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Primary failure of tooth eruption: Etiology and management

Tetsutaro Yamaguchi[a,*], Kazuyoshi Hosomichi[b], Tatsuo Shirota[c], Yoichi Miyamoto[d], Wanida Ono[e], Noriaki Ono[e]

[a] Department of Orthodontics, Kanagawa Dental University, Kanagawa, Japan
[b] Department of Bioinformatics and Genomics, Graduate School of Advanced Preventive Medical Sciences, Kanazawa University, Ishikawa, Japan
[c] Department of Oral and Maxillofacial Surgery, Showa University School of Dentistry, Tokyo, Japan
[d] Department of Biochemistry, Showa University School of Dentistry, Tokyo, Japan
[e] University of Texas Health Science Center at Houston School of Dentistry, Houston, TX, USA

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ABSTRACT

Primary failure of eruption (PFE) is a rare disorder defined as incomplete tooth eruption despite the presence of a clear eruption pathway. PFE is known to be caused by rare variants in the parathyroid hormone 1 receptor gene (*PTH1R*). Although several *PTH1R* variants have been reported, the etiology of PFE remains unclear. However, important studies that help elucidate the pathology of PFE have recently been published. The purpose of this review is to summarize current treatment options, clinical symptoms or phenotypes for diagnosis, genetic information including solid evidence in mouse disease models and disease-specific induced pluripotent stem cells, thus approaching the etiology of PFE from the perspective of the latest research.

Contents

1. Introduction

Primary failure of eruption (PFE) is defined as impaired tooth eruption despite the presence of an unobstructed eruption pathway (Fig. 1). PFE involves partial eruption or non-eruption of an initially non-ankylosed tooth due to a disturbed eruption mechanism, resulting in a posterior open bite [1]. The key manifestations were first described in 1981 by Proffit and Vig [2]. Selection of an appropriate treatment strategy depends on the correct diagnosis; however, orthodontic extrusion must be avoided as it can lead to ankylosis [1]. Unfortunately, diagnosis of PFE relies principally on a process of elimination in which all possible causative factors must be considered [3,4], and many patients have received unsuccessful orthodontic treatment because PFE was not correctly diagnosed. For this reason, a good understanding of the clinical symptoms of PFE is necessary for correct diagnosis and effective treatment. Additionally, genetic information may be useful for diagnostic purposes. The discovery of causative variants of the parathyroid hormone 1 receptor gene (*PTH1R*) has led to research involving a mouse disease model and disease-specific induced pluripotent stem cells (iPSCs)

* Correspondence to: Department of Orthodontics, Kanagawa Dental University, 82 Inaoka-Cho, Yokosuka, Kanagawa 238-8580, Japan.
E-mail address: t.yamaguchi@kdu.ac.jp (T. Yamaguchi).

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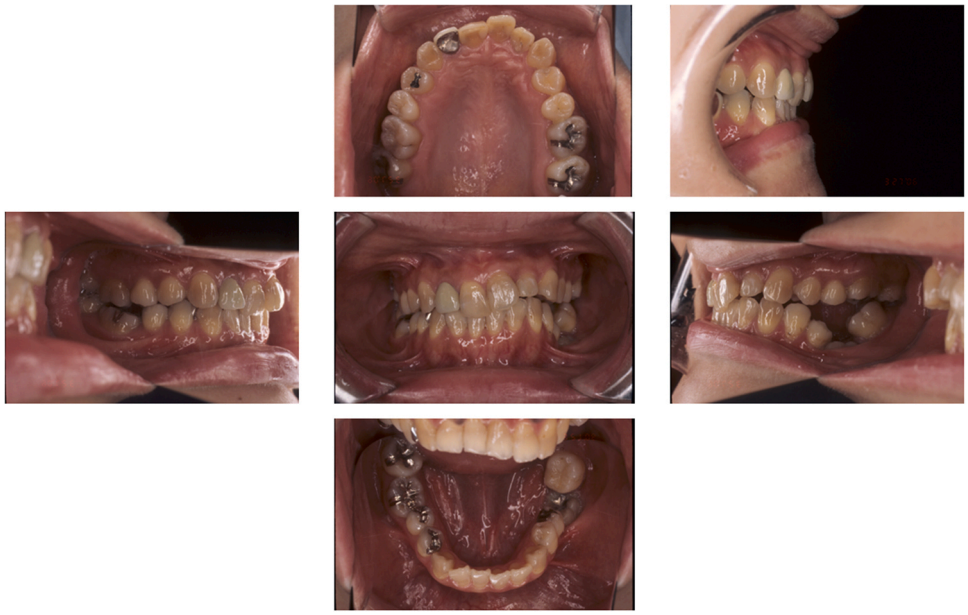

Fig. 1. a. Oral photographs. The patient was a 29-year-old female with primary failure of tooth eruption. The mandibular first molar was impacted vertically in both sides, and mandibular second pre-molar on the left side was inclined distally, and the mandibular second molar on the right side was inclined mesially. Fig. 1b. Cephalograms. Lateral cephalograms revealed skeletal Class III. The posterior-anterior cephalogram revealed asymmetry with deviation to right side. Fig. 1c. Panoramic radiograph. Panoramic radiograph revealed impaction of the mandibular first molar in both sides. (The permission to reprint of these materials from the Showa Univ J Med Sci 2010;22:151-156.)

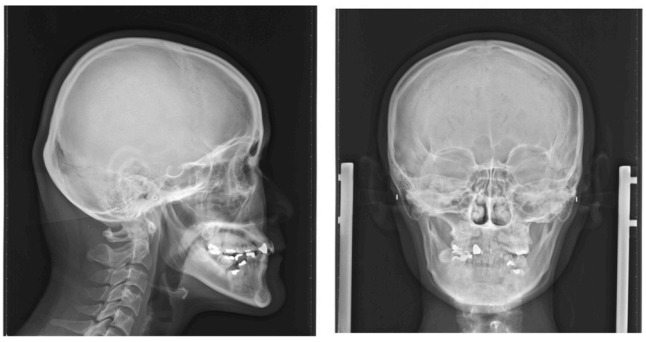

Fig. 1. (*continued*)

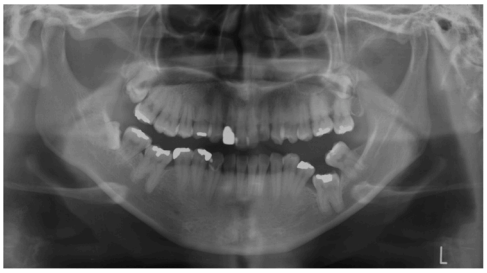

Fig. 1. (*continued*)

that has deepened understanding of PFE etiology. Moreover, current studies are expanding the knowledge of PFE pathological conditions. Accordingly, this review summarizes current treatment options, clinical symptoms or phenotype and genetic information, and insights gained from research investigating PFE pathology.

2. Management of PFE

In PFE, tooth extrusion cannot be performed because orthodontic force applied to the erupted tooth can lead to ankylosis. Thus, orthodontic treatment is considered insufficient to improve malocclusion caused by PFE [2]. Treatment strategies for PFE vary depending on the clinical conditions. If only a few teeth have moderately abnormal eruption, prosthodontic restoration is recommended to establish satisfactory occlusion. In moderately severe cases, small-segment osteotomy and simultaneous elastic traction of the affected teeth will improve the level of the occlusal plane. Prosthetic treatment for these teeth has been shown to further improve malocclusion [5]. If the use of prosthetic teeth is not sufficient, occlusion may be effectively restored by extracting the affected teeth and replacing them with implants with alveolar ridge augmentation. In more severe cases with many incomplete erupted teeth and a significantly deformed alveolar ridge, prosthetic rehabilitation with a removable prosthetic appliance is effective in improving occlusion at an early stage [6]. In terms of surgical approaches to occlusion, bone grafting can be performed to improve occlusion. Specifically, segmental osteotomy of the alveolar bone affected by PFE can be performed to reposition the segment and subsequently improve the occlusal plane, and a bone graft can be placed between the bone segment and base of the alveolar bone [2,7]. However, this technique may not be suitable for the maxilla because the thick and poorly elastic palate mucosa resists movement of the segment. This makes it difficult to reposition the segment at an appropriate location. Notably, there is high risk of causing inferior alveolar nerve damage when performing this procedure in the mandible. As such, studies have reported the use of distraction osteogenesis (DOG) of the alveolar bone in patients with severe lateral open bite [8,9]. However, DOG of the alveolar bone is challenging in terms of controlling the direction of growth because the movement of the distraction divide can only be linear, and the segment tends to be displaced to the palatal side as the bone grows. In these cases, the floating bone concept may be more effective as it allows for 3-dimentional control of the position of the segment by continuously applying pressure to the segment before the bone heals completely [10]. Researchers previously performed DOG of the maxillary alveolar bone in a PFE case with severe lateral open bite, controlling the position of the segment with elastic traction and removing the device before the bone healed completely. This procedure successfully improved the morphology of the dental arch and achieved stable occlusion [11].

Table 1
Clinical symptoms of primary failure of tooth eruption (PFE).

population	Sex distribution	Affected teeth	Primary teeth affected by PFE	Unilateral/bilateral	Family history	Skeletal class	Additional dental anomalies	References
American, English, German, Saudi Arabian, Indian, French, Japanese, Irish, Danish	male (42.3%), female (57.7%)	Only molars (31.4%); both molars and premolars (68.6%)	Primary teeth affected (24.3%); deciduous teeth not affected (75.7%)	Teeth affected on both sides (64.1%) teeth affected on only one side (35.9%)	Family members affected (84.1%); family members not affected 15.9%	Skeletal classes I (5.9%), II (14.7%), III (79.4%)	Root morphology, impacted teeth, delayed eruption of further teeth, hypodontia, hyperdontia, transposition of teeth, peg-shaped teeth, Mechanical failure of eruption, hyperdontia, hypercementosis	[1]
Japanese	4 females and 2 males	2 patients with only molars; 2 patients with both molars and premolars; 1 patient with molars, premolars, and incisor; 1 patient with molars and incisor.		4 patients with teeth affected on both sides; 2 patients with teeth affected on only one side	3 family members affected; 2 family members not affected	All skeletal class III	Spontaneous reeruption, cervical root resorption	[63]
Brazilian	3 females and 7 males		Including an affected member with affected deciduous teeth	Affected teeth on both sides; affected teeth on only one side	Three generations of a family with 18 members; 10 members affected by PFE.			[54]
Caucasian	2 females and 1 male		Including an affected member with affected deciduous teeth	Affected teeth on both sides; affected teeth on only one side	Two generations of a family with 3 members clinically affected by PFE.			[64]
Italian	1 male			Bilateral				[32]

(*continued on next page*)

Table 1 (*continued*)

population	Sex distribution	Affected teeth	Primary teeth affected by PFE	Unilateral/bilateral	Family history	Skeletal class	Additional dental anomalies	References
Italian	26 males and 18 females	14 patients with teeth distal to a PFE-affected molar	31 patients with affected permanent molars; 20 patients with affected deciduous teeth.	14 patients with teeth affected bilaterally				[24]

Table 2
Causes of eruption failure.

Local causes	Systemic causes
Ankylosis	Anemia
Ankylosis of decidous teeth	Celiac disease
Apical periosontitis of decidous teeth	Cerebral palsy
Arch-length deficiency and skeletal pattern	Endocrine disorders:
Cysts	Hypothyroidism (cretinism)
Ectopic eruption	Hypopituitarism
Enamel pearls	Hypoparathyroidism
Gingival fibromatosis / gingival hyperplasia	Pseudohypoparathyroidism
Impacted primary tooth	Drugs: phenytoin
Impaction	Exposure to hypobaria
Injuries to primary teeth	Genetic disorders
Lack of resorption of decidous tooth	Heavy metal intoxication
Mucosal barriers-scar tissue	HIV infection
Neoplasms	Ichthyosis
Nonodontogenic tumors	Idiopathy
Odontogenic tumors	Long-term chemotherapy
Oral clefts	Nutrition
Premature loss of primary tooth	Oral clefts
Primary retention	Prematurity/low birth weight
Radiation damage	Radiation damage
Regional odontodysplasia	Renal failure
Segmental odontomaxillary dysplasia	Vitamin D-resistant rickets
Supernumerary teeth	
Tongue or lip interpositioning	

Evaluating the severity of clinical symptoms on an individual basis is needed to select the most appropriate treatment option for patients diagnosed with PFE. In other words, familiarity with the clinical symptoms of PFE is extremely important.

3. Clinical symptoms for the diagnosis of PFE

PFE is reported in approximately 0.06% of the population [12]. A prevalence among different populations has not been reported. Hanisch et al. compiled a systematic review of studies on PFE published until 2016 [1]. The review and subsequent articles are summarized in Table 1.

First and foremost, the easiest way to diagnose PFE is to check for occlusion in parents of patients suspected of having PFE. Almost 85% of patients with PFE had a family member affected by PFE (Table 1) [1]. However, parents may not recognize healthy occlusion since they experienced PFE at a young age; thus, it is strongly recommended to evaluate occlusion in the parents. Indeed, the father or mother may actually have severe malocclusion, even though they declared the absence of any dental problems. The next step in the diagnosis of PFE primarily relies on exclusion, in which all possible causative factors must be considered and eliminated. Table 2 lists the causes of eruption failure, divided into local and systemic causes. In many cases, local factors causing mechanical impairment are responsible for eruption failure. Infraocclusion, immobility, metallic sound on percussion, and radiographic obliteration of the periodontal ligament space are a clue to the diagnosis for mechanical failure of eruption (ankylosis). These characteristics might be differentiated from PFE. However, actuality, mechanical failure of eruption and PFE are often difficult to distinguish [1,13,14]. A genetic testing for variants in the *PTH1R* may be expected to avoid unnecessary treatment intervention [15,16].

4. Genetic testing for PFE

Eruption failure has been found to be a feature in many genetic disorders and syndromes as listed in Table 3. The gene(s) responsible for various disorders and syndromes associated with eruption failures have been identified. Moreover, Decker et al. [15] first reported that a variant in *PTH1R* was associated with PFE.

PTH1R variants have also been associated with diseases of bone and cartilage. Table 4 summarizes the *PTH1R* variants reported so far. A loss-of-function variant in *PTH1R* can result in Blomstrand osteochondrodysplasia (BOC; Orphanet # 50945; OMIM # 215045), a rare autosomal recessive skeletal dysplasia characterized by advanced endochondral bone maturation and premature ossification of skeletal elements. BOC causes short-limbed dwarfism and perinatal lethality [17]. Similarly, a homozygous *PTHIR* variant results in Eiken syndrome (Orphanet # 79106; OMIM # 600002), a rare autosomal recessive skeletal disorder characterized by extremely retarded ossification and multiple epiphyseal dysplasia [18]. Patients with Eiken syndrome exhibit abnormal bone modeling in their hands and feet, abnormal pelvic cartilage persistence, and mild growth retardation [18]. In contrast, gain-of-function *PTH1R* variants have been reported in patients with Jansen's metaphyseal chondrodysplasia (Orphanet # 33067; OMIM # 156400), an autosomal dominant disorder characterized by pronounced short-limb dwarfism resulting from decelerated chondrocyte differentiation [19].

In *PTH1R*, 48 are registered as pathogenic or likely pathogenic in Human Gene Mutation Database (HGMD) [https://www.hgmd.cf.ac.uk]. In addition, the functional classification of these variants includes 24 missense variants, 9 nonsense variants, 6 frameshift deletions, 3 frameshift insertions, 1 non-frameshift deletion, and 5 intronic variants. Lollipops software [20] was used to confirm the accumulation of genetic regions and functional domains of these variants, and the locations of *PTH1R* variants associated with PFE and other diseases are shown in Fig. 2. The location of the pathogenic *PTH1R* variant was observed scattered throughout the gene, with no domain accumulation, and no phenotype-dependent features were observed.

One of the reasons for the large variety of phenotypes associated with *PTH1R* variants is allelic dose. Strong evidence supports that PFE is an autosomal dominant condition associated with heterozygous variants in *PTH1R* in most cases, whereas homozygous variants are present in extremely rare cases [21–24]. Although the heterozygous missense *PTH1R* variant c 0.395 C > T (see Table 4) was reported in Japanese sporadic cases of PFE [25], the homozygous genotype has also been associated with the BOC phenotype [26]. Similarly, the heterozygous *PTH1R* variants c 0.310 C > T [27,28], c 0.395 C > T [25,26,31,52], c.1093delG [27,29,30], and c 0.1148 G > A [17,25,27,31], have been reported in patients with PFE, while homozygous genotypes have also been associated with the BOC phenotype. Moreover, Jelani et al. [21] reported that the homozygous or biallelic *PTH1R* variant c 0.611 T > A (see Table 4), which caused a PFE phenotype that appeared to be unique to the family and also caused clinodactyly and nasal bridge deformity, was also identified as a heterozygous genotype associated with the Jansen's metaphyseal chondrodysplasia phenotype. Moirangthem et al. [22] reported that a patient with autosomal recessive Eiken syndrome (c 0.103 G > A) (see Table 4) also had malposition and impaction in most teeth. In practice, similar to these examples, the disease overlap with PFE may not be a small number of patients. The reason may be due to unconversant oral examinations [15,31].

As shown in Table 1, almost 15% of patients with PFE had no family members affected by PFE [1]. The patient of PFE without family history, may have spontaneous variant. Therefore, even in sporadic case, a genetic testing brings a valuable advantage for expecting the potential contribution of orthodontic intervention [32].

Although variable phenotypic expression can be observed, almost all *PTH1R* variants causing PFE are thought to exhibit complete penetrance [31]. However, one study documented a patient with severe PFE that carried the *PTH1R* variant c 0.505 G > T inherited from an unaffected mother, providing a typical example of

Table 3
Genetic disorders of eruption failure.

Disease name	Orphanet number	OMIM number	Responsible gene
Aarskog syndrome	915	100050, 305400	*FGD1*
Amelogenesis imperfecta	88661	104500, 104510, 104530, 130900, 204650, 204700, 301200, 301201, 612529, 613211, 614832, 615887, 616221, 616270, 617217	*AMELX, ENAM*
Apert syndrome	87	101200	*FGFR2*
Incontinentia pigmenti	464	308300	*IKBKG*
Carpenter syndrome	65759	201000, 614976	*RAB23, MEGF8*
Cherubism	184	118400	*SH3BP2*
Cleidocranial dysplasia	1452	119600, 216330	*RUNX2*
Down syndrome	870	190685	trisomy 21
Hypertrichosis lanuginosa congenita	2222	145700	
Costello syndrome	3071	218040	*HRAS*
Dentin dysplasia	1653	125400, 125420	*DSPP*
Junctional epidermolysis bullosa	305	-	*COL17A1, ITGA6, ITGB4, LAMA3, LAMB3, LAMC2, ITGA3*
GAPO syndrome	2067	230740	*ANTXR1, TEM8*
Gardner syndrome	79665	175100	*APC*
Gaucher disease	355	230800, 230900, 231000, 231005, 608013, 610539	*GBA, PSAP*
Hereditary gingival fibromatosis	2024	135300, 605544, 609955, 611010, 617626	*SOS1, REST*
Gorlin syndrome	377	109400	*PTCH2, PTCH1, SUFU*
Hallermann-Streiff syndrome	2108	234100	-
Hyperimmunoglobulinemia (Buckley syndrome) Autosomal dominant hyper-IgE syndrome	2314	147060	*STAT3*
Hypodontia-dysplasia of nails syndrome (Ectodermal dysplasia 3, Witkop type)	2228	189500	*MSX1*
Mucolipidosis type II	576	252500	*GNPTAB*
Incontinentia pigmenti (Bloch-Sulzberger syndrome)	464	308300	*IKBKG*
Menkes disease	565	309400	*ATP7A*
Mucopolysaccharidosis type 6	583	253200	*ARSB*
Neurofibromatosis type 1	636	162200 162210 613675	*NF1*
Osteogenesis imperfecta	666	166200 166210 166220 166230 259420 259440 610682 610915 610967 610968 613848 613849 613982 614856 615066 615220 616229 616507 619131	*COL1A1, COL1A2, etc.*
Osteoglophonic dwarfism	2645	166250	*FGFR1*
Osteopetrosis	53, 2783, 667, etc.	16600, 607634, 259700, 259710, 611490, 615085, etc.	*TCIRG1, ClCN7, LRP5, etc.*
Otodental dysplasia	2791	166750	-
Parry-Romberg syndrome (progressive hemifacial atrophy)	1214	141300	-
Rapp-Hodgkin syndrome	3022	129400	*TP63*
Regional odontodysplasia	834500	-	-
Rothmund-Thompson syndrome	-	-	-
Sclerosteosis	3152	269500, 614305	*SOST, LRP4*
SHORT syndrome	3163	269880	*PIK3R1*
Singleton-Merten dysplasia	85191	182250, 616298	*IFIH1, DDX58*
Infantile spasms syndrome (West Syndrome)	3451	300672, 308350, 613477, 613722, 615006, 616139, 616341, 617065, 617929, 618298	trisomy 21, the 1p36 deletion or mutations in the *ARX* or *CDKL5 (SPTAN1, PLCB1, ST3GAL3, GRIN2B, SIK1, GUF1, CNPY3, PHACTR1)*
Neurofibromatosis type 1	636	162200 162210 613675	*NF1*
22q11 deletion syndrome	567	188400, 192430	deletion of 22q11.2, *TBX1*

incomplete penetrance [32]. This should be considered when interpreting the results of a genetic testing.

It remains unclear whether variants in only *PTH1R* cause PFE because *PTH1R* variants are not found in all patients with PFE [1,27,30]. The histone methyltransferase 2C gene (*KMT2C*) is reportedly strongly associated with PFE [33]. However, affected families in which this gene was identified included family members without all permanent teeth, and the phenotype was somewhat more severe than that in simple PFE. In any case, it is clear that performing a genetic testing for *PTH1R*, whenever possible, provides useful information to confirm a diagnosis, even in sporadic case [24].

5. PTH1R signaling and tooth eruption

PTH1R encodes parathyroid hormone (PTH) receptor type 1 (PTH1R), a Class B G protein-coupled receptor (GPCR) with 7 transmembrane spanning helixes. PTH1R is activated by two similar ligands with distinct functions, PTH and PTH-related protein (PTHrP), which control the hormonal and local functions of the receptor, respectively. PTH and PTHrP bind to PTH1R in equivalent affinity [34,35]. Upon ligand binding, PTH1R activates two major second messenger signaling systems, including the adenylyl cyclase/protein kinase A pathway and the phospholipase C/protein kinase C pathway [36]. As a locally acting autocrine and paracrine ligand, PTHrP exerts pleiotropic effects on cell proliferation and differentiation. During development, the PTHrP-PTH1R pathway mediates epithelial-mesenchymal interactions in various organs, such as the skin, hair follicles, mammary glands, pancreas, and developing teeth [37–41]. This pathway also regulates bone formation in the endochondral pathway [42].

As a result, the PTHrP-PTH1R pathway regulates tooth eruption in multiple aspects. Tooth eruption occurs in three distinct phases:

Table 4
Potentially pathogenic variants in *PTH1R*.

Phenotype	position in chr3 (GRCh37)	HGMD Variant Class	coding DNA (NM_000316.2)	protein (NP_000307.1)	dbSNP	References
Eiken skeletal dysplasia with pseudoepiphyses in the hands and primary failure of tooth eruption	46935424	Pathogenic	c 0.103 G > A	p.Glu35Lys		[22]
Primary failure of tooth eruption / Blomstrand chondrodysplasia	46937356	Pathogenic	c 0.310 C > T	p.Arg104Ter	rs121434604	[27,28]
Primary failure of tooth eruption	46937391	Likely pathogenic	c.313 + 32 A > G		rs113566258	[24]
Primary failure of tooth eruption	46939352	Pathogenic	c.322delT	p.Cys108ValfsTer82		[27]
Primary failure of tooth eruption	46939362	Pathogenic	c 0.331 G > T	p.Glu111Ter		[27,30]
Primary failure of tooth eruption	46939387	Likely pathogenic	c 0.356 C > T	p.Pro119Leu	rs1364327639	[25,27,30,31]
Primary failure of tooth eruption / Blomstrand chondrodysplasia	46939426	Pathogenic	c 0.395 C > T	p.Pro132Leu	rs121434599	[25,26,31,65]
Eiken skeletal dysplasia	46939432	Pathogenic	c.401 A > C	p.Tyr134Ser		[18]
Primary failure of tooth eruption	46939564	Pathogenic	c 0.425 G > T	p.Gly142Val		[64]
Primary failure of tooth eruption	46939575	Pathogenic	c 0.436 C > T	p.Arg146Ter		[27,30]
Primary failure of tooth eruption	46939578	Likely pathogenic	c 0.439 C > T	p.Arg147Cys	rs1323321129	[25,27,31]
Ollier disease	46939587	Pathogenic	c 0.448 C > T	p.Arg150Cys	rs121434601	[67]
Primary failure of tooth eruption	46939602	Pathogenic	c 0.463 G > T	p.Glu155Ter	rs121434605	[15,30,31]
Primary failure of tooth eruption	46939644	Pathogenic	c 0.505 G > T	p.Glu169Ter		[24,32]
Primary failure of tooth eruption	46939683	Pathogenic	c.543 + 1 G > A			[15,27,30,66]
Primary failure of tooth eruption	46939683	Pathogenic	c.543 + 1 G > T			[27]
Primary failure of tooth eruption	46939842	Pathogenic	c.544–25_544–23delCTG			[31]
Pseudohypoparathyroidism 1b with neurological involvement	46939881	Pathogenic	c 0.557 G > A	p.Arg186His	rs201499146	[68]
Primary failure of tooth eruption	46939895	Pathogenic	c.572delA	p.Tyr191SerfsTer14		[58]
Primary failure of tooth eruption (Hypodontia, skeletal abnormalities of the nasal bridge, clinodactyly, polydactyly, and hallux valgus)	46939935	Pathogenic	c 0.611 T > A	p.Val204Glu		[21]
Primary failure of tooth eruption	46939957	Pathogenic	c.636dupT	p.Arg213Ter		[27,30]
Primary failure of tooth eruption	46940150	Pathogenic	c.639–2 A > C			[27,30]
Primary failure of tooth eruption	46940150	Pathogenic	c.639–2 A > G			[27]
Metaphyseal chondrodysplasia	46940181	Pathogenic	c.668 A > G	p.His223Arg	rs121434597	[19,69]
Ollier disease	46940277	Pathogenic	c 0.764 G > A	p.Arg255His	rs1027263198	[27]
Primary failure of tooth eruption	46940325	Pathogenic	c.813dupT	p.Ala272CysfsTer127		[27,30]
Primary failure of tooth eruption	46940850	Pathogenic	c 0.892 T > G	p.Trp298Gly		[31]
Primary failure of tooth eruption	46940905	Pathogenic	c 0.947 C > A	p.Ser316Ter		[31]
Primary failure of tooth eruption	46942515	Pathogenic	c 0.989 G > T	p.Gly330Val		[31]
Primary failure of tooth eruption	46942519	Pathogenic	c.996dupC	p.Ala333ArgfsTer66		[58]
Primary failure of tooth eruption	46942542	Pathogenic	c 0.1016 G > A	p.Trp339Ter	rs760037270	[27,30]
Primary failure of tooth eruption	46942559	Pathogenic	c.1036delC	p.Leu346TrpfsTer9		[27]
Blomstrand chondrodysplasia	46942604	Pathogenic	c.1049 + 29 C > T			[28]
Primary failure of tooth eruption	46942901	Pathogenic	c.1050–3 C > G			[15,30,31,66]
Primary failure of tooth eruption	46942936	Pathogenic	c 0.1082 G > A	p.Trp361Ter	rs1415520107	[31]
Primary failure of tooth eruption	46942946	Pathogenic	c.1092delG	p.Val365CysfsTer140		[70]
Primary failure of tooth eruption / Blomstrand chondrodysplasia	46942945	Pathogenic	c.1093delG	p.365CysfsTer141	rs1304201852	[27,29,30]
Primary failure of tooth eruption / Blomstrand chondrodysplasia	46943287	Pathogenic	c 0.1148 G > A	p.Arg383Gln	rs398122843	[17,25,27,31]
Metaphyseal chondrodysplasia	46944032	Pathogenic	c.1228 A > C	p.Thr410Pro	rs121434598	[71]
Metaphyseal chondrodysplasia	46944033	Pathogenic	c 0.1229 C > G	p.Thr410Arg	rs121434602	[72]
Primary failure of tooth eruption	46944150	Pathogenic	c.1348_1350delTTC	p.Phe450del		[31]
Primary failure of tooth eruption	46944238	Pathogenic	c.1354–1 G > A			[16,31]
Metaphyseal chondrodysplasia	46944258	Pathogenic	c 0.1373 T > A	p.Ile458Lys		[73]
Metaphyseal chondrodysplasia	46944258	Pathogenic	c 0.1373 T > G	p.Ile458Arg	rs121434600	[69]
Eiken skeletal dysplasia	46944817	Pathogenic	c 0.1453 C > T	p.Arg485Ter	rs121434603	[18]
Primary failure of tooth eruption	46944956	Likely pathogenic	c.1595delC	p.Pro532LeufsTer85		[24]
Primary failure of tooth eruption	46945129	Pathogenic	c 0.1765 T > C	p.Trp589Arg		[24,74]

pre-eruptive tooth movement (Phase 1), intra-osseous and supra-osseous eruptive tooth movement (Phase 2), and post-eruptive tooth movement (Phase 3) [43,44]. Phase 1 (pre-eruptive tooth movement) occurs during the early stages of tooth development, lasting until the commencement of tooth root formation. Enamel and dentin formation at this stage prepares the tooth crown for emergence into the oral cavity. Phase 2 (eruptive tooth movement) occurs during tooth root formation, lasting until the tooth crown reaches the occlusal plane. This phase is divided into two stages: intra-osseous and supra-osseous eruptive tooth movement, and involves the formation of the tooth root, alveolar bone, and periodontal ligament. It also involves the osteoclast-mediated bone resorption of the cortical shell overlaying the tooth crown, which jointly facilitate the emergence of the tooth crown into the oral cavity. Phase 3 (post-eruptive tooth movement) maintains the tooth crown in occlusion as the alveolar bone continues to grow and remodel, which requires continuous maturation of the periodontal attachment apparatus. In this phase, the PTHrP-PTH1R pathway directly regulates the

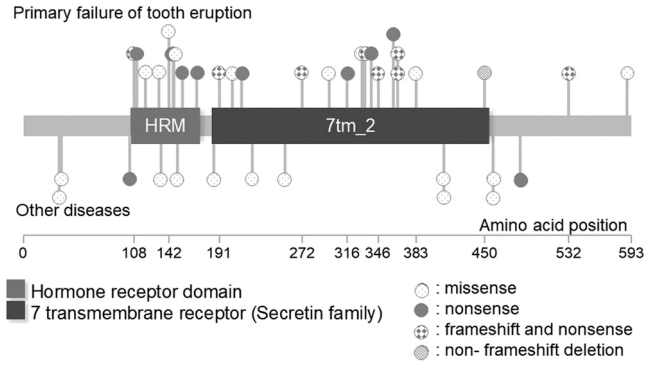

Fig. 2. Location of variants in the *PTH1R*, schematized using Lollipops software [20].

proliferation of dental mesenchymal progenitor cells and their differentiation into cementoblasts, periodontal ligament cells, and alveolar bone osteoblasts. It also indirectly regulates bone-resorbing osteoclasts through the RANKL-RANK axis.

Importantly, tooth eruption requires the formation of the eruption path and the motive force. The sources of the motive force include the dental follicle surrounding the tooth bud, osteogenic activities in the alveolar bone surrounding the tooth root, the formation of the periodontal ligament (PDL) and traction forces generated by the fibers therein, and the development of the tooth root and the cementum in the apical region. Traditionally, tooth eruption has been regarded as a separate and distinct process from tooth root formation, as teeth can emerge into the oral cavity without roots or PDLs [45,46]. However, recent studies support the emerging theory that these two processes are intertwined [36,39]. Because the eruption path is cleared in PFE, defective tooth eruption in this condition is likely to be induced by deficiency motive forces, many of which are regulated by the PTHrP-PTH1R pathway.

6. Mouse models of PFE

Various putative loss-of-function mutations in *PTH1R* are present in patients with PFE [15,25,27,31,47]. The majority of these *PTH1R* mutations are heterozygous, while in extremely rare cases, these mutations are also present in homozygous forms [21–24]. Studies with genetically engineered mice present solid evidence that loss-of-function mutations in *Pth1r* cause similar skeletal abnormalities as those observed in humans. For example, mice harboring two copies of the Pth1r^{tm1Hmk} allele (*Pth1r*$^{-/-}$), which lacks most of the coding region of the *Pth1r* gene, exhibit perinatal lethality that recapitulates Blomstrand osteochondrodysplasia (BOC) [48]. Interestingly, heterozygous *Pth1r* mutant mice (*Pth1r*$^{+/-}$) do not show overt defects in tooth eruption [49], indicating that *Pth1r* haploinsufficiency is not sufficient to induce PFE in mice. It is possible that mouse molars are less sensitive to *Pth1r* gene dosage changes than human molars. Therefore, a better mouse disease model for PFE is needed to understand mechanisms that exclusively affect tooth eruption in molars.

A conditional gene deletion approach based on the *Cre-loxP* recombination system provides a practical modality to circumvent perinatal lethality of *Pth1r*$^{-/-}$ mice and test the function of PTH1R in tooth eruption that exclusively occur during postnatal stages. In the *Pth1r*-floxed allele (Pth1r^{tm2Hmk}), exon 1 of the *Pth1r* gene, which is essential for ligand binding, is flanked by *loxP* sites [50]. This allele can be rendered nonfunctional upon *Cre-loxP* recombination and inactivate PTH1R in a cell type-specific manner. For example, *Pth1r* can be specifically deleted in dental mesenchymal cells that express *osterix* (*Osx*, also known as *Sp7*) using *Osx-cre* and *Pth1r*-floxed alleles. This causes severe failure of tooth eruption in molars associated with truncated roots lacking periodontal ligaments [49], representing an extreme phenotype induced by PTH1R loss-of-function variants. However, these mutant mice do not survive beyond weaning owing to the inability to consume food. A delayed molar eruption phenotype is also observed by *Pth1r* deletion in Prrx1-expressing progenitor cells using *Prrx1-cre* [51]. Notably, cells marked by *Osx-cre* are distributed throughout the alveolar bone and the periodontal tissue surrounding the incisor and molars, while cells marked by *Prrx1-cre* are predominantly observed in the alveolar bone surrounding incisors and at the base of molars. Delayed eruption, instead of complete failure of eruption, observed in *Prrx1-cre*-mediated *Pth1r* mutant mice, is likely due to the restricted distribution of cells marked by *Prrx1-cre*. Reduced formation of the alveolar bone and PDL at the base of molars, instead of the unresorbed overlaying cortical shell, is likely to explain delayed eruption of *Prrx1-cre*-mediated *Pth1r* mutant molars. These findings emphasize the role of the alveolar bone formation in providing the motive force for tooth eruption. The major limitation of these models is that PTH1R is inactivated in the given cell types from embryogenesis. As a result, other bone compartments, including the mandible, skull and long bones, are also severely affected, making it difficult to discern the contribution of each component to the failure to tooth eruption. Therefore, these models lack the phenotypic specificity for tooth eruption in molars and present as conditions that are far more severe than those typically manifested in human PFE.

To inactivate PTH1R postnatally in a tooth root-specific manner, a dental follicle-specific, tamoxifen-inducible *PTHrP-creER* line can be used to delete PTH1R using *PTHrP-creER* and *Pth1r*-floxed allele [52]. By administering tamoxifen at a specific postnatal time point (in this case, postnatal day 3), this inducible cell type-specific approach enables biallelic inactivation of PTH1R in a small number of specific cell types (in this case, PTHrP^{+} dental follicle cells) at the onset of tooth root formation. This approach can create a cell type-specific "low mosaicism" of PTH1R-deficient cells during tooth root formation, providing substantial mechanical insights into the altered cellular dynamics underlying PFE. Postnatal PTH1R deletion in dental follicle cells exclusively induces failure of tooth eruption in molars, which essentially recapitulate human PFE. The mutant molars exhibit a significant delay in tooth eruption especially first molars, without involving other bone components. Furthermore, the affected molars exhibit dilacerated tooth roots and cementum anomalies, which are often observed in human PFE molars [30]. Interestingly, the mutant mouse PFE phenotype, particularly PFE in first molars, demonstrates aggravated open bite in adult stages [53], which is similar to human cases of PFE reported during a long-term follow-up study [54]. A mouse PFE phenotype is also observed when *Pth1r* is postnatally inactivated in a much broader type of Osx^{+} cells using *Osx-creER* [52], indicating that PTHrP^{+} dental follicle cells represent an important functional subset of dental mesenchymal cells that orchestrate tooth eruption.

Although these mutant mice do not completely represent the same genetic condition as human patients with PFE, these studies provide important insights into the pathogenesis of PFE (Table 5). PTH1R inactivation drives dental follicle cells to shift from physiological periodontal ligament fibroblasts and cryptal bone alveolar bone osteoblasts to non-physiological precocious cellular cementoblasts. It remains to be determined whether similar mechanisms of cell fate shift also occur in human PFE.

7. Etiological study of PFE using the PFE-specific induced pluripotent stem cells (iPSCs)

Yamanaka and his colleagues created mouse and human iPSCs by inducing the reprogramming of somatic cells through the ectopic expression of the four factors (Yamanaka factors), namely, OCT3/4, KLF4, SOX2, and c-Myc [55,56]. Since iPSCs are free from the ethical

Table 5
Mouse models of PFE.

Genotype	Gene symbol: *PTH1R*	Gene symbol: *Cre/CreER* drivers	Induction time (tamoxifen)	Tooth eruption phenotype	Reference
***PTH1R*$^{-/-}$**	PTH1R^{tm1Hmk}	N/A	N/A	Perinatal lethal (BOC)	[48]
***PTH1R*$^{+/-}$**	PTH1R^{tm1Hmk}	N/A	N/A	No phenotype	[49]
***Osx-Cre; PTH1R*$^{fl/fl}$**	PTH1R^{tm2Hmk}	Tg(Sp7-tTA,tetO-EGFP/cre)1Amc	N/A	Complete failure of eruption, truncated molar root	[49]
***Prrx1-Cre; PTH1R*$^{fl/fl}$**	PTH1R^{tm2Hmk}	Tg(Prrx1-cre)1Cjt	N/A	Delayed eruption	[51]
***Osx-CreER; PTH1R*$^{fl/fl}$**	PTH1R^{tm2Hmk}	Tg(Sp7-cre/ERT)1Hmk	P3	Failure of eruption (especially M1), small mandible	[49]
***PTHrP-CreER; PTH1R*$^{fl/fl}$**	PTH1R^{tm2Hmk}	Tg(Pthlh-cre/ERT2)909Nono	P3	Failure of eruption (especially M1), no bone phenotype	[52]

problem of using a fertilized egg and the immunological rejection accompanied by embryonic stem cells, human iPSCs are regarded as promising tools for regenerative medicine. Also, disease-specific iPSCs are developing new research tactics in medical sciences. It made it possible to investigate the diseases' pathogenic mechanisms and find therapeutic methods using the disease-specific iPSCs [57].

Several heterozygous variants in the *PTH1R* have been identified in PFE patients, indicating a close relationship between these genetic variations and the pathogenesis of PFE [25,31,47,58]. Examination of the effects of the introduction of variations in the *PTH1R* on the cellular functions and observation of the phenotypes of the animals having the modified *Pth1r* are considered adequate to demonstrate the pathogenic role of *PTH1R* variation in PFE patients. In addition to these measures, the study using PFE-specific iPSCs is regarded as another potent approach to clarify the pathogenesis of PFE. We established iPSC clones from hematopoietic progenitor cells obtained from a patient with the heterozygous 395 C > T substitution in the *PTH1R* [59] by introducing the Yamanaka factors using a Sendai virus vector [60]. Using the PFE-specific iPSCs, we tried to explain the role of the genetic variation in *PTH1R* in the pathogenesis of PFE in *in-vitro* studies [59].

Alveolar bone resorption is one of the critical events of tooth eruption [61]. Furthermore, it is known that the PTH1R-expressing osteoblasts are responsible for the differentiation and activation of osteoclasts, the bone-resorbing multinucleated giant cells [61]. Hence, we examined the differentiation of the PFE-specific iPSCs and the control iPSCs derived from a healthy volunteer into osteoblast-like cells after cultivation in the medium containing the osteoblast differentiation-inducing factors (β-glycerophosphate, ascorbic acid, and dexamethasone). Differentiation of PFE-specific iPSCs to osteoblast-like cells evaluated by mineralization of the extracellular matrix and the expression of the osteoblast differentiation-related genes (*RUNX2*, *SP7*, and *BGLAP*) was comparable to that of the control iPSCs. Notably, both the osteoblast-like cells derived from PFE-specific iPSCs and those from the control iPSCs expressed equivalent levels of the mRNA and protein of PTH1R [59].

On the other hand, the expression of the mRNA and protein of receptor activator of nuclear factor-κB ligand (RANKL), the essential molecule for osteoclast differentiation and activation [62], in response to PTH was significantly suppressed in the osteoblast-like cells from PFE-specific iPSCs compared to those from the control iPSCs. Active vitamin D_3 induced the expression of the mRNA and protein of RANKL comparably in osteoblast-like cells derived from PFE-specific and those from the control iPSCs, indicating that the PTH-PTH1R signaling system leading to the RANKL expression is affected in the osteoblast-like cells derived from PFE-specific iPSCs [59].

The heterozygous 395 C > T variant in the *PTH1R* is supposed to result in the expression of both standard and P132L amino acid substituted PTH1R in osteoblasts. Our study above indicated that the PTH1R with P132L amino acid substitution in osteoblasts possibly contributed at least in part to the retarded tooth eruption through the incomplete induction of differentiation and activation of osteoclasts in the PFE patient. Detection of gene variants in patients with rare diseases, including PFE, through the techniques such as whole-exome sequencing coupled with studies employing the disease-specific iPSCs, may be a promising approach to clarify the etiology of the diseases.

8. Conclusions

The patient's clinical symptoms need to be carefully scrutinized. Moreover, genetic testing for *PTH1R* variants is recommended to avoid unnecessary and ultimately unsuccessful orthodontic intervention. Screening for such variants in a patient with PFE will help in the selection of an appropriate management strategy and allow

more realistic treatment options to be offered to the patient. Treatment options must be evaluated on an individual basis, depending on the patient's age, background, and preferences. Many aspects of PFE pathophysiology remain unclear; however, disease-specific iPSCs present an unprecedented opportunity to replicate both normal and pathological human tissue formation in vitro, thereby enabling the disease to be investigated and an innovative treatment to be developed to be achieved. Use of a mouse disease model is also expected to offer a way to investigate PFE and act as a guide to the discovery of an effective drug.

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