth rather than supernumerary teeth[28]), Nance-Horan syndrome,[29] Noonan syndrome,[30] Robinow syndrome,[31] SOX2 anophthalmia syndrome[32] and Trichorhinophalangea.[33]

Sequence similarity family 20 (FAM20) is a group of highly evolutionarily conserved molecules, including FAM20A, FAM20B and FAM20C. In human, mutations in FAM10A caused a supernumerary premolar, while mutations in FAM20C showed dental abnormalities and gingival hyperplasia but no supernumerary teeth, which was similar to the FAM10A null mice. However, FAM20B knock out mice occurred supernumerary incisors. Mutations in IL11RA in human appeared supernumerary teeth, but loss function of IL11RA in mice did not displayed supernumerary teeth,[22,34] so was the same as Elli-Van Creveld syndrome and EVC2 null mice.[35-37] These atypical findings suggested that the function of IL11 signaling pathway and EVC2 in dental development are different in human and mice. For Fabry syndrome, although there were cases of supernumerary teeth appeared, dental dysplasia was not detected in $Aga^{-/-}$ mice.[38,39] That might be a coincidence or the species differences. Supernumerary teeth in Hallerman-Streiff syndrome used to be a accompanied manifestation, but recently, scientists suggested that were prematurely unerupted teeth rather than extra teeth.[28,40]

TABLE 1. Syndrome related supernumerary teeth.

Syndrome	OMIM	Gene
Amelogenesis Imperfecta[21]	204690	FAM20A
Bloch-Sulzberger syndrome[85]	308300	IKBKG
Cleidocranial dysplasia[86]	119600	RUNX2
Craniosynostosis[22]	614188	IL11RA
Crouzon syndrome[23]	123500	FGFR2
Ehlers-Danlos Type III.[87]	130020	COL3A1
Ehlers-Danlos Type IV.[25]	225400	PLOD
Ellis–Van Creveld.[26]	225500	EVC, EVC2
Fabry disease.[38]	301500	GLA
Gardner's.[88]	175100	APC
Hallerman-Streiff.[40]	234100	Unknown
Nance-Horan.[89]	302350	NHS
Noonan syndrome.[30]	163950	PTPN11
Oro-facio-digital type I.[90]	311200	OFD1
Rothmund–Thomson syndrome.[91]	268400	RECQL4
Robinow.[31]	180700	ROR2
SOX2 Anophthalmia syndrome.[32]	184429	SOX2
Trichorhinophalangeal.[33]	190350	TRPS1

Thus, the early diagnosis of syndrome-related supernumerary teeth is quite important. For example, approximately 70% of all Gardner's syndrome patients had dental anomalies, including supernumerary teeth and others.[41] Without treatment, intestinal polyps have a 100% chance of becoming malignant.[42] Usually, finding the tooth anomalies occurs earlier than detecting osteoma and intestinal polyps, so dentists need to be acquainted with these anomalies to diagnose Gardner's syndrome as early as possible.

SIGNALING PATHWAYS INVOLVED IN SUPERNUMERARY TEETH FORMATION

The formation of the tooth is a result of a series of signal interactions between the epithelium and

the neural crest-derived ectomesenchyme of the maxilla and mandible. Remarkable advancements in the genetic mechanisms have improved our understanding of supernumerary teeth formation and development. The initiation of tooth germs has a decisive effect on the number of teeth, and cells in the enamel knot, which forms at the center of the tooth germ at the onset of the cap stage, will produce several signaling molecules to control the development of tooth germs, including bone morphogenetic protein (BMP), fibroblast growth factor (FGF), tumor necrosis factor (TNF) and molecules of the sonic hedgehog (Shh) and wingless-related (Wnt) pathways.[20,43-45] The stable and accurate expression of signaling molecules is the foundation of tooth development, and up- or downregulation of any of these molecules leads to tooth and dentition anomalies. We summarized the signaling pathways and molecules involved in supernumerary teeth in Fig. 1.

The tooth morphogenesis of different vertebrates is similar, from thickened dental lamina to bud, cap and bell stage, then the hard tissue deposited and gradually become matured. Usually, the research of supernumerary teeth was performed in mice. A number of mouse mutant strains for supernumerary teeth have been established (Table 2).[43] In the mouse dentition, there is a tooth-less region, called diastema, between the incisor and molars in each quadrant. In the early stages of embryonic development, there are rudimentary tooth buds, and later in development, all of the tooth buds go through apoptosis, leading to the tooth-less regions. The general consensus is that signaling molecules in the mesenchyme arrest the development of the tooth at the bud stage.[46] However, the impropriated modulation of the signaling pathways may rescue the vestigial tooth rudiments and lead to supernumerary teeth.[47] Thus, the models of supernumerary teeth in mice can be classified into 2 categories, one is the extra tooth buds developed in the incisor or molar region, the other is the continues development of primary tooth buds in the diastema region.

FIGURE 1. Molecules and syndromes associated with supernumerary teeth.

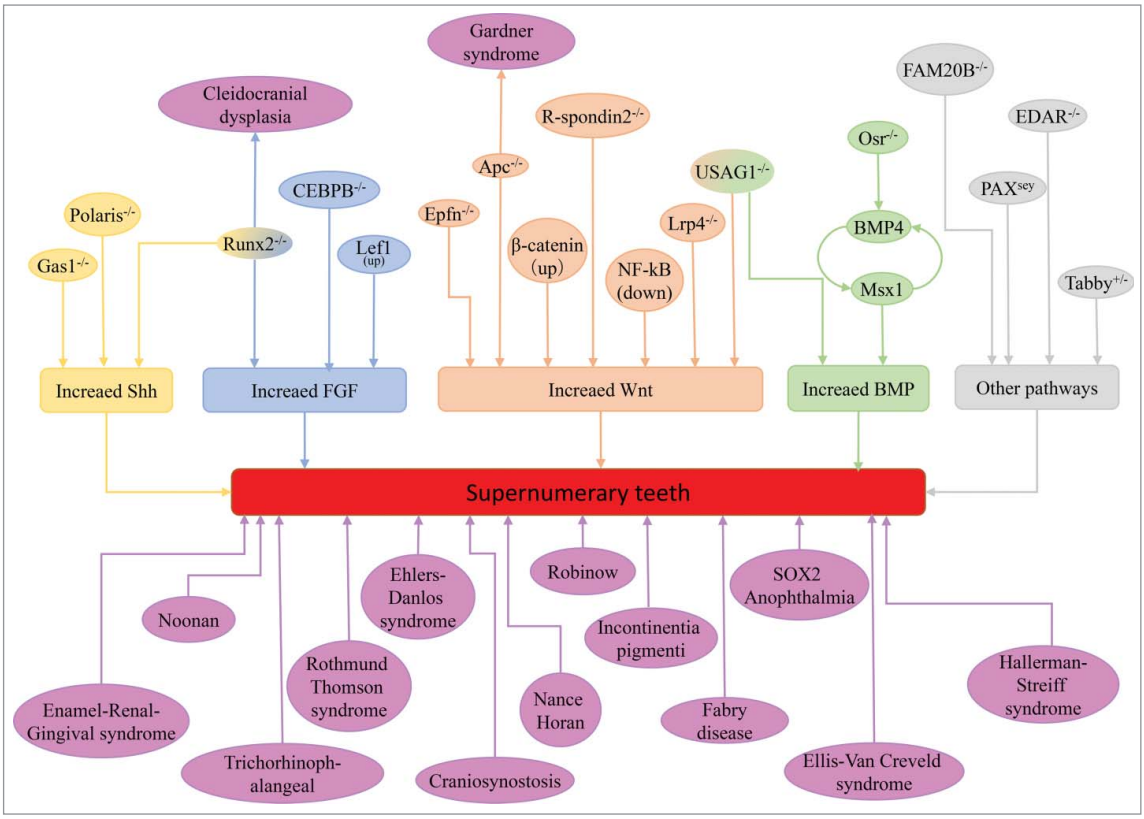

TABLE 2. Mouse models associated with supernumerary teeth.

Pathway	Mouse mutant	Supernumerary teeth
Shh	Gas1$^{-/-}$	Premolar mesial to first molar, both jaws (100% penetrance).[49]
	Gas1$^{-/-}$;Shh$^{+/-}$	Mandibular molar (associated with jaw duplication).[92]
	Tg737^{orpk}hypomorph	Premolar mesial to first molar, both jaws (100% penetrance).[93]
Wnt	Wnt-Cre; Polaris$^{flox/flox}$	Premolar mesial to first molar, both jaws (100% penetrance).[49]
	Epiprofin$^{-/-}$	Multiple incisors (> 50) and molars (> 8) in both jaws[94]
	K14-Cre; Apc$^{cko/cko}$	Multiple incisor and molar tooth buds[95]
	K14-Cre8^{Brn}; Apc$^{cko/cko}$	Numerous labial and lingual incisor and molar teeth (↑with age) derived from oral epithelium, vestibular lamina, principle and supernumerary teeth themselves[60]
	K14-Cre1^{Amc}; Apc$^{cko/cko}$	Numerous epithelial buds from E14.5[60]
	K14-CreER^{TM}; Apc$^{cko/cko}$	Numerous labial and lingual incisors (age P5–10/12) P5–8 supernumeraries associated with oral epithelium, incisors and molars[60]
	K14-CreER^{TM}; Ctnb1$^{(ex3)/fl+}$	Numerous labial and lingual incisors (age P5–6/12) P5 molar supernumeraries[60]
	K14-Cre$^{-/+}$; β-cateninex$^{\Delta ex3fl/+}$	Multiple incisor and molar epithelial invaginations in both jaws.[96]
	K14-Cre; Ctnnb1$^{(ex3)fl/+}$	Multiple molar epithelial invaginations.[97]
	K14-Lef1	Rudimentary teeth at inappropriate sites.[71]
	R-spondin2$^{-/-}$	Superunmerary teeth in the mandible diastema (66.7%)[73]
FGF	Spry2$^{-/-}$	Premolar mesial to first molar; maxilla (> 5%), mandible (97%: 92% bilateral; 5% unilateral).[98]
	Spry4$^{-/-}$	Both jaws? 16% penetrance (most unilateral).[68]
BMP	Ectodin-/-(Sostdc1, USAG1, Wise)	Supernumerary incisors in the maxilla and mandible Premolar mesial to first molar, peg-shaped tooth lingual to first molar Variable penetrance, ↓ in mandible[99]
	Lrp4$^{-/-}$(Megf7) hypomorph	Supernumerary incisors in the maxilla and mandible.[62] Premolar mesial to first molar (varying penetrance in both jaws) Lingual peg-shaped tooth (maxilla, variable penetrance)
	Wise$^{-/-}$,Lrp5$^{-/-}$	Supernumerary maxillary incisors (77.8%).[61]
	Wise$^{-/-}$,Lrp5$^{+/-}$	Supernumerary maxillary incisors (100%)[61]
	Wise$^{-/-}$,Lrp6$^{+/-}$	Supernumerary incisors (maxillary 10%).[61]
	Osr2$^{-/-}$	Lingual molars[52]
TNF	K14-Eda	Premolar mesial to first molar; incomplete penetrance (mandible>maxilla; unilateral>bilateral).[100]
	K14-Edar	Premolar mesial to first molar; incomplete penetrance[101]
	B6CBACa-A^{w-J}/A-Eda^{Ta}/0	Molar (1%; mandible>maxilla).[102]
Others	Pax^{Sey}	Incisor supernumeraries: 35% unilateral; 45% bilateral incisors[103]
	Tabby$^{+/-}$	Molar (2.5%; mandible>maxilla).[104]
	Di	Mandibular incisors (right>left).[105]
	K14-Cre; Fam20B$^{flox/flox}$	Supernumerary incisors at the mesial sides of the lower incisors (100%)[81]

Supernumerary teeth formed in incisor and molar region

The development of supernumerary teeth was closely related to the upregulation or sensitivity to Wnt, Shh, BMP and FGF signaling. In the early stage of tooth germ development, the Shh signal is indispensable for dental placodes, and over activated Shh signal is an important premise for supernumerary teeth formation.[48,49] BMPs belong to the TGFβ family, and are expressed widely between the epithelium and mesenchyme in the developing tooth germs, BMP2, BMP4, BMP6 and BMP7 are all detected.[50] Among them, BMP4 in the dental mesenchyme have vital function in inducing the tooth germ develop from bud stage to bell stage. In the mesenchyme, BMP4 acts in a

positive feedback loop with Msx1 to regulate the tooth development.[51,52] The transcription factor Osr2 and Dkk2 maintain this interation mainly act as an inhibitor to this positive feedback and restrict the area of presumptive odontogenic meshenchyme. In the deletion of Osr2 or Dkk2, BMP4, Msx1 and Shh signal were over activited and extra teeth came up.[53,54] USAG1 is a secreted BMP signal inhibitor, USAG1 null mice exhibit supernumerary teeth in the incisor region, and the other BMP signal inhibitor noggin could rescue the phenotype of extra teeth in vitro.[55] Further research showed the antagonistic interaction between USAG1 and BMP7.[56] Wnt is a secreted glycoprotein that can activate several intercellular signaling pathways, including canonical and non-canonical signaling pathways. Wnt4, Wnt5a, Wnt6, Wnt10a and Wnt10b are all detected during early stage of tooth development.[57,58] The stable expression of canonical Wnt signaling has great significance of tooth number, the overactivation of the Wnt/β-catenin signaling pathway in the dental epithelium results in the formation of supernumerary teeth. Apc is the inhibitor of canonical Wnt signaling.[59] Epithelial deletion of Apc in both mouse embryos and young mice resulted in continuous supernumerary teeth formation from multiple regions of the jaw. Additionally, the genetic deletion of Apc or the activation of β-catenin in the oral epithelium of old adult mice produced multiple supernumerary teeth in the incisor region.[60] Delete the other Wnt signaling antagonist USAG1 or Lrp4 also result supernumerary teeth.[61,62] Mouse model which overexpression of IKKβ, a major component of NF-κB signaling, showed supernumerary teeth in the lingual of incisor region, and the phenotype was similar to the model of Ectodin deletion.[63] Scientists reported that NF-κB signaling can activate Wnt signaling in colon cancer.[64] Thus, the supernumerary teeth in IKKβ overexpression mouse may due to the activation of Wnt signaling.

Supernumerary teeth in diastema region

In the embryonic period, there are rudimentary tooth primordia in the diastema region called R1 and R2 in maxillary and MS and R2 in mandible. From the embryonic day 13.5, these tooth buds became apoptosis and finally formed the tooth-less region.[65] The cyclin-dependent kinase inhibitor p21 is the marker for tooth bud apoptosis in diastema, and many molecules like FGFs and CCAAT/enhancer-binding protein β(CEBPB) are involved in the apoptosis procedure.[65,66] The supernumerary teeth in diastema region is result from the inhibit of apoptosis. In Tg737^{orpk} mice, there are extra tooth and p21 expression is downregulated obviously.[49] Three of the 4 Sprouty (Spry) homologues that are expressed during tooth development are Spry1, Spry2 and Spry4, which are proteins that can negatively regulate FGF signaling.[67] Genetic deletion of Spry or CEBPB, cell proliferation instead of apoptosis and then came out extra teeth.[66,68,69] In Runx2 null mice, excess transcription factor Twist1 activated FGF signaling to rise supernumerary teeth, and that might be the mechanism of human cleidocranial dysplasia disease (CCD).[70] Wnt signaling also involved in the formation of diastema. Inactivation of USAG1, which binds to the extracellular domain of the Wnt co-receptors Lrp5 and Lrp6, can lead to the upregulation of Wnt signaling and therefore the development of supernumerary teeth.[61] Over expression of Lef1, a target gene of β-catenin, results in numerous tooth-like structures in the non-tooth region of the mouse[71]; meanwhile, Lef1 can relay Wnt signal to cascade FGF4 activity.[72] R-spondins are Wnt signaling activator, and in R-spondin null mice, diastema teeth occurred. However, the Wnt signal was in low expression.[73] Ectopic Shh signal in dental lamina is an important reason for supernumerary teeth in diastema, and its expression is regulated by some molecules in dental mesenchyme. Inhibit the expression of Shh signal antagonistic molecules in mesenchyme leading the formation of supernumerary teeth, like Gas1, Polaris and Runx2.[49,74-76]

There are some other mouse models for supernumerary teeth, but the exactly mechanisms were not clear. That ectodysplasin-A (EDA) molecule functions to suppress BMP signaling and up-regulate Shh signaling, and overexpression of EDA induces supernumerary

teeth by counteracting BMP4 activity during teeth development.[77] Local loss Epiprofin Protein 6 (Sp6), a Kruppel-like family transcription factor, in the mesenchyme of the incisor region results in supernumerary incisors.[78,79] Pax6 gene homozygous mutant mice or Fam20B null mice showed extra teeth in incisor region.[80-82]

CONCLUSIONS AND PERSPECTIVES

Supernumerary teeth could be isolated findings or developmental abnormalities with systemic syndromes. It can be important clue for early diagnosis in some distinctive disorders. In 2015, scientists find that human with Lrp6 mutant have supernumerary teeth but no systemic syndrome.[83] A Japanese research found some new genes may play role in human supernumerary teeth.[84] Thus, we believed that there must be genetic background of supernumerary teeth, even in non-syndromic cases. Although mouse dentitions are different from human being, the molecular mechanism research of supernumerary teeth in mouse is still meanful.

The field of tooth number interference is still in its infancy, lots of questions need to be answered. Animals more similar to human development patterns like chimpanzee need to be established to identified the genetic background of supernumerary teeth. How can researchers control or take advantage of the abnormal expression genes that found in supernumerary teeth into tooth regeneration?

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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AUTHOR CONTRIBUTIONS

X.L. and F.Y.: conception and design and manuscript writing; J.L. and W.C.: discussion and interpretation; Y.Z., S.Z. and S.L.: conception and design, manuscript editing, and final approval of manuscript.

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