Development of dentition: From initiation to occlusion and related diseases

Hiroshi Kurosaka*, Shinsuke Itoh, Chisato Morita, Takayuki Tsujimoto, Yuka Murata, Toshihiro Inubushi, and Takashi Yamashiro

Department of Orthodontics and Dentofacial Orthopedics, Graduate School of Dentistry, Osaka University

Author for correspondence
Hiroshi Kurosaka, DDS, PhD
Associate Professor
Department of Orthodontics and Dentofacial Orthopedics, Graduate School of Dentistry, Osaka University
Email: kurosaka@dent.osaka-u.ac.jp
Tel: +81-6-6879-2958
Fax:+81-6-6879-2960

Abbreviations

AXIN : AXIS INHIBITOR, EDA : ECTODYSPLASIN A, EDAR : ECTODYSPLASIN A RECEPTOR, PAX : PAIRED BOX GENE, WNT : WINGLESS-TYPE MMTV INTEGRATION SITE FAMILY, MSX : MSH HOMEOBOX, LRP : LOW DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN, BMP : BONE MORPHOGENETIC PROTEIN, NF-kB : NUCLEAR FACTOR KAPPA-B, RANK : RECEPTOR ACTIVATOR OF NF-KAPPA-B, RANKL : RECEPTOR ACTIVATOR OF NF-KAPPA-B LIGAND, CSF1 : COLONY-STIMULATING FACTOR 1, OPG : OSTEOPROTEGERIN, SFRP : SECRETED FRIZZLED-RELATED PROTEIN, GNAS : GNAS COMPLEX LOCUS.

Abstract

Background:

The development of dentition begins in the embryonic oral cavity and progresses in the branchial arches and alveolar bone. Continuous cellular and molecular crosstalk occurs during crown formation, after which the tooth germ begins to migrate apically through the alveolar process into the oral cavity. It eventually comes in contact with its antagonist in the contralateral jaw to establish functional occlusion. Any defect in either step can result in delayed tooth development, the spectrum of which varies from a congenitally missing tooth to an impacted tooth (infraocclusion) with an eruption problem, both of which can impair oral function.

Highlight:

Congenitally missing teeth or eruption problems may result from genetic mutations. Several different mutations have been identified, each causing a distinct phenotype. Thus, it is imperative that medical providers understand the fundamentals of these genetic principles that govern such dental diseases.

Conclusion:

In this review, we focus on several diseases, including congenitally missing teeth and tooth eruption problems. We review these diseases with aspect to their association with a

particular syndrome, as well as independently in a non-syndromic capacity. We also review previously identified genetic mutations and discuss the possible mechanisms that cause individual phenotypes by analyzing previous investigations. We also discuss future prospects of how genetic diagnosis and precision medicine could impact the clinical environment in the field of dentistry.

Ethical Approval:

Present study has been carried out in accordance with The Code of Ethics of the World Medical Association and approved by Institutional Review Board of Osaka University Graduate School of Dentistry.

Keywords: Tooth development, Tooth agenesis, Tooth eruption, Primary failure of eruption.

Introduction

The dentition comprises one of the major organs in the oral cavity and plays a significant role in multiple orofacial functions. Its developmental process is initiated during the mid-gestation stage, and after the crown is formed, the tooth will start to erupt and eventually come into contact with the opposing tooth to establish functional occlusion. Many previous

investigations have revealed cellular and molecular mechanisms in each step of tooth development using human and animal models. In particular, because of the rapid progression of genomic sequencing technology, multiple genetic causes of missing teeth, including oligodontia, have been identified, including AXIN2, EDA, LRP6, MSX1, PAX9, WNT10A, and WNT10B, which cover more than 90% of reported cases of oligodontia [1]. Interestingly, most of these genes have already been shown to be critical for tooth development in animal experiments (Figure 1). Additionally, recent genetic investigations have revealed new genetic causes of congenital missing teeth [2-4]. After crown formation, the tooth root begins to form. During root formation, teeth usually emerge inside the oral cavity, and occasionally, individuals present problems with tooth eruption (Figure 1). Tooth eruption can be divided into intraosseous and supraosseous eruption [5]. Deficits in each step may lead to distinguished clinical phenotypes, such as impacted teeth or infraocclusion. Some congenital systemic diseases may be associated with these dental anomalies, which strongly indicates a mechanistic connection between specific gene mutations and developmental deficits in dentition at a specific stage. In this review, we describe current knowledge of the genetic causes of dental anomalies, especially focusing on tooth agenesis and failure of eruption. Furthermore, we discuss future directions, such as methods of diagnosing and appropriate clinical management for these conditions.

The roles of specific genes which may cause tooth agenesis in humans

Tooth development initiates with the patterning of the dental placode and thickening of the embryonic oral epithelium. Signal transduction from the thickened dental epithelium induces cell proliferation of the underlying mesenchyme, delivering cranial neural crest cells in order to progress the development of dentition. A number of studies have revealed critical genetic and environmental factors for tooth development [6, 7]. After identification, some of the genes were deemed the causative agents in congenital missing teeth in humans. The Human Gene Mutation Database (HGMD) reported that more than 90% of the cases of tooth agenesis harbor mutations either in PAX9, WNT10A, MSX1, WNT10B, LRP6, AXIN2, or EDA [1]. Among these genes, MSX1 was one of the first discovered to cause congenital missing teeth in humans by missense mutations [8]. Intense expression of Msx1 can be seen in the mesenchyme of the developing dentition [9]. Accordingly, null mutations in *Msx1* in mice leads to missing molars by inhibiting the proliferation of mesenchyme cells [10]. Later, nonsense heterozygous mutations in *MSX1* were reported to cause Witkop syndrome, which is also associated with nail deformities and tooth agenesis [11].

Pax9 is strongly expressed in the dental mesenchyme and null mice exhibit tooth developmental arrest at the bud stage, most likely because of the loss of the transcription of other critical genes for tooth development, such as *Msx1* and *Bmp4* [12, 13]. Canonical *Wnt* signaling is widely accepted to be critical at various stages of tooth development [14]. *Wnt10a* is known to be expressed at the enamel knot in mice, which is a signaling center in the epithelium of developing teeth during the initiation stage [15]. Unlike the phenotype in humans, eliminating *Wnt10a* from mice did not result in the loss of teeth, but rather caused the development of successional teeth [16]. Interestingly, there was still some phenotypic overlap between human patients and mouse models, such as smaller crown size and tourodontism [16]. It is obvious that different molecular mechanisms for developing teeth between humans and rodents result in this puzzling finding. However, the detailed reason for this phenotypic discrepancy is yet to be explained. *Wnt10b* has also been expressed at the enamel knot similar to *Wnt10a*, and its mutation has been shown to cause oligodontia in humans [15, 17]. Although it is speculated that a delayed *WNT* signaling pathway gives rise to tooth agenesis in humans with the mutation of *WNT10B*, there is still no reliable animal model to explain the molecular and cellular mechanisms underlying this situation [18, 19]. *Lrp5* and *Lrp6* function as co-receptors of *Wnt* signaling [20]. Mutations in *LRP6* in humans have also been reported to result in oligodontia [21]. Additionally, eliminating *Lrp6*

from mouse embryos resulted in a substantial reduction in *Wnt* activity around the developing frontonasal process, which, in turn, causes a cleft lip phenotype [22]. Specific *LRP5* mutations in humans cause significant notches in both the mesio- and disto-labial developmental grooves, resulting in a fork-like morphology in incisors [23]. These results indicate that canonical *Wnt* signaling through *Lrp5* and *Lrp6* plays a critical role in the development of dentition, and can result in a variety of tooth phenotypes, such as tooth agenesis and/or morphological defects. *Axin2* is expressed in both the epithelium and mesenchyme during mouse tooth development, and its mutation causes tooth agenesis in humans [24]. *Axin2* is known to play an inhibitory role in canonical *Wnt* signaling, and thus, its mutation is estimated to result in exaggerated canonical *Wnt* signaling. These results indicate that both enhanced and reduced canonical *Wnt* signaling could disturb tooth development and result in congenital missing teeth in humans. Mutation of genes related to the Eda/Edar/NF-kB signaling pathway in humans is well known to cause ectodermal dysplasia, the primary phenotype of which includes a lack of ectodermal appendages such as hair, nails, various secreting glands, and teeth [25, 26]. Animal experiments revealed that EDA and EDAR interactions regulate the epithelial signaling center of the tooth germ and thus, a lack of either of these genes would lead to dental anomalies such as smaller teeth and enamel hypoplasia, which phenocopy human ectodermal dysplasia [27, 28].

Problem of eruption

After the tooth crown forms in the embryonic facial prominences, the tooth migrates vertically and emerges in the oral cavity and eventually occludes with its antagonist. This process is roughly divided into two phases: intraosseous eruption and supraosseous eruption [5, 29]. During intraosseous eruption, dental follicle cells were identified as the critical tissue for recruiting and activating osteoclasts around the crown of the tooth [30]. Continuous molecular investigations, especially in the field of bone metabolism, have identified many common molecules that are critical for tooth eruption. *Rankl* and its receptor *rank* were shown to be irreplaceable for osteoclastogenesis as well as tooth eruption, and elimination of these factors results in osteopetrosis with unerupted molars in mice [31, 32]. Interestingly, *the Rankl* mutation was discovered in cases of osteopetrosis in humans, who also frequently exhibit impacted teeth [33]. These results indicate that the normal process of osteoclast development plays a crucial role in intraosseous tooth eruption.

Dental follicle cells are considered critical for the generation of osteoclast cells during tooth eruption. Additionally, previous research has revealed that developing dental follicle cells express multiple genes that are important for bone metabolism [34]. Among these genes,

CSF1 has been shown to differentiate monocytes into preosteoclasts, which, in turn, expresses RANK on its surface to bind to RANKL, which is expressed at the surface of osteoblasts for the maturation of osteoclasts [35]. Strong expression of CSF1 has been detected in developing dental follicle cells [36]. Importantly, loss of *Csf1* function in both mouse and rat models results in impacted molar and osteopetrosis with deficient osteoclastogenesis, which phenocopies the knockout mice of either *Rank* or *Rankl* [37, 38]. The detailed roles of CSF1 in dental follicles were also shown to inhibit the expression of OPG, which is a negative regulator of *the RANK* signaling pathway [39] (Figure 2). Other factors secreted from dental follicles have also been investigated their roles in osteoclastogenesis, such as SFRP1 [34]. On the other hand, there are diseases in humans that exhibit problems in intraosseous eruption, such as cleidocranial dysplasia (CCD). In CCD, multiple impacted teeth as well as supernumerary teeth can be seen [40]. In contrast, mice with disrupted *Runx2* show delayed tooth development [41]. This phenotypic paradox has not been fully understood, but it is probably due to the fact that in humans, most impacted and supernumerary teeth are successors, while mice do not have successor teeth. Interestingly, human CCD dental follicle cells have been shown to exhibit altered gene expression profiles compared to healthy controls, especially the level of OPG or the Rankl/OPG ratio, which may underlie the etiology of impacted teeth in CCD patients [42].

These results indicate that intraosseous eruption results in impacted teeth, and its etiology is highly related to the activity of osteoclast cells around the tooth germ, which is regulated by the Rank/Rankl signaling pathway. For intraosseous tooth eruption, dental follicle cells play pivotal roles in activating osteoclastogenesis around the superior alveolar bone of the tooth germ, and its dysregulation could also result in impacted teeth (Figure 2).

After the crown emerges in the oral cavity, other mechanisms distinguished from intraosseous eruption, called supraosseous eruption, take place until the tooth contacts the antagonist to create a functional unit of occlusion. This supraosseous eruption is supported by tooth eruption and vertical alveolar growth [43]. Tooth ankylosis is a representative situation that can delay both of these mechanisms and result in the failure of occlusal contact. Ankylosis is known result from the physical fusion of the cementum and alveolar bone without periodontal ligament space, which could result in infraocclusion [44]. Primary failure of eruption (PFE) is also represented by its infraocclusion because of the failure of supraosseous eruption and vertical growth of alveolar bone, while affected teeth still maintain the periodontal ligament [45, 46]. Interestingly, the function of the dental follicle in activating osteoclasts is not affected in PFE patients; therefore, the eruption path is superior to the dentition [47]. The genetic etiology of PFE is relatively well studied, and mutations in PTHR1 are known to cause this situation in humans [48]. The PTH signaling pathway is critical for

tooth eruption and eliminating PTHrP results in impacted teeth in mice [49]. Further, a recent study revealed that conditional knockout mice eliminated PTH1R from the dental follicle and its descendent cells phenocopy human PFE by showing unaffected eruption pathways and impacted dentition with malformed roots [29]. Other systemic diseases caused by homozygous mutations in PTHR1 include severe chondrodysplasia [50, 51] and Eiken syndrome [52], which are associated with multiple impacted deciduous teeth. These results indicate that the PTH signaling pathway exhibits a dose-dependent phenotype, as homozygous mutation of PTHR1 results in more severe systemic defects, while PFE harbors a heterozygous mutation. A previous study also revealed that not all cases that exhibit the typical phenotype of PFE harbor mutations in PTHR1, and negative genetic tests cannot completely exclude the possibility of PFE [46]. Grippaudo et al. revealed that 8 out of 29 familial cases that exhibited typical infraocclusion in mixed dentition harbored a mutation in PTHR1 [53]. Indeed, new genes have been reported in patients with PFE by comprehensive genomic sequencing [54]. These results strongly indicate that there are still other genetic factors responsible for infraocclusion or PFE [46]. GNAS is a G-coupled protein that directly binds to PTHR1 to transduce the intercellular PTH signaling pathway [55]. Interestingly, mutations in *GNAS* in humans cause pseudohypoparathyroidism type 1a (PHP1a), which also results in tooth eruption defects [56, 57]. It is still unclear whether there are any

differences in terms of the reaction for orthodontic traction by different mutations in different genes or genomic loci. It is also important to point out that these dental phenotypes frequently co-exist in the same patient, which indicates genetic interaction or shared common mechanisms between missing teeth and delayed eruption [58, 59].

Recently, because of the increase in comprehensive genetic sequencing, a genotype-phenotype correlation in various tooth eruption defects has been revealed at a rapid speed. The ultimate goal of precision medicine in the dental field is to make a precise diagnosis and provide the most efficient treatment for individual patients.

Therapeutic strategies for congenitally missing teeth and retarded eruption

There are a wide variety of treatment options for congenital missing teeth, including no treatment, prosthodontic replacement, autotransplantation, and orthodontic space closure. Considering the improvements in technology and appliances in modern orthodontic treatment, recent trends in space management for congenital missing teeth are moving towards orthodontic space closure rather than prosthodontic treatment [60]. However, cases with multiple missing teeth, such as oligodontia, usually require a combination of treatments in order to achieve ideal occlusion [61]. A recent investigation revealed that the systemic phenotype, which includes missing teeth of X-linked hypohidrotic ectocermal

dysplasia (XLHED), could be ameliorated by the administration of recombinant fusion protein, which consists of the constant domain of IgG1 and the receptor binding domain of EDA in the amniotic fluid at certain stages of pregnancy [62]. As for non-syndromic congenital missing teeth, possible therapeutic protocols have been investigated to regenerate dentition by targeting specific molecules using animal models of tooth agenesis [63]. For eruption problems, if the etiology of delayed tooth eruption is caused by mechanical obstruction or problems of intraosseous eruption, surgical fenestration and luxation followed by the application of orthodontic traction is considered standard procedure [46]. Impacted teeth in CCD patients are usually successfully tracted in the oral cavity by removing the supernumerary teeth and providing fenestration and orthodontic traction (Figure 3). On the other hand, PFE, in which the etiology of infraocclusion is mainly due to supraosseous eruption, has a challenging prognosis. It is known that teeth affected by PFE are highly resistant to orthodontic traction and usually require either or both alveolar osteotomy and prosthodontic approaches in order to achieve functional occlusion (Figures 3 and 4). Genetic testing of PTHR1 is one way to obtain a definitive diagnosis before orthodontic force is applied. However, incomplete penetration of the PTRH1 mutation has been reported; thus, continuous research is required to fully understand the molecular and cellular etiology of PFE [64]. Precision medicine selects different therapeutic protocols

based on individual genetic information. It is now widely applied to cancer treatment, especially for the selection of specific drugs for different gene mutations [65]. Considering the mechanism of tooth defects, congenital missing teeth or eruption problems by different sets of genes require different treatment approaches. For example, congenital missing teeth caused by different genes would require different strategies that target individual signaling pathways to reactivate tooth development. One of the practical applications of precision medicine in the field of orthodontics is the sequencing of PTHR1 to genetically diagnose PFE in order to help patients make decisions or select individual treatment protocols (Figure 4).

Acknowledgements

The authors thank the members of the Department of Orthodontics and Orthopedics, Graduate School of Dentistry, Osaka University, for their insights and comments throughout the project. The work was supported by grants-in-aid for scientific research from the Japan Society for the Promotion of Science (19H03858 to HK, 20K10202 to SI, 20K18755 to CM).

Conflict of interest

The authors have no conflicts of interest to declare.

References

[1] Yu M, Wong SW, Han D, Cai T. Genetic analysis: Wnt and other pathways in nonsyndromic tooth agenesis. Oral Dis. 2019;25:646-51.

[2] Kantaputra PN, Kaewgahya M, Hatsadaloi A, Vogel P, Kawasaki K, Ohazama A, Ketudat Cairns JR. GREMLIN 2 Mutations and Dental Anomalies. J Dent Res. 2015;94:1646-52.

[3] Zeng B, Lu H, Xiao X, Yu X, Li S, Zhu L, Yu D, Zhao W. KDF1 is a novel candidate gene of non-syndromic tooth agenesis. Arch Oral Biol. 2019;97:131-6.

[4] Noor A, Windpassinger C, Vitcu I, Orlic M, Rafiq MA, Khalid M, Malik MN, Ayub M, Alman B, Vincent JB. Oligodontia is caused by mutation in LTBP3, the gene encoding latent TGF-beta binding protein 3. Am J Hum Genet. 2009;84:519-23.

[5] Richman JM. Shedding new light on the mysteries of tooth eruption. Proc Natl Acad Sci U S A. 2019;116:353-5.

[6] Thesleff I. Epithelial-mesenchymal signalling regulating tooth morphogenesis. J Cell Sci. 2003;116:1647-8.

[7] Thesleff I, Nieminen P. Tooth morphogenesis and cell differentiation. Curr Opin Cell Biol. 1996;8:844-50.

[8] Vastardis H, Karimbux N, Guthua SW, Seidman JG, Seidman CE. A human MSX1 homeodomain missense mutation causes selective tooth agenesis. Nat Genet. 1996;13:417-21.

[9] Jowett AK, Vainio S, Ferguson MW, Sharpe PT, Thesleff I. Epithelial-mesenchymal interactions are required for msx 1 and msx 2 gene expression in the developing murine molar tooth. Development. 1993;117:461-70.

[10] Satokata I, Maas R. Msx1 deficient mice exhibit cleft palate and abnormalities of craniofacial and tooth development. Nat Genet. 1994;6:348-56.

[11] Jumlongras D, Bei M, Stimson JM, Wang WF, DePalma SR, Seidman CE, Felbor U, Maas R, Seidman JG, Olsen BR. A nonsense mutation in MSX1 causes Witkop syndrome. Am J Hum Genet. 2001;69:67-74.

[12] Peters H, Neubuser A, Kratochwil K, Balling R. Pax9-deficient mice lack pharyngeal pouch derivatives and teeth and exhibit craniofacial and limb abnormalities. Genes Dev. 1998;12:2735-47.

[13] Wang Y, Groppe JC, Wu J, Ogawa T, Mues G, D'Souza RN, Kapadia H. Pathogenic mechanisms of tooth agenesis linked to paired domain mutations in human PAX9. Hum Mol Genet. 2009;18:2863-74.

[14] Liu F, Millar SE. Wnt/beta-catenin signaling in oral tissue development and disease. J Dent Res. 2010;89:318-30.
[15] Dassule HR, McMahon AP. Analysis of epithelial-mesenchymal interactions in the initial morphogenesis of the mammalian tooth. Dev Biol. 1998;202:215-27.
[16] Yang J, Wang SK, Choi M, Reid BM, Hu Y, Lee YL, Herzog CR, Kim-Berman H, Lee M, Benke PJ, Lloyd KC, Simmer JP, Hu JC. Taurodontism, variations in tooth number, and misshapened crowns in Wnt10a null mice and human kindreds. Mol Genet Genomic Med. 2015;3:40-58.
[17] Yu P, Yang W, Han D, Wang X, Guo S, Li J, Li F, Zhang X, Wong SW, Bai B, Liu Y, Du J, Sun ZS, Shi S, Feng H, Cai T. Mutations in WNT10B Are Identified in Individuals with Oligodontia. Am J Hum Genet. 2016;99:195-201.
[18] Sarkar L, Sharpe PT. Expression of Wnt signalling pathway genes during tooth development. Mech Dev. 1999;85:197-200.
[19] Magruder S, Carter E, Williams MA, English J, Akyalcin S, Letra A. Further evidence for the role of WNT10A, WNT10B and GREM2 as candidate genes for isolated tooth agenesis. Orthod Craniofac Res. 2018;21:258-63.
[20] Kokubu C, Heinzmann U, Kokubu T, Sakai N, Kubota T, Kawai M, Wahl MB, Galceran J, Grosschedl R, Ozono K, Imai K. Skeletal defects in ringelschwanz mutant mice reveal that Lrp6 is required for proper somitogenesis and osteogenesis. Development. 2004;131:5469-80.
[21] Massink MP, Creton MA, Spanevello F, Fennis WM, Cune MS, Savelberg SM, Nijman IJ, Maurice MM, van den Boogaard MJ, van Haaften G. Loss-of-Function Mutations in the WNT Co-receptor LRP6 Cause Autosomal-Dominant Oligodontia. Am J Hum Genet. 2015;97:621-6.
[22] Song L, Li Y, Wang K, Wang YZ, Molotkov A, Gao L, Zhao T, Yamagami T, Wang Y, Gan Q, Pleasure DE, Zhou CJ. Lrp6-mediated canonical Wnt signaling is required for lip formation and fusion. Development. 2009;136:3161-71.
[23] Yamada M, Kubota K, Uchida A, Yagihashi T, Kawasaki M, Suzuki H, Uehara T, Takenouchi T, Kurosaka H, Kosaki K. Fork-shaped mandibular incisors as a novel phenotype of LRP5-associated disorder. Am J Med Genet A. 2021;185:1544-9.
[24] Lammi L, Arte S, Somer M, Jarvinen H, Lahermo P, Thesleff I, Pirinen S, Nieminen P. Mutations in AXIN2 cause familial tooth agenesis and predispose to colorectal cancer. Am J Hum Genet. 2004;74:1043-50.
[25] Cui CY, Schlessinger D. EDA signaling and skin appendage development. Cell Cycle. 2006;5:2477-83.
[26] Mikkola ML. Molecular aspects of hypohidrotic ectodermal dysplasia. Am J Med Genet A. 2009;149A:2031-6.

[27] Tucker AS, Headon DJ, Schneider P, Ferguson BM, Overbeek P, Tschopp J, Sharpe PT. Edar/Eda interactions regulate enamel knot formation in tooth morphogenesis. Development. 2000;127:4691-700.
[28] Srivastava AK, Pispa J, Hartung AJ, Du Y, Ezer S, Jenks T, Shimada T, Pekkanen M, Mikkola ML, Ko MS, Thesleff I, Kere J, Schlessinger D. The Tabby phenotype is caused by mutation in a mouse homologue of the EDA gene that reveals novel mouse and human exons and encodes a protein (ectodysplasin-A) with collagenous domains. Proc Natl Acad Sci U S A. 1997;94:13069-74.
[29] Takahashi A, Nagata M, Gupta A, Matsushita Y, Yamaguchi T, Mizuhashi K, Maki K, Ruellas AC, Cevidanes LS, Kronenberg HM, Ono N, Ono W. Autocrine regulation of mesenchymal progenitor cell fates orchestrates tooth eruption. Proc Natl Acad Sci U S A. 2019;116:575-80.
[30] Cahill DR, Marks SC, Jr. Tooth eruption: evidence for the central role of the dental follicle. J Oral Pathol. 1980;9:189-200.
[31] Kong YY, Yoshida H, Sarosi I, Tan HL, Timms E, Capparelli C, Morony S, Oliveira-dos-Santos AJ, Van G, Itie A, Khoo W, Wakeham A, Dunstan CR, Lacey DL, Mak TW, Boyle WJ, Penninger JM. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. Nature. 1999;397:315-23.
[32] Dougall WC, Glaccum M, Charrier K, Rohrbach K, Brasel K, De Smedt T, Daro E, Smith J, Tometsko ME, Maliszewski CR, Armstrong A, Shen V, Bain S, Cosman D, Anderson D, Morrissey PJ, Peschon JJ, Schuh J. RANK is essential for osteoclast and lymph node development. Genes Dev. 1999;13:2412-24.
[33] Sobacchi C, Frattini A, Guerrini MM, Abinun M, Pangrazio A, Susani L, Bredius R, Mancini G, Cant A, Bishop N, Grabowski P, Del Fattore A, Messina C, Errigo G, Coxon FP, Scott DI, Teti A, Rogers MJ, Vezzoni P, Villa A, Helfrich MH. Osteoclast-poor human osteopetrosis due to mutations in the gene encoding RANKL. Nat Genet. 2007;39:960-2.
[34] Liu D, Wise GE. A DNA microarray analysis of chemokine and receptor genes in the rat dental follicle--role of secreted frizzled-related protein-1 in osteoclastogenesis. Bone. 2007;41:266-72.
[35] Crockett JC, Rogers MJ, Coxon FP, Hocking LJ, Helfrich MH. Bone remodelling at a glance. J Cell Sci. 2011;124:991-8.
[36] Heinrich J, Bsoul S, Barnes J, Woodruff K, Abboud S. CSF-1, RANKL and OPG regulate osteoclastogenesis during murine tooth eruption. Arch Oral Biol. 2005;50:897-908.
[37] Van Wesenbeeck L, Odgren PR, MacKay CA, D'Angelo M, Safadi FF, Popoff SN, Van Hul W, Marks SC, Jr. The osteopetrotic mutation toothless (tl) is a loss-of-function frameshift mutation in the rat Csf1 gene: Evidence of a crucial role for CSF-1 in osteoclastogenesis and

endochondral ossification. Proc Natl Acad Sci U S A. 2002;99:14303-8.
[38] Yoshida H, Hayashi S, Kunisada T, Ogawa M, Nishikawa S, Okamura H, Sudo T, Shultz LD, Nishikawa S. The murine mutation osteopetrosis is in the coding region of the macrophage colony stimulating factor gene. Nature. 1990;345:442-4.
[39] Wise GE, Yao S, Odgren PR, Pan F. CSF-1 regulation of osteoclastogenesis for tooth eruption. J Dent Res. 2005;84:837-41.
[40] Kreiborg S, Jensen BL. Tooth formation and eruption - lessons learnt from cleidocranial dysplasia. Eur J Oral Sci. 2018;126 Suppl 1:72-80.
[41] Wang XP, Aberg T, James MJ, Levanon D, Groner Y, Thesleff I. Runx2 (Cbfa1) inhibits Shh signaling in the lower but not upper molars of mouse embryos and prevents the budding of putative successional teeth. J Dent Res. 2005;84:138-43.
[42] Dorotheou D, Gkantidis N, Karamolegkou M, Kalyvas D, Kiliaridis S, Kitraki E. Tooth eruption: altered gene expression in the dental follicle of patients with cleidocranial dysplasia. Orthod Craniofac Res. 2013;16:20-7.
[43] Iseri H, Solow B. Continued eruption of maxillary incisors and first molars in girls from 9 to 25 years, studied by the implant method. Eur J Orthod. 1996;18:245-56.
[44] Biederman W. Etiology and Treatment of Tooth Ankylosis. Am J Orthod Dentofac. 1962;48:670-&.
[45] Proffit WR, Vig KW. Primary failure of eruption: a possible cause of posterior open-bite. Am J Orthod. 1981;80:173-90.
[46] Rhoads SG, Hendricks HM, Frazier-Bowers SA. Establishing the diagnostic criteria for eruption disorders based on genetic and clinical data. Am J Orthod Dentofacial Orthop. 2013;144:194-202.
[47] Frazier-Bowers SA, Puranik CP, Mahaney MC. The etiology of eruption disorders - further evidence of a 'genetic paradigm'. Semin Orthod. 2010;16:180-5.
[48] Decker E, Stellzig-Eisenhauer A, Fiebig BS, Rau C, Kress W, Saar K, Ruschendorf F, Hubner N, Grimm T, Weber BH. PTHR1 loss-of-function mutations in familial, nonsyndromic primary failure of tooth eruption. Am J Hum Genet. 2008;83:781-6.
[49] Philbrick WM, Dreyer BE, Nakchbandi IA, Karaplis AC. Parathyroid hormone-related protein is required for tooth eruption. Proc Natl Acad Sci U S A. 1998;95:11846-51.
[50] Jobert AS, Zhang P, Couvineau A, Bonaventure J, Roume J, Le Merrer M, Silve C. Absence of functional receptors for parathyroid hormone and parathyroid hormone-related peptide in Blomstrand chondrodysplasia. J Clin Invest. 1998;102:34-40.
[51] Schipani E, Kruse K, Juppner H. A constitutively active mutant PTH-PTHrP receptor in Jansen-type metaphyseal chondrodysplasia. Science. 1995;268:98-100.
[52] Eiken M, Prag J, Petersen KE, Kaufmann HJ. A new familial skeletal dysplasia with

severely retarded ossification and abnormal modeling of bones especially of the epiphyses, the hands, and feet. Eur J Pediatr. 1984;141:231-5.
[53] Grippaudo C, Cafiero C, D'Apolito I, Ricci B, Frazier-Bowers SA. Primary failure of eruption: Clinical and genetic findings in the mixed dentition. Angle Orthod. 2018;88:275-82.
[54] Assiry AA, Albalawi AM, Zafar MS, Khan SD, Ullah A, Almatrafi A, Ramzan K, Basit S. KMT2C, a histone methyltransferase, is mutated in a family segregating non-syndromic primary failure of tooth eruption. Sci Rep. 2019;9:16469.
[55] Mantovani G, Bastepe M, Monk D, de Sanctis L, Thiele S, Usardi A, Ahmed SF, Bufo R, Choplin T, De Filippo G, Devernois G, Eggermann T, Elli FM, Freson K, Garcia Ramirez A, Germain-Lee EL, Groussin L, Hamdy N, Hanna P, Hiort O, Juppner H, Kamenicky P, Knight N, Kottler ML, Le Norcy E, Lecumberri B, Levine MA, Makitie O, Martin R, Martos-Moreno GA, Minagawa M, Murray P, Pereda A, Pignolo R, Rejnmark L, Rodado R, Rothenbuhler A, Saraff V, Shoemaker AH, Shore EM, Silve C, Turan S, Woods P, Zillikens MC, Perez de Nanclares G, Linglart A. Diagnosis and management of pseudohypoparathyroidism and related disorders: first international Consensus Statement. Nat Rev Endocrinol. 2018;14:476-500.
[56] Ritchie GM. Dental manifestations of pseudohypoparathyroidism. Arch Dis Child. 1965;40:565-72.
[57] Reis MT, Matias DT, Faria ME, Martin RM. Failure of tooth eruption and brachydactyly in pseudohypoparathyroidism are not related to plasma parathyroid hormone-related protein levels. Bone. 2016;85:138-41.
[58] Ahmad S, Bister D, Cobourne MT. The clinical features and aetiological basis of primary eruption failure. Eur J Orthod. 2006;28:535-40.
[59] Shalish M, Peck S, Wasserstein A, Peck L. Increased occurrence of dental anomalies associated with infraocclusion of deciduous molars. Angle Orthod. 2010;80:440-5.
[60] Naoum S, Allan Z, Yeap CK, Razza JM, Murray K, Turlach B, Goonewardene MS. Trends in orthodontic management strategies for patients with congenitally missing lateral incisors and premolars. Angle Orthod. 2021;91:477-83.
[61] Kuroda S, Sugawara Y, Yamashita K, Mano T, Takano-Yamamoto T. Skeletal Class III oligodontia patient treated with titanium screw anchorage and orthognathic surgery. Am J Orthod Dentofacial Orthop. 2005;127:730-8.
[62] Schneider H, Faschingbauer F, Schuepbach-Mallepell S, Korber I, Wohlfart S, Dick A, Wahlbuhl M, Kowalczyk-Quintas C, Vigolo M, Kirby N, Tannert C, Rompel O, Rascher W, Beckmann MW, Schneider P. Prenatal Correction of X-Linked Hypohidrotic Ectodermal Dysplasia. N Engl J Med. 2018;378:1604-10.
[63] Murashima-Suginami A, Kiso H, Tokita Y, Mihara E, Nambu Y, Uozumi R, Tabata Y, Bessho K, Takagi J, Sugai M, Takahashi K. Anti-USAG-1 therapy for tooth regeneration through

enhanced BMP signaling. Sci Adv. 2021;7.
[64] Grippaudo C, Cafiero C, D'Apolito I, Re A, Genuardi M, Chiurazzi P, Frazier-Bowers SA. A novel nonsense PTH1R variant shows incomplete penetrance of primary failure of eruption: a case report. BMC Oral Health. 2019;19:249.
[65] Dienstmann R, Vermeulen L, Guinney J, Kopetz S, Tejpar S, Tabernero J. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. Nat Rev Cancer. 2017;17:79-92.

Figure Legends

Figure.1. Tooth development from initiation to occlusion. Genes which are known to be mutated in tooth agenesis shown in red, intraosseous eruption in blue and extraossesus eruption in purple.

Figure.2. Molecular mechanism of intraosseous eruption. Monocytes stimulated by CSF1 and RANK signaling pathway will differentiate into matured osteoclast and play central roles for intraosseous eruption.

Figure.3. Reaction of impacted teeth for orthodontic traction in patients with Cleidocranial dysplasia (CCD) and Primary failure of eruption (PFE). Multiple impacted teeth (black asterisk) with supernumerary teeth are detected in the orthopantomogram in patient with CCD (A). Orthodontic traction is usually efficient for moving impacted teeth into the oral cavity (B). Persistent posterior open bite even after orthodontic traction is observed in patient with PFE (C and D).

Figure.4. Scheme of current medicine and precision medicine for selecting the treatment protocol for PFE.