

Review

# Phenotypes, Genotypes, and Treatment Options of Primary Failure of Eruption: A Narrative Review

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**Abstract:** Tooth eruption is a complex process, during which a series of factors can cause a failure of it. Among this, primary failure of eruption (PFE) is a non-syndromic condition that leads to an incomplete tooth eruption despite the presence of a clear eruption pathway. The aim of this narrative review is to provide an overall view about clinical considerations, genetics-related aspects, and possible treatments of PFE based on the latest findings. A literature search using the PubMed/Medline and Scopus database was performed. The search terms used were “PFE”, “orthodontics”, “primary failure of eruption”, and “treatment”, and all the articles, according to the inclusion criteria, from 2008 until June 2022 were screened. Among them, 12 articles were considered useful to highlight some of the main genotypical and phenotypical aspects and several treatment options. Indeed, if there is a suspicion of primary failure of eruption, a *PTH1R* screening should be performed, because a mutation in this gene is responsible for an altered balance between the resorptive and the appositional processes during the eruption. This is important to know before starting an orthodontic treatment because it could lead to ankylosis of the affected tooth, exposing patients to iatrogenic damage. Treatment options depend on the growth phase of the patient and on the clinical situation.

**Keywords:** PFE; tooth eruption; failure of eruption; eruption disorder



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## 1. Introduction

Tooth eruption is the movement of the tooth towards its functional position in the oral cavity, entering into contact with the opposing tooth of the upper or lower arch from its developmental site within the alveolar process [1]. Three factors contribute to this complex process: bone resorption, gingival resorption, and root elongation at the apex of the follicle [2].

This is a complex process in which the tooth follicle interacts with osteoclasts and osteoblasts [3,4]. The mononuclear cells that inflow into the coronal part of the tooth follicle are responsible for bone resorption [5]. Tooth eruption is known as a localized and genetically programmed process governed by time.

Both systemic and local factors can cause the failure of tooth eruption. When a systemic cause is involved, often the patient is affected by a systemic syndrome. In particular, the genetic disorders associated with tooth eruption failure are cleidocranial dysplasia, osteopetrosis, Rutherford syndrome, ectodermal dysplasia, and Down syndrome [6]. When the patient has one of these complex systemic diseases, many teeth are usually affected. Instead, when the responsible for the failure of eruption is a local factor, usually only single teeth are affected, mainly the upper canine [7] and the lower wisdom teeth [8]. The local factors that hinder the eruption can be the lack of space, tooth germ deformity, abnormal tooth germ position [9], or a physical barrier in the eruption pathway, such as an odontoma, supernumerary teeth, or cysts [6]. This condition is known as mechanical failure of eruption (MFE). In this case, there is a mechanical obstruction on the eruption pathway, whose removal can cause the resolution of the missing eruption [10].

Among the mechanisms of tooth eruption failure, it is important to cite the primary and the secondary retention. In the first case, a dental element, before the emergence in the oral cavity, ceases to erupt in absence of a mechanical obstruction. The secondary retention involves the unexplained cessation of further eruption after a tooth has penetrated the oral mucosa [8,11].

Primary failure of eruption (PFE) [12] is a condition in which non-ankylosed teeth fail to erupt, despite the presence of a clear eruption pathway. Alterations in the balance between the resorptive and the appositional processes during the eruption are the putative factors underlying the development of primary failure of eruption [13]. This condition is generally linked to the mutation of the parathyroid hormone 1 receptor gene (*PTH1R*) [13]. The reviewers decided to focus on the studies conducted from 2008 onwards because in this year articles about the connection between *PTH1R* mutation and PFE were published [14].

Despite several articles having been published in recent years, no review has been recently published that summarizes and organizes the most recent findings about the topic. Starting from the last reviews about PFE, this article has the task of summarizing the latest information based on the most recent research about the genetic bases of primary failure of eruption. Indeed, since the article of Hanisch et al. in 2018, several findings have been introduced, especially regarding the genotypical aspects by Grippaudo et al. in 2018 and 2021. These findings have also changed the clinical approach to PFE. According to this, the aim of the current review is to provide an updated overall view of PFE, from the epidemiology to the treatment going through clinical and genetical aspects.

Furthermore, the research underlines a lack of information about treatment options: further studies are needed to assess which is the best way to treat PFE patients.

## 2. Materials and Methods

A literature search of the PubMed/Medline and Scopus database, including all English language papers published after 2008 until June 2022, was performed. For the research, the terms used were as follows: "PFE", "Orthodontics", "Treatment", and "Primary failure of eruption". The keywords were combined in several ways: "PFE" AND "Treatment", "PFE" AND "Orthodontics", "Primary failure of eruption" AND "Orthodontics", etc.

The article types selected were systematic reviews, clinical research, clinical randomized studies, and observational studies. Case reports and case series were excluded by this study.

Two calibrated reviewers (FS and CS) independently conducted the search from April to June 2022 and identified 41 articles. After removing the duplicates, just 20 articles remained to be screened. According to the inclusion criteria, the authors examined the articles and removed every study with lower quality of evidence, such as case reports and case studies.

For the eligibility of inclusion, only 12 articles were selected and analyzed.

## 3. Results

The subjects of the 12 different articles included and discussed in the current narrative review have been summarized in Table 1. Ten out twelve articles discussed the genotypical aspects of PFE, eight out of twelve discussed phenotypes, five out of twelve discussed the epidemiological aspects, and only three out of twelve (25%) discussed the treatment options. To be more precise, Stellzig-Eisenhauer et al. (2013) [6], Milani et al. (2014) [15], Hanisch et al. (2018) [16], Tokavanich et al. (2020) [17], and Grippaudo et al. (2021) [10] provide a general view of the epidemiology of PFE. Each of the selected articles considers the genotypical aspects and the correlation between *PTH1R* mutation and primary failure of eruption except for the articles by Stellzig-Eisenhauer et al. (2013) [6] and Rizzo et al. (2020) [18]. Regarding the phenotypical aspects, Stellzig-Eisenhauer et al. (2013) [6], Izumida et al. (2020) [19], Tokavanich et al. (2020) [17], and Rizzo et al. (2020) [18] did not expose new findings about the clinical and phenotypical aspects of this complex pathology. Unfortunately, in the above mentioned studies, treatment options are not as well treated as every other aspect: only Milani et al. (2014) [15], Hanisch et al. (2018) [16], and Rizzo et al. (2020) [18] debate this topic.

#### 4. Discussion

As stated by Baccetti in 2000, primary failure of eruption is a rare disease with a prevalence of 0.06% [20]. Several published studies of different authors in several countries confirmed the abovementioned percentage [6,16]. On the other hand, the data about gender distribution are not unanimous: several studies confirm the findings of Baccetti's article, in which he reported a prevalence ratio of 1:2.25 (male:female) for PFE [20]. In contrast, Stellzig-Eisenhauer et al. [6], in the sample analyzed, found a 1:1.1 distribution between females and males. Maybe this difference could be related to the small size analyzed in the previously mentioned study. Considering the important contrast observed between these studies, further research is required to accurately assess the gender prevalence of PFE. In all the reported cases of the studies selected, only molars or molars and premolars were involved [21]. This observation could lead to the conclusion that only molars and premolars can be affected by PFE. Hanisch et al. [16] observed a prevalence of 64.1% for the bilateral distribution and a prevalence of 35.9% for the unilateral distribution. A prevalence for the unilateral distribution can be observed also in the impacted second molars [22]. On the other hand, in the article by Pilz et al. (2014), the ratio of bilateral versus unilateral PFE was 20:3. Pilz et al. stated that PFE is usually asymmetric, which means there is a bilaterally unbalanced eruption of the teeth. In other words, the presentation is more severe on one of the two sides [23]. The permanent dentition is more affected than the deciduous dentition [16]. This epidemiological difference can probably be explained by the small sample size of the abovementioned study. For this reason, further studies are needed to better examine the exact gender prevalence and the lateral or bilateral distribution.

There are different types of PFE [17]. In type 1, patients show a similar loss of eruption potential of all affected teeth, which leads to a progressively open bite extending from anterior to posterior. In the second type, the tooth distal to the furthest mesial involved tooth exhibits larger, but still inadequate, eruption potential. In Type 3, both forms appear in the various quadrants.

Proffit and Vig in 1981 [12] identified the following characteristics typical of PFE: involved teeth may initially erupt and then cease to erupt further or may fail to erupt entirely. Therefore, the non-eruption can be partial or complete. Posterior teeth are more commonly involved. Both primary and permanent teeth may be affected. Involved permanent teeth tend to become ankylosed. The application of orthodontic forces leads to ankylosis. The involvement may be unilateral or bilateral. The condition shows an absence of affected family members. Although several findings of Proffit and Vig's article can still be considered valid, the hereditary aspect has been revised. Indeed, many recently published studies have found an important familial-based aspect for this condition.

Hanisch et al. in their review [16] found that 84.1% of the patients of their sample had family members that reported having had PFE. In fact, patients with PFE revealed a mutation in the parathyroid hormone 1 receptor gene (*PTH1R*) that is transmitted by autosomal dominant inheritance [14]. This mutation is transmitted with an incomplete penetrance [21]. This gene encodes a member of the G-protein coupled receptor, and it is a receptor for parathyroid hormone (PTH). Normally, the PTH receptor is expressed in bone tissue on the surface of the osteoblast. A key function of PTH is the regulation of calcium metabolism [24]. After the activation of the receptor, the osteoclasts are stimulated to increase bone resorption, allowing tooth eruption. Other variants in *PTH1R* have also been associated with Jansen chondrodysplasia and Ollier enchondromatosis. These conditions are characterized by abnormal skeletal development [25]. PFE is now the fifth disease to be associated with mutations in the *PTH1R* gene [6]. Grippaudo et al. have hypothesized that the PFE phenotype could also be the result of a dose-dependent inactivation of *PTH1R* [2]. Considering the heritability of this condition, it is important to do an evaluation of the patient's family history through interviews. After that, it is helpful to analyze the *PTH1R* gene before planning the treatment. In 2021, Grippaudo et al. [10], through saliva samples, examined a cohort of patients that demonstrated clinical signs of PFE. DNA was extracted from saliva and subjected to PCR and sequencing. Some of the patients analyzed were

genetically identified as carriers of variants of the *PTH1R* gene, while in others no variants were found. Through molecular analysis, they found 14 different variants. To be more specific, there were nine exonic *PTH1R* variants that had different effects on the protein structure. Above these there were a nonsense variant, a frameshift variant and missense variants. In patients with *PTH1R* variants that alter the protein structure, they found that the open bite is more severe and that Type 1 PFE is more frequently associated with a bilateral manifestation. On the other hand, not all the patients with an intronic variant had typical PFE. Other patients that did not demonstrate the presence of a *PTH1R* variant showed a less defined phenotype, sometimes limited to the involvement of a single tooth when compared to *PTH1R*-positive patients. According to this study, the typical traits of PFE are more often present in patients with pathogenic variants of the *PTH1R* gene. In addition, a patient who has signs of PFE may not have variants of the *PTH1R* gene. Furthermore, in their functional analysis of *PTH1R* variants [19], Izumida et al. showed that amino acid substitutions found in *PTH1R* from a patient with PFE lowered the responsiveness of the cells to PTH. These differences might have effects on the functions of osteoblasts and osteocytes. In fact, as said before, alterations in the balance between the resorptive and the appositional processes during the eruption are the putative factors underlying the development of PFE.

In addition to the clinical features of the PFE exposed by Proffit, subsequent articles reported that in patients with this condition, if an anterior tooth is affected, the posterior teeth are also affected; affected teeth resorb the alveolar bone coronal but do not erupt totally or erupt incomplete [23]; the growth of the alveolar process is impaired in the affected areas (in fact, the affected teeth appear at the base of a large vertical defect) [6]; a severe lateral open bite, unilateral or bilateral, is present [16]; and the affected molars show roots with dilacerations and truncation [17].

Regarding the possible treatment options for PFE, it is important to highlight that a dental element with PFE, if subjected to an orthodontic force, becomes ankylosed before achieving occlusion [12,13,26]. Considering this, treatment options are extremely limited. Before starting a treatment on these elements, it is important to wait until the end of the vertical growth of the patient. The treatment may be different considering the severity of the non-eruption. In particular, in patients that show a mild severity, the best option is a conservative restoration, for example, through onlays or crowns in order to close the open bite [15]. Instead, when the case is moderately severe, treatment options may include extraction or surgical removal of the teeth and subsequent implantation or orthodontic space closure. Another option is the segmental osteotomy to place in occlusion the element; in this case, all the segments involved are repositioned. Roulias et al. stated that when more than one tooth is affected, this type of treatment increases the chance of success [27]. If this is not possible, often a removable prosthesis is the only solution.

**Table 1.** Lists of the articles reviewed, with the subject of their main findings, type of article, and sample size. (Letter U = Unspecified).

Article	Epidemiology	Genotype	Phenotype	Treatment	Type of Article	Sample Size
Decker et al. (2008) [14]		✓	✓		Clinical research	15
Frazier-Bowers (2010) [24]		✓	✓		Clinical research	12
Stellzig-Eisenhauer et al. (2013) [6]	✓	✓			Clinical research	15
Frazier-Bowers et al. (2014) [21]		✓	✓		Clinical study	54
Milani et al. (2014) [15]	✓		✓	✓	Review	U
Pilz et al. (2014) [23]		✓	✓		Clinical research	36
Hanisch et al. (2018) [16]	✓	✓	✓	✓	Systematic review	314
Grippaudo et al. (2018) [2]		✓	✓		Clinical research	29
Izumida et al. (2020) [19]		✓			Clinical research	U
Tokavanich et al. (2020) [17]	✓	✓			In vivo animal study	U
Rizzo et al. (2020) [18]				✓	Review	U
Grippaudo et al. (2021) [10]	✓	✓	✓		Clinical research	38

## 5. Conclusions

To summarize, most of the analyzed articles agree on the importance of a differential diagnosis between PFE and other possible mechanisms, such as MFE or ankylosis [18], when a failure in a tooth eruption is observed, in the absence of systemic disorders. Considering the relevance of the genetic aspects that were exposed in this review, a *PTH1R* screening can be helpful to understand the reason of the non-eruption in order to choose the best treatment prior to any orthodontic treatment to avoid the ankylosis and avoid unnecessary and long-lasting therapies for patients that result in failure and expose them to iatrogenic damage. On the other hand, the research underlines a lack of information about treatment options: further studies are needed to assess which is the best way to treat PFE patients. Thus far, every treatment plan must be evaluated individually.

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## References

- Schour, I.; Massler, M. Studies In Tooth Development: The Growth Pattern Of Human Teeth Part II. *J. Am. Dent. Assoc.* **1940**, *27*, 1918–1931. [[CrossRef](#)]
- Grippaudo, C.; Cafiero, C.; D’Apolito, I.; Ricci, B.; Frazier-Bowers, S.A. Primary Failure of Eruption: Clinical and Genetic Findings in the Mixed Dentition. *Angle Orthod.* **2018**, *88*, 275–282. [[CrossRef](#)] [[PubMed](#)]
- Wise, G.E.; King, G.J. Mechanisms of Tooth Eruption and Orthodontic Tooth Movement. *J. Dent. Res.* **2008**, *87*, 414–434. [[CrossRef](#)] [[PubMed](#)]
- Ono, W.; Sakagami, N.; Nishimori, S.; Ono, N.; Kronenberg, H.M. Parathyroid Hormone Receptor Signalling in Osterix-Expressing Mesenchymal Progenitors Is Essential for Tooth Root Formation. *Nat. Commun.* **2016**, *7*, 11277. [[CrossRef](#)]
- Marks, S.C.; Cahill, D.R.; Wise, G.E. The Cytology of the Dental Follicle and Adjacent Alveolar Bone during Tooth Eruption in the Dog. *Am. J. Anat.* **1983**, *168*, 277–289. [[CrossRef](#)] [[PubMed](#)]
- Stellzig-Eisenhauer, A.; Decker, E.; Meyer-Marcotty, P.; Rau, C.; Fiebig, B.S.; Kress, W.; Saar, K.; Rüschen-dorf, F.; Hubner, N.; Grimm, T.; et al. Primary failure of eruption (PFE). Clinical and molecular genetics analysis. *Orthod. Fr.* **2013**, *84*, 241–250. [[CrossRef](#)]
- Impellizzeri, A.; Palaia, G.; Horodyski, M.; Pergolini, D.; Vernucci, R.A.; Romeo, U.; Galluccio, G. Co2 laser for surgical exposure of impacted palatally canines. *Dent. Cadmos* **2020**, *88*, 122–126. [[CrossRef](#)]
- Raghoobar, G.M.; Boering, G.; Vissink, A.; Stegenga, B. Eruption Disturbances of Permanent Molars: A Review. *J. Oral Pathol. Med. Off. Publ. Int. Assoc. Oral Pathol. Am. Acad. Oral Pathol.* **1991**, *20*, 159–166. [[CrossRef](#)]
- Alligri, A.; Putrino, A.; Cassetta, M.; Silvestri, A.; Barbato, E.; Galluccio, G. The Mandibular Permanent Second Molars and Their Risk of Impaction: A Retrospective Study. *Eur. J. Paediatr. Dent. Off. J. Eur. Acad. Paediatr. Dent.* **2015**, *16*, 246–250.
- Grippaudo, C.; D’Apolito, I.; Cafiero, C.; Re, A.; Chiurazzi, P.; Frazier-Bowers, S.A. Validating Clinical Characteristic of Primary Failure of Eruption (PFE) Associated with PTH1R Variants. *Prog. Orthod.* **2021**, *22*, 43. [[CrossRef](#)]
- Raghoobar, G.M.; Boering, G.; Vissink, A. Clinical, Radiographic and Histological Characteristics of Secondary Retention of Permanent Molars. *J. Dent.* **1991**, *19*, 164–170. [[CrossRef](#)]
- Proffit, W.R.; Vig, K.W. Primary Failure of Eruption: A Possible Cause of Posterior Open-Bite. *Am. J. Orthod.* **1981**, *80*, 173–190. [[CrossRef](#)]
- Frazier-Bowers, S.A.; Puranik, C.P.; Mahaney, M.C. The Etiology of Eruption Disorders—Further Evidence of a “Genetic Paradigm”. *Semin. Orthod.* **2010**, *16*, 180–185. [[CrossRef](#)] [[PubMed](#)]
- Decker, E.; Stellzig-Eisenhauer, A.; Fiebig, B.S.; Rau, C.; Kress, W.; Saar, K.; Rüschen-dorf, F.; Hubner, N.; Grimm, T.; Weber, B.H.F. PTHR1 Loss-of-Function Mutations in Familial, Nonsyndromic Primary Failure of Tooth Eruption. *Am. J. Hum. Genet.* **2008**, *83*, 781–786. [[CrossRef](#)] [[PubMed](#)]
- Milani, M.S.; Kuijpers, M.A.R. Primary failure of eruption: Diagnostics, treatment, casus and review of literature. *Ned. Tijdschr. Tandheelkd.* **2014**, *121*, 227–232. [[CrossRef](#)]

16. Hanisch, M.; Hanisch, L.; Kleinheinz, J.; Jung, S. Primary Failure of Eruption (PFE): A Systematic Review. *Head Face Med.* **2018**, *14*, 5. [[CrossRef](#)]
17. Tokavanich, N.; Gupta, A.; Nagata, M.; Takahashi, A.; Matsushita, Y.; Yatabe, M.; Ruellas, A.; Cevidanes, L.; Maki, K.; Yamaguchi, T.; et al. A Three-Dimensional Analysis of Primary Failure of Eruption in Humans and Mice. *Oral Dis.* **2020**, *26*, 391–400. [[CrossRef](#)]
18. Rizzo, M.; Colard, T.; Bocquet, E.; Leverd, C. Primary failure of eruption: Combined vision between paediatric dentist and orthodontist. *Orthod. Fr.* **2020**, *91*, 47–55. [[CrossRef](#)]
19. Izumida, E.; Suzawa, T.; Miyamoto, Y.; Yamada, A.; Otsu, M.; Saito, T.; Yamaguchi, T.; Nishimura, K.; Ohtaka, M.; Nakanishi, M.; et al. Functional Analysis of PTH1R Variants Found in Primary Failure of Eruption. *J. Dent. Res.* **2020**, *99*, 429–436. [[CrossRef](#)]
20. Baccetti, T. Tooth Anomalies Associated with Failure of Eruption of First and Second Permanent Molars. *Am. J. Orthod. Dentofac. Orthop. Off. Publ. Am. Assoc. Orthod. Its Const. Soc. Am. Board Orthod.* **2000**, *118*, 608–610. [[CrossRef](#)]
21. Frazier-Bowers, S.A.; Hendricks, H.M.; Wright, J.T.; Lee, J.; Long, K.; Dibble, C.F.; Bencharit, S. Novel Mutations in PTH1R Associated with Primary Failure of Eruption and Osteoarthritis. *J. Dent. Res.* **2014**, *93*, 134–139. [[CrossRef](#)] [[PubMed](#)]
22. Calasso, S.; Cassetta, M.; Galluccio, G.; Barbato, E. Impacted lower second molars. *Dent. Cadmos* **2008**, *76*, 41–54.
23. Pilz, P.; Meyer-Marcotty, P.; Eigenthaler, M.; Roth, H.; Weber, B.H.F.; Stellzig-Eisenhauer, A. Differential Diagnosis of Primary Failure of Eruption (PFE) with and without Evidence of Pathogenic Mutations in the PTHR1 Gene. *J. Orofac. Orthop. Fortschr. Kieferorthop.* **2014**, *75*, 226–239. [[CrossRef](#)]
24. Frazier-Bowers, S.A.; Simmons, D.; Wright, J.T.; Proffit, W.R.; Ackerman, J.L. Primary Failure of Eruption and PTH1R: The Importance of a Genetic Diagnosis for Orthodontic Treatment Planning. *Am. J. Orthod. Dentofac. Orthop. Off. Publ. Am. Assoc. Orthod. Its Const. Soc. Am. Board Orthod.* **2010**, *137*, 160.e1–160.e7; discussion 160–161. [[CrossRef](#)] [[PubMed](#)]
25. Schipani, E.; Kruse, K.; Jüppner, H. A Constitutively Active Mutant PTH-PTHrP Receptor in Jansen-Type Metaphyseal Chondrodysplasia. *Science* **1995**, *268*, 98–100. [[CrossRef](#)]
26. O’Connell, A.C.; Torske, K.R. Primary Failure of Tooth Eruption A Unique Case. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodontology.* **1999**, *87*, 714–720. [[CrossRef](#)]
27. Roulias, P.; Kalantzis, N.; Doukaki, D.; Pachiou, A.; Karamesinis, K.; Damanakis, G.; Gizani, S.; Tsolakis, A.I. Teeth Eruption Disorders: A Critical Review. *Children* **2022**, *9*, 771. [[CrossRef](#)]