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The Orthodontic Treatment Scheme for Primary Failure of Eruption Patient without PTH1R Mutation

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Abstract

Primary failure of eruption (PFE) is observed as a defect in the tooth eruption mechanism with the heterozygous mutations of parathyroid hormone receptor gene (PTH1R). The present study reported 2 families suffered from non-syndromic tooth eruption disorder in successive generations. Genetic analysis and standardized assessments, including clinical and radiographic examinations, of the dental condition of all patients were performed to give a clear understanding of the disease. The mutation of PTH1R was detected in patient II-1 (Family I) by PCR and sanger sequencing. Sequencing analysis reviewed heterozygous presence of c.439C>T in exon 2 of PTH1R. According to the UniprotKB database, PTH1R is highly conserved among several mammalian species. RNA-seq was performed to further analyze the role of PTH1R in tooth development and eruption. It showed that during tooth development, the expression of PTH1R decreased in the early stage of tooth development in rat and mouse. However, the mutations of PTH1R were not detected in 2 patients from family II. With extensive analysis of the radiographs and physical examination, we attempted to use orthodontic methods to create enough room for tooth eruption, which shows therapeutic result to the submerged tooth. The results suggested new orthodontic scheme for the PFE patient without PTH1R mutation. Both clinical and genetic diagnosis should be considered in the treatment planning.

Keywords: Primary failure of eruption; PTH1R mutation; Tooth development; Orthodontic treatment

Introduction

Primary Failure of Eruption (PFE; OMIM 125350) is a rare autosomal dominant disorder characterized by incomplete eruption of teeth without mechanical obstruction or ankylosis **[1].** Both primary and permanent teeth could be involved with no other identifiable local or systemic involvement **[2].** Epidemiological studies evaluated that the prevalence of PFE is about 0.06% **[3].** Tooth involvement might be anterior- posterior axis, affecting molar rather than anterior teeth, resulting in open bite in posterior teeth. So far, the treatment for PFE is limited. Orthodontic treatment has beenproved no beneficial effect for tooth eruption, even cause ankylosis, which makes it important to establish a clinical genetic diagnosis before planning any orthodontic treatment plan for the patient **[4].** The heterozygous mutations of Parathyroid Hormone Receptor Gene (PTH1R) has beenreported to be associated with PFE **[8-10].** PTH1R is a receptor for Parathyroidhormone (PTH) and Parathyroid Hormone-Like Hormone (PTHLH), which relates to bone remodeling and metabolism. Since the first reported 3 PTH1R mutations (c.463G>T, c.543+1G>A, c.1050-3C>G) in patients with PFE, the spectrum of PTH1R mutations has been expanded to more than 40 potentially pathogenic mutations (including 8 nonsense mutations, 12 missense mutations, 9 splicing mutations, 9deletion mutations, 3 insertion mutations) **[16-19].** However, the road to unravel the genotype-phenotype correlation is still quite elusive and even more puzzling since the spectrum of disorders arising from PTH1R mutations is so broad. Reporters indicated that dominant mutations in PTH1R could also cause skeletal disorders, such as Jansen's metaphyseal chondrodysplasia, which cause a disorder of bone and cartilage development, leading to short limbed dwarfism **[13-15].** The complete understanding of this wide phenotypic spectrum for similar mutations is enigmatic, requiring a complete understanding of the structure and function of the PTH1R gene. This report presented 2 cases suffered from non-syndromic tooth eruption disorder in successive generations, who are referred to the department of orthodontics at the afflicted stomatological hospital of Fudan University. Genetic analysis was conducted for causative gene identification in each proband with PFE phenotype. One proband was found to carry a reported PTH1R variant (c.439C>T). However, the mutation of PTH1R was not detected in the second case, whose father showed same symptoms with impact upper left second molar. Standardized assessment, including clinical and radiographic examinations, of the dental condition of all patients was performed to give a clear understanding of the disease. We attempted to apply orthodontic force in patientwithout PTH1R mutation, which obtained therapeutic outcome. We therefore posit thateven in isolated cases of PFE, the genetic analysis offers a valuable metric to predict the potential success of orthodontic intervention. Better defining the clinical presentation of PFE in relationship to mutations will aid in elucidating the mechanism of PTH1R in the somatic system, and allow us to add to the body of knowledge definingthe eruption process in general.

Materials and Methods

Ethical approval. The scientific research ethics committee of the Shanghai Stomatological Hospital approved the study protocols. Written informed consents for genetic testing, clinical examination & pictures and radiographs (panoramic, orthopantomograms) were obtained from all available subjects prior to participation. Incase of minors (participants under the age of 18), informed consents were obtained fromparents. This study included 2 families with 3 individuals (2 males and 1 female) havingprimary failure of tooth eruption. Samples collection. 3 ml peripheral blood samples were drawn for the present study from 6 available individuals, including 3 affected patients and 2 normal individuals (Figure1). DNA samples from these individuals were available for molecular analysis. Clinical examination of patients. A comprehensive radiographic and clinical evaluation was performed to determine a positive diagnosis of PFE. Any possible involvement of mechanical or secondary obstacles were ruled out. All participants were in good state of health. General physical

examination and extra oral examination did not show any abnormalities. Mutation analysis. After informed consent was obtained per approval by the Medical Ethics Committee of Fudan University, venous blood samples were obtained from the affected patients and a number of unaffected members of the PFE family. An unaffected member [Family I: I-1] was chosen as the control. Whole blood samples were processed for genomic Deoxyribonucleic Acid (DNA) extraction using the TIANamp genomic DNA kit (TIANamp, DP304, China). The concentration and purity of DNA were determined using absorbance- and fluorescence-based quantification methods. Based on the nucleotide sequence of the parathyroid hormone 1 receptor (PTH1R) (GenBank: NM_000316.2) (https://www.ncbi.nlm.nih.gov/nuccore/1519313 776), we designed 11 pairs of primers for 16 exons (Table 1). The PTH1R gene was amplified by polymerase chain reaction (PCR) and sequenced using our PTH1R primers. ClustalW2 software was used to align the sequencing results (http://www.ebi.ac.uk/Tools/msa/clustalw2), and the DNA sequence was viewed with Chromas software.

Table 1: The primers of PTH1R.

Primer Name	Primer (5′ to 3′)	Sizes (bp)
PTH1R F1	GGTCTTTTCTTGTCCCCAGC	242
PTH1R R1	AGCACGGCCCAGGTATTTAG	
PTH1R F2	CACCCTCGTGGAAACTAAAC	168
PTH1R R2	GAGTCTGGGCTAAGCAACAG	
PTH1R F3	AGCTCTGCACCCCCTACC	232
PTH1R R3	AAGACTGCGTGCCTTAGACC	
PTH1R F4	CTGCCTGTGGTCTGACCTTC	226
PTH1R R4	AGCCTTCACCTGGCTCTGTA	
PTH1R F5	TACCACCCTGGTTTCTCCAG	233
PTH1R R5	TCACATCAGAGGGACAGTGC	
PTH1R F6+7+8	TGTATTCATCCTTCTGGGTCAC	701
PTH1R R6+7+8	CCACCTAAAGTAGGCCAGGA	
PTH1R F9+10	ACAACCCAGCTTCCTGTCC	854
PTH1R R9+10	TGTGAAGCCCCACAGGTACT	
PTH1R F11+12	GAATGACCTTGTGGACAGCA	514
PTH1R R11+12	CACAATGGAGGCCAGGAT	
PTH1R F13	CCCAGAGATGCAGTGACAGA	325
PTH1R R13	AGTCAGACGCTGGGTCCTTT	
PTH1R F14+15	TGCTTGTTGAAGGGGAAGTG	394

PTH1R R14+15	GGAGAAATGAGCCTTGAGGA	
PTH1R F16	CCATTTTCATTCCGTGCTG	666
PTH1R R16	GGAGTGAGTCCCCAGTTTGG	

Sanger sequencing. Sanger sequencing was used to validate the potentially causative variant in all available family members and ethnically matched healthy control chromosomes. The reference sequence of PTH1R (ENSG00000160801) was obtainedfrom the Ensembl genome browser (http://www.ensembl.org/). The amplicon was amplified in each sample and screened by DNA cycle sequencing using a Big Dye Terminator v3.1Cycle Sequencing Kit in an ABI 3500 Genetic Analyzer (Applied Biosytems, Foster City, CA). Sequence variants were identified via BioEdit sequence alignment editor version 6.0.7 (http://www. mbio.ncsu.edu /bioedit/bioedit.html). RNA-Seq. To construct the cDNA library, total RNA from first pre-molars of healthy teenagers and mouse/rat dental germ cells in the Embryonic (E) and postnatal (PN) phases (E13.5, E14.5, E16.5, E18.5, PN1, PN3, PN5, PN7) were extracted using Trizol reagent (Invitrogen, USA, California, Carlsbad). Library construction was performed following the manufacturer's suggestions. The libraries were sequenced on the Illumina HiSeq 2000 platform. RNA- seq analysis was performed to identify and visualize the expression of the PTH1R gene in human teeth and mouse/rat tooth germ development.

Results

Clinical features

Case I: 23-year-old male (II-1) was referred to the Orthodontic Department because ofposterior teeth open-bite **(Figure 1A).** The parents declined the history of any relevant medical condition, dental trauma, inflammation of the relevant alveolar area, or congenital anomalies such as cleft lip and palate or craniofacial malformations. Clinically, both sides of posterior teeth, including second premolars, first molars and second molars were submerged **(Figure 1B).** Besides the left mandibular first molar, the panoramic radiograph showed no mechanical interference of all affected teeth. The panoramic radiograph showed inclusion of all primary pre-molars and molars of the affected side, with no discernible mechanical interference **(Figure 1C).** A CBCT was carried out, showing a clear eruption pathway for all submerged teeth **(Figure 1D).** Physical examination revealed no exceptional skeletal deformation or enchondromatosis. His parents (I-1 and I-2) showed no relative signs of PFE **(Figure 1A).** Blood samples for genetic analysis were taken only after the patient and his father received a detailed explanation of the nature and possible consequence of the study and granted informed consent.

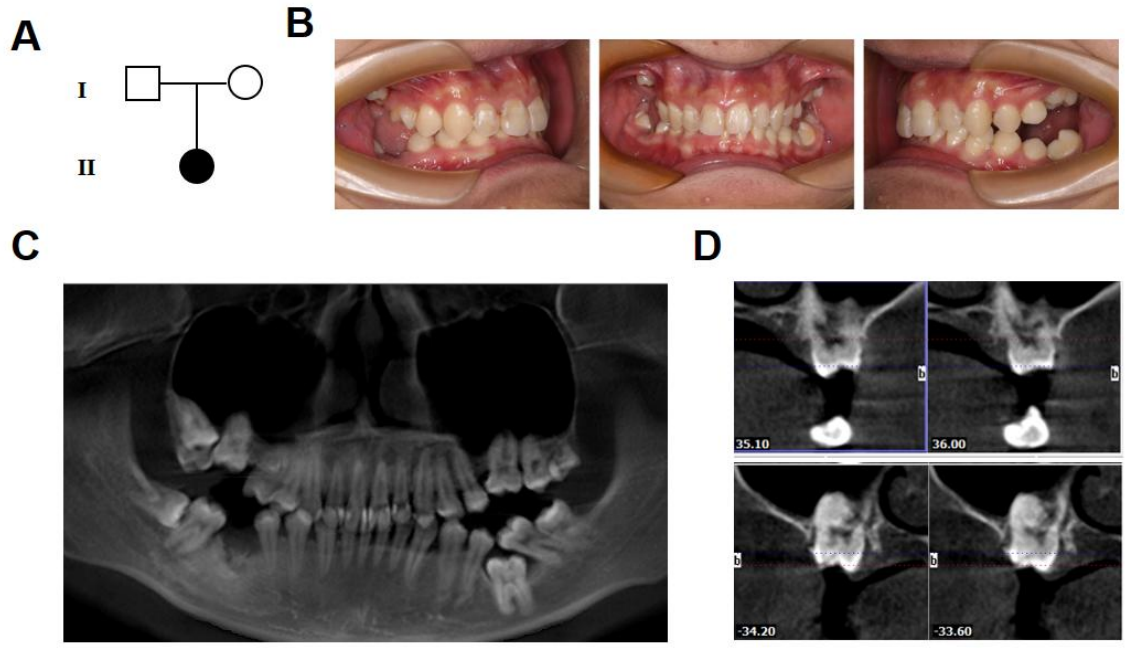

Figure 1: Pedigree of the Primary Failure of Eruption (PFE) family 1. (A) Pedigree ofthe 23-year-old proband's family 1 from China; (B) Oral examination of the PFE family; (C) Panoramic radiograph of the PFE patient; (D) CBCT tomographic imagesof affected teeth.

Case II: 8-year-old girl (II-1) was referred to the Orthodontic Department because of anterior teeth crossbite **(Figure 2A).** A unilateral posterior open bite was observed at the right side. The teeth were severely submerged from both maxillary and mandibular primary canines to second molar. The mandible right permanent first molar was submerged **(Figure 2E).** However, the right permanent maxillary first molar was completely present in the oral cavity. Her 40-year-old father (I-1), also suffered from unilateral posterior teeth submerge, affecting maxillary left first and second molar **(Figure 2A and B).** A dental panoramic radiograph and CBCT were carried out, showing overlying bone resorption and a clear eruption pathway **(Figure 2C-G).** Physical examination of both patients revealed no exceptional skeletal deformation or enchondromatosis. No obvious signs of metabolic impairment. Blood samples for genetic analysis were taken only after each patient received a detailed explanation of the nature and possible consequences of the study and granted informed consent.

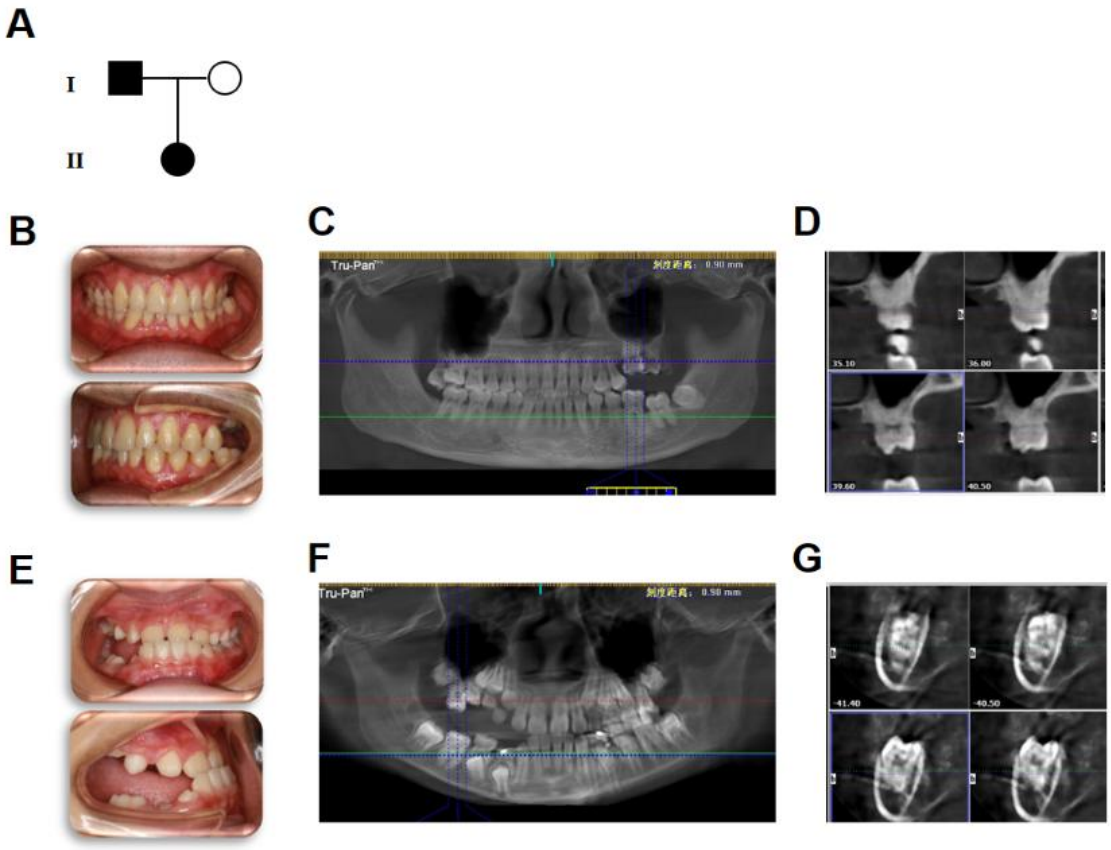

Figure 2: Pedigree of the Primary Failure of Eruption (PFE) family 2. (A) Pedigree of the 8-year-old proband's family 2 from China; (B) Oral examination of the 40-year- old proband's father (I-1). Left upper first and second molar are impacted; (C) Panoramic radiograph of proband's father; (D) CBCT tomographic images of affectedteeth; (E) Oral examination of the 8-year-old proband (II-1); (F) Panoramic radiograph of the patient; (G) CBCT tomographic images of affected teeth.

Mutation analysis

Mutation analysis revealed that PTH1R was the key mutation associated with submerged teeth in family I **(Figure 3).** The mutation was confirmed by PCR and subsequent sequencing of the PCR products, which revealed one mutation in the PTH1R gene when compared with the Single Nucleotide Polymorphism (SNP) Database in NCBI (http:// www.ncbi.nlm.nih.gov/snp/) and the Human Gene Mutation Database (http://www.hgmd.org/). it revealed the heterozygous presence of c.439C>T in patient II-1 **(Figure 3A).** Together with a clear clinical presentation, c.439C>T was classified as the genetic cause of PFE in Family I. The genotyping failed to detect a common region of homozygosity among the family II. However, to date, 40 variants ofPTH1R have been reported for the pathogenicity of PTH1R in PFE patients. This mutation was verified homozygous in the affected individuals. The unaffected parents were homozygous for the wild-type allele **(Figure 3B).** The mutation lies in exon 2 of PTH1R, and results in the substitution of T with C at cDNA position 439. According to the UniprotKB database, PTH1R is highly conserved among several mammalian species **(Figure 4).**

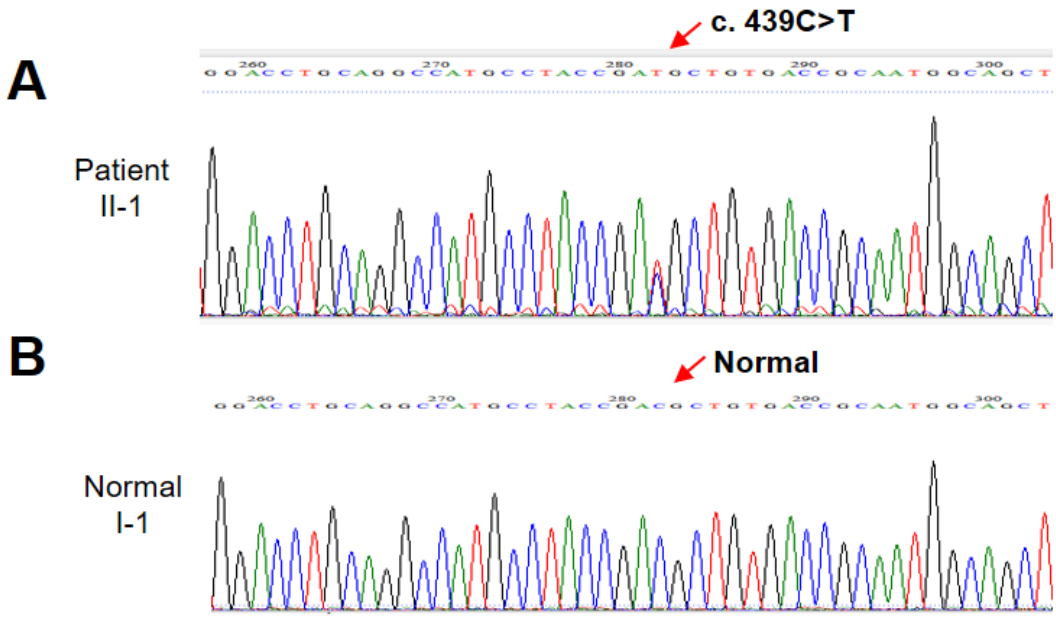

Figure 3: Partial DNA sequences of exon 2 of the PTH1R gene from the proband's family 1. (A) The arrow indicates the substitution of T with C at cDNA position 439,which is associated with submerged teeth in PFE patient II-1; (B) The normal DNA sequence of PTH1R in normal proband I-1. The arrow indicates the normal sequenceat position 439.

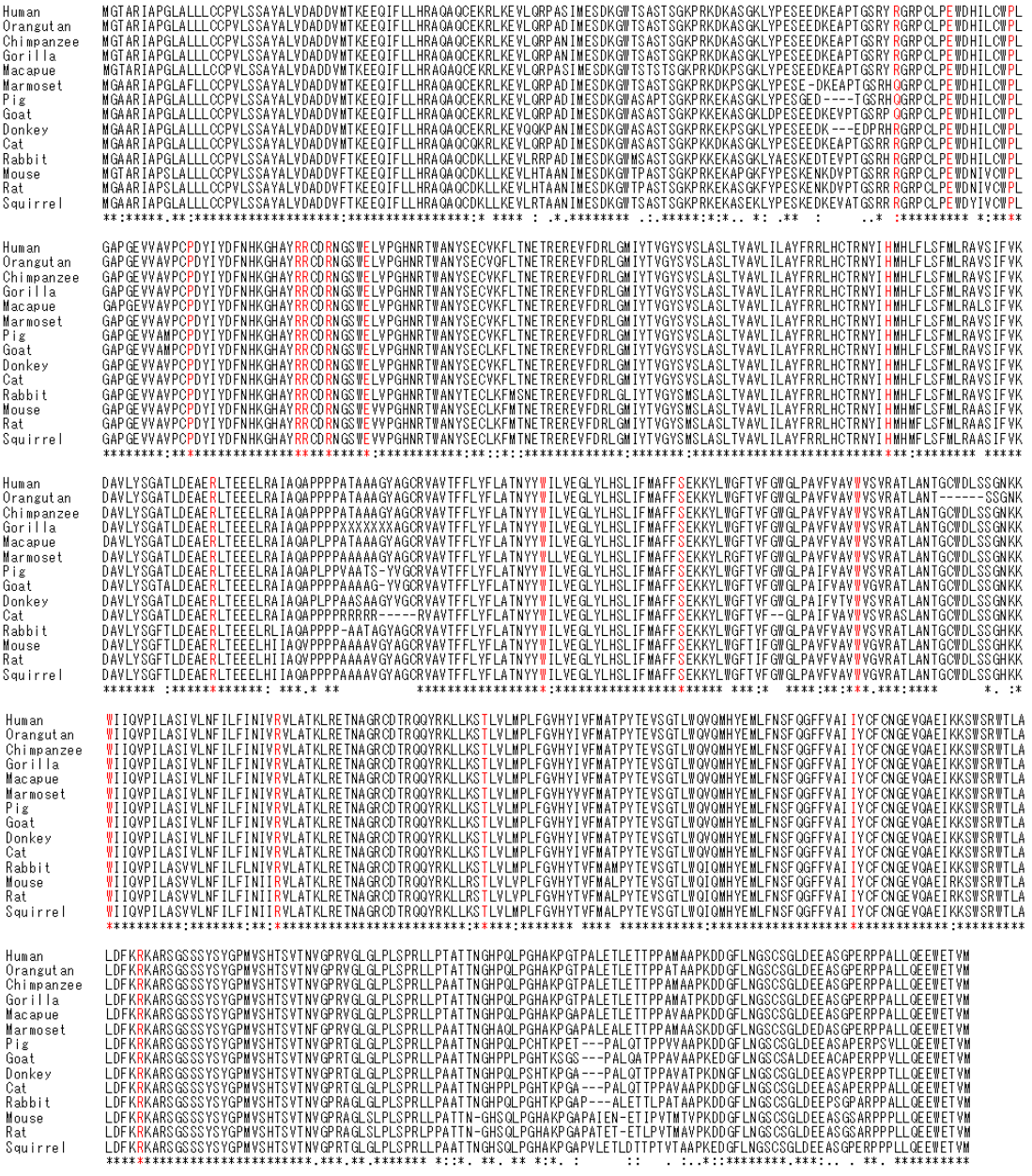

Figure 4: A portion of the amino acid sequence of PTH1R is shown from 14 diverse species. Alignments of amino acid sequences for human, orangutan, chimpanzee, gorilla, macapue, marmoset, pig, goat, donkey, cat, rabbit, mouse, rat, squirrel PTH1Rproteins. Red means published associated mutations in PTH1R gene; "*" means that the residues or nucleotides in that column are identical in all sequences in the alignment; ":" means that conserved substitutions have been observed; "." means thatsemi-conserved substitutions are observed.

Functional analysis

To further analyze the role of PTH1R in tooth development and eruption. We generatedthe odontoblast from rat, mouse from different time point of tooth development (E14.5,E16.5, E18.5, P1, P3, P5, P7). In addition, human dental pulp stem cells and odontoblasts derived from teenager pre-molars were cultured to demonstrate the expression of PTH1R in tooth development **(Figure 5).** Results showed that during tooth development, the expression of PTH1R decreased in the early

stage of tooth development in rat and mouse **(Figure 5A and B).** However, it mainly expressed in human odontoblast than pulp tissue, indicating its role in dentin development and tootheruption **(Figure 5C).**

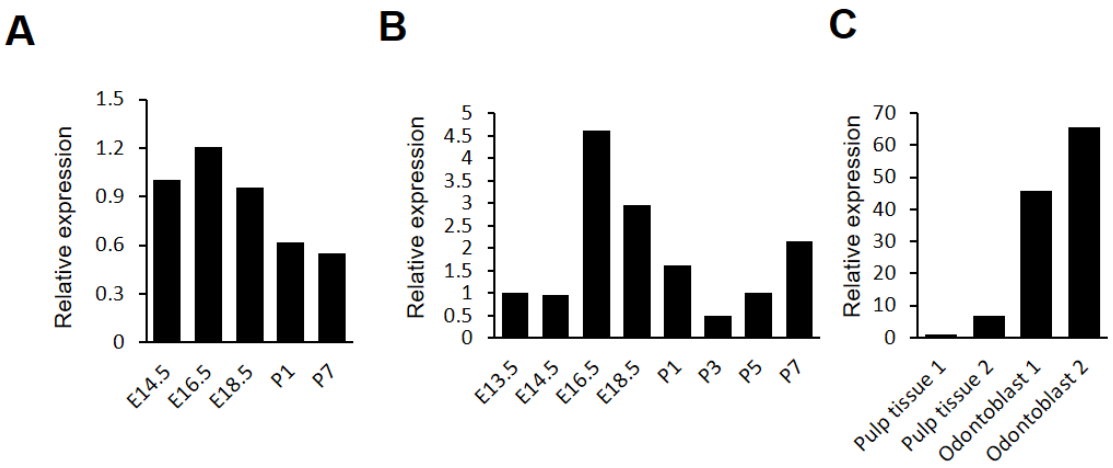

Figure 5: PTH1R expression profile in mouse and rat tooth germ, human pulp tissues and odontoblasts. (A) PTH1R expression levels in rat teeth germ indifferent ages (E14.5, E16.5, E18.5, P1 and P7) based on RNA-seq; (B) PTH1R expression profile analysis of mouse tooth germ development by RNA-seq. (C) PTH1R expression profile analysis of human dental pulp tissues and odontoblastsgenerated from healthy pre-molar by RNA-seq.

Clinical intervention

To further explore the effective treatment for PFE, we carefully analyze the radiographsand the physical examination of two patients. We found that the upper right second premolar of II-1 (family II) may be impacted because of the distal inclined first premolar and mesial inclined first molar. Although orthodontic treatment has been proved no beneficial effect for tooth eruption, even cause ankylosis for PFE, we thoughtthat create the enough space for eruption would do no harm to the situation. Then coil-spring was used to create enough room for tooth eruption **(Figure 6A).** After 6 months of effort, the second premolar was successfully erupted into the dentition with no signs ofankylosis or inclination of adjacent teeth (Fig.6B). This result suggested that there maybe other potential treatment for PFE to clear the pathway for tooth eruption. The pathogenesis and diagnosis of the disease still needs to be discovered.

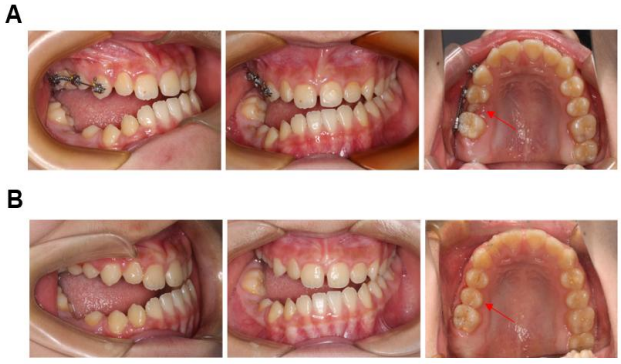

Figure 6: Clinical intervention for patient II-1 in family 2. (A) Spring-coil was used to expand room for tooth eruption. Arrow shows the submerge of second premolar. (B) Right upper second pre-molar was successfully erupted into the dentition. Arrow indicates no ankylosis in second pre-molar or inclination of adjacent teeth.

Discussion

All patients showed typical clinical features of PFE, with submerged teeth, clear eruption pathway and no ankylosis in this report. Mutation analysis revealed a nonsense mutation, c.439C>T, in the second exon of PTH1R in case I. The patient showed bilateral openbite in posterior teeth. However, in case II, with the inherited history from the proband's father and all the related symptoms, we didn't detect any mutation in PTH1R. Till now, orthodontic treatment was convinced to show no beneficial to the situation **[20].** After careful examination in the oral cavity and analysis of radiographs, we found that the upper right second premolar of II-1 (case II) may be impacted because of the distal inclined first premolar. Then coil-spring was used to create enough room for tooth eruption. After 6 months of effort, the second premolar was successfully erupted into the dentition with no signs of ankylosis or inclination of adjacent teeth. This result suggesting that there may be other potential genes and therapeutic target associated with PFE. The pathogenesis and diagnosis of the disease still needs to be discovered. Tooth eruption is a unique biological process determined by many aspects, including tooth formation, root development, bone resorption and periodontal attachment. Dental Follicle Cells (DFCs) are mesenchymal progenitor cells surrounding the tooth germ, which coordinates with multiple pathways to establish tooth morphology and eruption. Many pathways and transcription factors like Gli1, Notch, RANKL, MMPs, Nfic, Wnt, and Runx2 are responsible for tooth development and alveolar bone turnover, which are critical for tooth eruption and normal dentition development **[21].** In this study, none of the mutation in PTH1R is detected in family II, suggesting that the underlying mechanism of PFE still remains unclear. To further analyze the possible gene that may be related to PFE, a whole-exome sequencing needs to be carried out. The odontoblasts, periodontal ligament stem cells from extracted teeth from PFE patient and normal individuals can be collected and cultured under consent to figure out the mechanisms. Parathyroid Hormone Type I Receptor (PTH1R), is highly expressed in osteoblasts and renal tubular cells, which mediates a number of important biological processes, such as endochondral bone formation and plasma calcium levels. PTH1R is a critical gene during life cycle. Various autosomal dominant or recessive mutations in the PTH1R gene have been identified to be associated with different diseases, like Jansen's metaphyseal chondrodysplasia, Eiken syndrome, Blomstrand osteochondrodysplasia, and Ollier disease **[13-15].** PTH1R knockout mice usually die at mid-gestation. A complete loss of PTH1R function in human results in lethal Blomstrand chondrodysplasia (BOCD, OMIM #215045), characterized by advanced endochondral bone maturation and premature ossification of all skeletal elements. PTH1R can be activated by PTHrP, a paracrine hormone that also regulates epithelial-mesenchymal interactions in developing teeth. PTHrP cKO mice molars showed a delayed eruption, root malformation and defective formation of the inter-radicular bone **[24].** During tooth development, PTH1R is expressed both in the alveolar bone and in the adjacent dental mesenchyme **[25].** In our study, PTH1R is highly expressed in human odontoblasts and early stage of tooth germ, suggesting its pivotal role in tooth development. During tooth root formation and after tooth eruption, DFCs on the root surface robustly expressed PTH1R. PTH1R+ DFCs differentiate into PDLCs, alveolar cryptal bone osteoblasts, and cementoblasts in acellular cementum, which facilitates tooth formation and dentition development. However, insufficient studies have provided plausible explanations for the role of PTH1R in tooth defects or craniofacial development in PTH1R knockout mice as expected. A genetic diagnosis aimed at excluding or confirming the presence of pathogenic variants in the PTH1R gene should be carried out in every patient with suspected PFE to help confirm the diagnosis for further treatment planning. The traditional treatment like surgical intervention for PFE has resulted insufficient establishment of occlusion **[26].** Prosthetic approaches appear to be the most feasible option. However, it needs to be replaced frequently till children to grow into adults **[27]**. There are still several gaps in the comprehensive understanding of PFE pathogenesis and treatment plans. Orthodontic treatment appears to be a possible option to bring the teeth into

dentition. However, the continuous archwire in orthodontic treatment was convinced worsen posterior open bite **[20].** In this report, we underlined the importance of careful clinical examinations and radiographic studies to analyze the nature cause of tooth impairment. Moreover, we proved that the orthodontic treatment can be applied to create enough room for tooth eruption, giving an opportunity for children and teenagers to gain a functional dentition. Therefore, the early diagnosis and intervention of PFE are pivotal for tooth and dentition development. Considering the incomplete penetrance, as well as variable expressivity in the patients suffering from PFE, clinical examination and genetic diagnosis need to be fully considered in treatment planning **[28].** This case highlighted the utilization of conservative treatment options until a diagnosis was confirmed to minimize the risk of iatrogenic damage and unnecessary treatment. Along with the genetic diagnosis, appropriate intervention can be carried out or improved at the early stage, which may provide new insights into the pathological mechanisms of PFE.

Acknowledgments

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