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Genetic Basis of Supernumerary Tooth

Abstract - Odontogenesis is a complex process regulated by both genetic and molecular controls. The development of a tooth in the embryo stage is controlled by a series of signals which occur between tooth-forming epithelium and neural crest-derived ectomesenchyme. Though many genes are involved in tooth formation involving major signalling molecules, the bone morphogenetic protein and fibroblast growth factor are the most important ones involved in odontogenesis. Supernumerary tooth occurs because of imbalance in the expression of the signalling pathways and their inhibitors. This review highlights the various signalling molecules that play a role in odontogenesis in order to provide a better understanding ~~on~~ **of** the molecular mechanisms involved in the formation of supernumerary tooth in humans.

Keywords - **Genetics, odontogenesis, signalling molecules, supernumerary tooth**

1 INTRODUCTION

Teeth are highly mineralised tissues located at the entrance of the alimentary tract in both invertebrates and vertebrates [1]. Teeth are the elements of dermal skeleton that are present in a wide range of jawed vertebrates [2]. Though the main function of teeth is in chewing food, yet, they are also associated with defence, display of dominance as well as in the vocalisation in humans [3]. The human dentition comprises 20 teeth in the primary dentition and 32 in the permanent dentition [4, 5, 6]. Tooth agenesis denotes missing tooth/teeth as a result of developmental failure that results in decreased number of normal complement in human dentition [7]. Conversely, a supernumerary tooth denotes any tooth or odontogenic structure that is formed from a tooth germ resulting in more than the usual number of any given region in a dental arch [4, 5, 6].

A search was made in databases using the keywords 'supernumerary teeth, mouse, humans, genetics'. The articles collected were subjected to a systematic review to analyse the genetic basis of supernumerary teeth. Supernumerary teeth can be seen in many genetic disorders; but they are more common in syndromes like Gardner's syndrome, cleft lip and palate and cleidocranial dysplasia (CCD) and less commonly seen in Fabry disease, Nance-Horan syndrome, Ellis-Van Creveld syndrome, Rubinstein-Taybi syndrome and trichorhinophalangeal syndrome [8]. Genetic entities that represent supernumerary teeth as a salient finding have been attributed to autosomal dominant inheritance, X chromosome inheritance and to both the inheritance patterns based on their locus heterogeneity [9]. Also, there are many reports supporting the theory of familial tendency to supernumerary teeth which were more evident in the relatives of the affected individuals [10]. Moreover, Seema Gupta and Praveen Kumar reported based on their study that in 8.6% of cases, there was a history of the same abnormality observed in other members of the family, which ascertained the hereditary nature of hyperdontia to occur [11].

2 CONTROLLING MECHANISM OF TOOTH DEVELOPMENT

Teeth develop due to progressive interactions between the ectoderm and the underlying ectomesenchyme tissue [12]. Subsequently, the ectomesenchyme forms the dental laminae giving rise to human deciduous teeth at six weeks *in utero* [13]. The permanent successors, on the other hand**,** develop as lingual extensions of these primary laminae which occurs between 20 weeks *in utero* until the age of five [14]. The early

stage of tooth development or odontogenesis at the embryological stage is regulated by a series of signals occurring between tooth-forming epithelium and the neural crest-derived ectomesenchyme [12]. Each tissue layer then instructs the other to differentiate into incisors, canines, premolars, and molars [15]. The reciprocal interactions between ectoderm and ectomesenchyme regulate the different phases involved in odontogenesis [16] as well as in regulating the tooth number [17]. The different phases are ***Initiation phase*** which determines the tooth region and numbers; ***morphogenesis phase*** which determines the tooth type, size, shape, dimension and cusp number, and the ***cytodifferentiation phase*** which determines the tooth structure such as enamel and dentine formation and mineralization. Thus, odontogenesis is a complex process under tight control of genetic and molecular events.

Research on the roles of signals and tissue interactions in cultured tissue explants and in mutant mice have shown inductive signalling and hierarchies in downstream transcription factors during odontogenesis. The development of tooth occurs through a chain of signalling interactions between the oral epithelium as well as neural crest-derived mesenchyme, genetically controlled by various signalling molecules and pathways [18]. More than 200 genes have been found to have active functions in developing tooth. Most of the expression patterns can be viewed in a comprehensive graphical database of gene expression profiles at http://honeybee.helsinki.fi/toothexp [19]. The roles of signalling molecules and the expression of homeobox genes in odontogenesis indicate a complementary interaction between the 'field' and 'clone' theories [15]. The 'field' theory was first proposed by Butler [20], who postulated that each tooth within a class, e.g. molars, develop number, shape, size, and order of development because it belongs to a common field [21]. Nevertheless, a field gradient exists depending on the position of tooth in the field. Clone theory was proposed by Osborne [22], who reported that a single pre-programmed cell clone is responsible for the development of a specific class of tooth [23].

Major signalling molecules involved in the regulation of tooth embryogenesis belong to the bone morphogenetic protein (BMP), fibroblast growth factor (FGF), sonic hedgehog (SHH), and wingless-type (WNT) families. BMPs and FGFs are the most important molecules of odontogenesis that are expressed in both ectoderm and ectomesenchyme, whereas, SHHs and WNTs are expressed only in the ectoderm [24]. Supernumerary tooth and tooth agenesis occur due to imbalance in the expression of these four major signalling pathways and their inhibitors. Their roles in regulating odontogenesis, in turn, determine the tooth number and patterning [16]. Various genes that play a role in causing dental anomalies are presented in Table 1 and a diagrammatic representation of the genes and signalling pathway involved in odontogenesis is shown in Fig. 1.

Table I: Genes involved in various dental anomalies

Gene	Mutation	Dental anomaly
Msx1, Msx2, Dlx1, Dlx2	Double mutant	Initiation stage arrest
Lhx6, Lhx7, Gli1, Gli3		
Pax9, Lef1, Runx2, Barx1	Null	Bud stage arrest
Shh, Fgfr2b		
Activin βA	Null	Bud stage arrest
		Lack of incisors and mandibular molars
Ctip2	Null	Late bell stage arrest
Gli2	Null	Abnormal maxillary incisors
Gli3	Heterozygous	Arrest maxillary incisor development
Edar	Downless	Small or absent enamel knot
Fgf10	Null	Small tooth germ
Wnt/β catenin	K14 conditional KO	Mishappen tooth bud
Ectodin, Sostdc1/wise	Null	Abnormal cusp
Ectodin, Apc, Sp6, Lrp4, IFT88	Null	Supernumerary teeth
Gas1, Osr2, Sprouty2, Sprouty4		
Msx2, Lama3, Sp3, Sp6, Amelx	Null	Enamel hypoplasia
Enamelin, Mmp20		
Smoothened	K14 conditional KO	
Connexin 43	Dominant negative	
Periostin	Null	Incisor enamel defect, thinner enamel
Eda, Follistatin, Wnt3	K14 transgenic	No enamel
Ameloblastin, Gdnf	Null	
Noggin	K14 transgenic	Abnormal ameloblast
DSPP, Msx2	Null	Dentinogenesis imperfecta
DMP1, Sp3, Sp6,	Null	Abnormal dentin structure
Msx2, Sp6	Null	Root malformation
Shh	Ptc^{neo}	Shorter root
Noggin	K14 transgenic	Failed to form multiple root

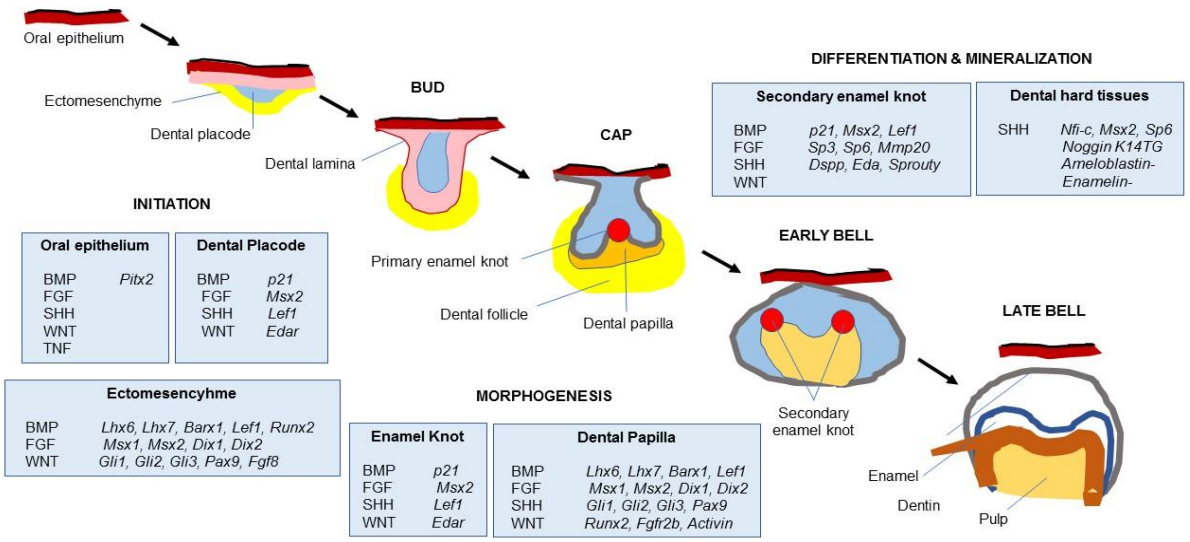

Figure 1: Genes and signalling pathways involved in odontogenesis

3 MAJOR SIGNALLING MOLECULES INVOLVED IN THE FORMATION OF SUPERNUMERARY TOOTH

3.1 Bone morphogenetic protein

One of the first signals identified in inductive interactions between epithelium and ectomesenchyme are growth factors belonging to the family of BMPs. The BMP family comprises a large group of proteins that are frequently expressed during tooth morphogenesis. For example, BMP2, BMP4 and BMP7 are expressed in the dental epithelium, BMP2 and BMP7 are expressed during the bud stage, and BMP4 is expressed during the thickening of the dental lamina. Also, BMPs can function as bidirectional signalling factors between the epithelium and ectomesenchyme. In ectomesenchyme, the BMPs stimulate the expression of transcription factors muscle segment homeobox 1 (MSX1), muscle segment homeobox 2 (MSX2), early growth response 1 (EGR1), and high mobility group (HMG) domain of the lymphoid enhancer-binding factor 1 (LEF-1) gene or transcription factor [21].

Among the BMP family, BMP4 is essential for normal tooth development. BMP4 is required to induce several target genes in the dental ectomesenchyme including *MSX1*. Any breakdown that occurs in these inductive interactions will arrest tooth development during the bud stage. The expression of BMP4 is initiated in the epithelium; however, the expression will then switch to the ectomesenchyme when inductive possibilities are acquired from the latter which suggests the ability of this molecule to induce its own expression in ectomesenchymal cells. The intense mesenchymal expression of BMP4 during the bud stage can be linked to the subsequent transfer of the inductive ability to the epithelium which leads to the formation of enamel knot [21], and later, the supernumerary tooth. Ectodin is a BMP-antagonist which is widely expressed in developing tooth germ, but noticeably absent from enamel knots. Mice with lack of function of Ectodin displayed several anomalies including the presence of a supernumerary molar. Similarly, supernumerary tooth develops due to failure in normal *Ectodin*-mediated inhibition from the adjacent ectomesenchyme. Ectodin can inhibit WNT signalling and the correct modulation of this pathway is critical in determining the correct number of tooth formation [25]. Murashima-Suginami *et al*., [26] reported that supernumerary teeth occurred due to increased BMP signalling in USAG-1-deficient mouse model.

3.2 Fibroblast growth factor (FGF)

In mammals, the FGF family comprises of 19 growth factors (FGF 1–19). FGF plays a significant role in regulating the growth and morphogenesis of tooth germ. They regulate gene expression in ectomesenchyme and stimulate the epithelial cellular division and proliferation. These take place during the different stages of tooth development; the early phases of morphogenesis, early epithelial invagination which generates tooth bud, and during the

assessment of epithelial folds which generates the dental cuspids [27]. FGF4 and FGF9 in the primary enamel knot epithelium induce proliferation of both dental epithelium and ectomesenchyme, and then, later regulate the cuspid development, whereas FGF3 and FGF10 in the underlying ectomesenchyme stimulate only cell division in dental epithelium to form the dental papillae. These signals are required for the expression of *SHH* in the primary enamel knot epithelium [25]. Study on mice showed that intracellular FGF antagonists such as Sprouty (SPRY) genes are produced in response to FGF signalling and modulate the transduction in target cells [28]. *SPRY2* and *SPRY4* are expressed in the epithelium and ectomesenchyme of developing tooth respectively. Any functional breakdown of these genes results in the formation of extra tooth [24].

3.3 Sonic hedgehog (SHH)

Early signalling interactions between oral epithelium and neural crest cells are envisaged to establish information pattern along the developing dental axis [19]. At this stage, high *SHH* expression acts as a mitogen that is essential for normal proliferation of tooth bud because it invaginates into the underlying ectomesenchyme [19]. Hedgehog signal transduction through *SHH* may influence tooth number. In the absence of normal *SHH* signal transduction, tooth development will be arrested. Appropriate restriction of *SHH* activity is important to ensure the correct number of tooth formation in the right positions [29]. Once the early tooth bud is formed, continuous and reiterative signalling between epithelium and ectomesenchyme enables further growth and morphogenesis, with the bud stage progressing into the cap and bell stage [30]. Therefore, dysregulation of *SHH* activity plays a key role in the formation of supernumerary tooth [25].

SHH signals are mediated by the presence of primary cilia, that projects from the surface of all eukaryotic cells. Mutations in several genes including the ciliary protein IFT88/Polaris can result in changes in *SHH* signalling activity and the development of teeth in mice [25]. Ciliary protein IFT88/Polaris encodes essential functional components of the primary cilia. Besides, research [29], has shown that the upregulation of *SHH* activity in diastema mesenchyme can produce ectopic tooth in mutant mice which suggests that the SHH signalling may play a role in tooth position. Another link between *SHH* signal transduction and the presence of additional teeth has been provided by runt-related transcription factor (RUNX2) in mutant mice. *RUNX2* is essential for the normal differentiation of bone-forming osteoblasts [31, 32]. In mice, *RUNX2* is expressed in mesenchymal compartment of a tooth and a complete loss of function is associated with arrested tooth development; however, in the heterozygous mutant, rudimentary supernumerary tooth formation takes place lingual to the first molar tooth germ. *RUNX2* transcription in the mesenchyme can repress *SHH* signalling in the epithelium. Thus, in the absence of adequate suppression of *SHH* transduction in these mice, additional teeth can develop in these regions [25]. Maisa Seppala and colleagues reported that SHH interacts at the molecular level with various other signalling pathways, Fgf and Wnt in particular, for normal progression of tooth development [33].

3.4 Wingless integrated (WNT)

WNT proteins form a large family of secreted ligands that activate several intracellular signalling pathways [34]. WNT signals drive multiple stages involved in odontogenesis, from the initiation stage until the tooth differentiation, which are broadly expressed in oral as well as dental epithelium. WNT pathways work through several mediators. For instance, β-catenin stabilization and activation of *LEF1* transcription factor activates the canonical signalling, crucial in normal tooth development [25]. *LEF1* is necessary for tooth development to progress beyond bud stage and inhibition of this WNT signalling pathway arrests odontogenesis. Evidence also suggests that the normal regulation of this pathway is important to determine the correct number of tooth formation [25]. Overexpression of *LEF1* in the oral epithelium in transgenic mice produced multiple invaginations in tooth forming regions [35].

There is a firm link associated between unregulated WNT signalling and hyperdontia in humans. In the case of Gardner's syndrome, an autosomal dominant disorder characterised by multiple adenomatous polyps of the colon and rectum, patients exhibited dental anomalies such as multiple supernumerary teeth, odontomas, and tooth impactions. The causative adenomatous polyposis coli (APC) tumour suppressor gene is a known inhibitor of WNT signalling [36]. The expression of ectodysplasin-A (EDA) gene is also regulated by WNT family of proteins [37]. If WNT signalling is blocked during the early bell stage

when secondary enamel knots form, the expression of *EDA* is reduced and the molars form with flattened cusps. Therefore, WNT signalling is important for the development of molar cusps [38], while, overexpression of *EDA* leads to the formation of supernumerary tooth. Thus, overexpression of canonical WNT signalling, through the loss of function of its inhibitors or by overexpression of its effectors, leads to the formation of supernumerary tooth [15]. Multiple teeth have also been seen in the molar field where β-catenin has been overexpressed in mice [36]. According to Bei [15], the number of teeth that can develop from the molar field appear**s** to be restricted by WNT signalling. Supernumerary teeth and altered morphology of the molar crown have been reported in *WNT10A* null mice, though it results in tooth agenesis phenotype in humans [39].

4 OTHER SIGNALLING MOLECULES

4.1 Tumour necrosis factor pathway

Mutation in the gene encoding *EDA* ligand (e.g. *EDA1*) or *EDA*-receptor can result in disruption of EDA signalling [40], which then can lead to the formation of a component of the tumour necrosis factor (TNF) pathway. *EDA* signalling is active in organs that develop through signalling between epithelium and ectomesenchyme [25] [19]. The levels of *EDA* signalling are important to determine the tooth number. Overexpression of *EDA1* splice variant in the oral epithelium of transgenic mice produces supernumerary premolar-like tooth. Therefore, signals from epithelium are essential for the initiation of tooth development. Deficiency of *EDA* signalling results in hypodontia, while, too much *EDA* can produce supernumerary tooth [12].

4.2 Runt-related transcription factor gene

Runt-related transcription factor (*RUNX2*) is a principal gene involved in bone and tooth development [41]. It is an osteoblast-specific transcription factor which is necessary for the differentiation of pluripotent mesenchymal cells into osteoblasts [42]. The presence of *RUNX2* in fully differentiated cells establishes the fact that *RUNX2* is also required in maintaining the full function of cells, especially those in bones [42]. *RUNX2* is also crucial in the formation of tooth. It is a key mesenchymal factor that influences tooth morphogenesis and the subsequent differentiation of ameloblasts, odontoblasts and osteoblasts lining the bone in the periodontal space [41, 43]. The length of *RUNX2* is 220 kb and has eight exons belonging to the runt domain (*RUNX*) family of genes. The genes, namely *RUNX1*, *-2* and *-3*, exhibit high amino acid homology. Their protein products form a heterodimer with the core-binding factor β (CBF-β). CBF-β is required for the function of *RUNX2* in skeletal development, which allosterically enhances DNA binding by RUNX proteins at runt homology domain (RHD). Moreover, it plays an important role in stabilizing the RUNX proteins against proteolytic degradation by the ubiquitin-proteasome system [43]. Several studies [31, 44, 45, 46, 47, 48, 49], on mutational analysis of *RUNX2* in cleidocranial dysplasia (CCD) patients, have shown that mutations in RUNX2 gene are accountable for this syndrome [31]. CCD is a syndrome that affects the development of bone and tooth. The most common features of CCD include delayed closure of skull sutures, hypoplastic or aplastic clavicles and multiple supernumerary teeth [50]. RUNX2 gene dysfunction in tooth-forming cells may directly result in dental anomalies in CCD patients [43]. Therefore, these dental abnormalities suggest the important role that *RUNX2* plays during odontogenesis [51]. Under normal condition, *RUNX2* acts as a cell growth inhibitor in immature osteoblasts by supporting an exit from the cell cycle and promoting increased expression of osteoblast phenotype [52]. Hence, *RUNX2* regulates cell proliferation and may have a specific control of the dental lamina and the subsequent formation of successive dentitions [43]. *In-vitro* genetic studies have proved that deletion or deficiency of *RUNX2* in knockout mice arrested the tooth development at the bud or early cap stage, and the osteoblasts lining bone in the periodontal space [41, 53]. In contrast, another study has reported that loss of function of RUNX2 gene would support the proliferation of dental lamina. For example, the reduced function of RUNX2 gene caused the development of supernumerary tooth in CCD patients [42].

Studies showed that both *RUNX2–/–* and *RUNX2+/–* mice displayed lingual buds in front of upper molars, and these were much more prominent than those in the wild-type mice [54]. It was assumed that these buds represent the secondary dentition and that *RUNX2* plays a role in inhibiting the formation of these buds [55]. It may appear contradictory that inhibition of RUNX2 gene function may arrest primary tooth development but stimulates the formation of secondary teeth [56]. Nevertheless, it is normal for the same gene to have different effects at

different developmental stages during the process of embryogenesis [54]. Thesleff [41], proposed that humans possess the potential to develop a third dentition which is normally inhibited by RUNX2 gene. This has been confirmed by Wang *et al*., [55] who showed that RUNX2 gene inhibits serial tooth formation [41, 57]. Analysing the regulations, expressions and functions of RUNX2 gene, particularly in non-syndromic patients with supernumerary tooth would enhance the understanding of tooth development in humans [41]. The lack of teeth, as well as formation of supernumerary teeth, were attributed to the mutations in *AXIN2* and *RUNX2*, respectively, which occurred due to Wnt/β-catenin signalling modulation in dental mesenchyme [58]. They also reported that increased mesenchymal Wnt/β-catenin signalling can result in the inhibition of tooth initiation.

5 RELEVANCE OF MOUSE MODEL TO HUMANS

Jussila and Thesleff [59], based on the phenotypes of two syndromes, namely CCD and craniosynostosis syndrome, suggested that the potential for continued tooth replacement may be unlocked in humans. The presence of supernumerary teeth has been suggested to denote a third dentition in CCD and in craniosynostosis syndrome due to mutations in the transcription factor *RUNX2* and the interleukin receptor *IL11RA*, respectively [60, 61]. However, in the mouse models of these syndromes, there are no supernumerary teeth; this could be attributed to the reason that the teeth in mouse are not normally replaced, and hence, unsuitable for studies involving tooth replacement [61, 62]. In mice, the number of teeth is lesser compared to humans and moreover, since mice have only a primary dentition, mouse models may not reflect the same to determine the cause of supernumerary teeth in humans [63]. Though in mouse models as well as in human syndromes, supernumerary teeth are induced by modulating signal pathways, this may not function in adult jaws, the reason being that these teeth are formed from the tissue associated with developing teeth which would not be present in the jaws of the adults [59]. D'Souza and Klein [64] reported that the use of multifaceted approaches involving mouse and human genetic researches were needed in order to reveal the precise aetiology of development of supernumerary tooth. Xi Lu and colleagues in their review reported that though the mouse dentitions were quite different from that of humans, exploration of the molecular mechanism in mouse was still useful. However, they suggested that animals such as chimpanzee, which have more similarities in the development patterns with humans, need to be investigated to identify the genetic basis of supernumerary teeth [65].

6 CONCLUSIONS

Recent studies have probed into the molecular mechanisms underlying tooth morphogenesis and differentiation. Although genetics may be implicated in the formation of supernumerary tooth, little is known about the initiation of tooth formation, the genetic regulation of successional teeth, as well as the underlying mechanisms involved in its formation. Nonetheless, a better understanding of the roles of these aforementioned signalling molecules, particularly WNT and RUNX2, will provide fundamental insights into the molecular genetics of supernumerary tooth in humans. This, in turn, may assist in future tooth regeneration and tooth engineering.

CONFLICTS OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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