Establishing the diagnostic criteria for eruption disorders based on genetic and clinical data

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Introduction: Proper diagnosis and management of eruption disturbances remains challenging but is critical to a functional occlusion. The objective of this study was to establish definitive criteria to differentiate and diagnose eruption disorders, specifically primary failure of eruption (PFE) and ankylosis. **Methods:** Sixty-four affected persons were placed into 3 cohorts: PFE diagnosed through confirmed *PTH1R* mutation (n = 11), PFE diagnosed based on clinical criteria (n = 47), and ankylosis diagnosed based on clinical criteria (n = 6). These groups were assessed to identify clinical features that differentiate PFE and ankylosis. **Results:** Ninety-three percent of the subjects in the genetic and clinical PFE cohorts combined (n = 58) and 100% in the genetic PFE cohort had at least 1 infraoccluded first permanent molar. Additionally, a novel functional *PTH1R* mutation, 1092delG, was identified and linked to PFE in the deciduous dentition. **Conclusions:** An infraoccluded, supracrestal first molar is a hallmark of PFE, often involving both arches in the permanent or deciduous dentition, and with unilateral or bilateral affection, infraoccluded second premolar or second molar, and multiple affected adjacent teeth. Our results further suggest that PFE and ankylosis might be clinically indistinguishable without knowledge of prior trauma, treatment history, genetic information, or obliteration of the periodontal ligament space. (Am J Orthod Dentofacial Orthop 2013;144:194-202)

The process of eruption in the human dentition is complex and poorly understood. Although advances in molecular biology have increased our understanding of the mechanisms underlying dental eruption, the clinical correlations remain elusive. Consequently, our understanding of eruption is based on multiple, yet differing, theories that are both controversial and ill-supported. Eruption disorders therefore create a rare and unique diagnostic challenge for general dentists seeking to monitor the dental development of their patients, but it is particularly complex for orthodontists and pediatric dentists who must manage these patients. The gestalt of this challenge is a lack of definitive clinical diagnostic criteria to distinguish between different types of eruption disorders and differentiate them from idiopathic delayed dental development.

Disturbances in dental eruption can occur for many reasons. Among these are 2 clinical problems that form the central basis of this article: primary failure of eruption (PFE; OMIM: 125350) and ankylosis. Ankylosis is histologically defined as the fusion of cementum to bone in at least 1 area lacking a periodontal ligament space.[1,2] The resultant occlusion has a tooth that ceases to erupt, drift, or move despite normal adolescent growth or orthodontic traction. In contrast to ankylosis, PFE does not include fusion of the cementum to the bone but is marked by a disturbance in the eruption mechanism itself, causing a nonankylosed tooth to fail to fully or partially erupt.[3] Surgeons extracting teeth diagnosed as PFE have noted that the tooth is mobile in the socket, further differentiating these teeth from ankylosed teeth[3] (Tim Turvey, personal communication, December 3, 2012). PFE was initially described based on its clinical appearance. This description of PFE is the most comprehensive diagnostic indicator to date and includes the following features: it primarily affects posterior teeth; it affects all teeth posterior to the most anteriorly affected tooth; the occlusion manifests as

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a lateral open bite; and the teeth do not respond favorably to orthodontic forces.[3] A common clinical dilemma is distinguishing PFE from ankylosis—mainly because the disorders have a similar clinical appearance and developmental fate. There is some evidence that PFE is often misdiagnosed as ankylosis.[4,5] It is important, however, to recognize that ankylosis and PFE dictate distinct treatment modalities, and inaccurate diagnosis could significantly alter the treatment success. The misdiagnosis and mismanagement of either eruption disorder could result in inappropriate and extended treatment, significant financial burdens, patient frustration, and an inferior occlusal condition.

The fact remains that PFE is a rare, yet handicapping, disorder in which the treatment options are unclear and unpredictable. The few current treatment options to improve the occlusion of a patient with PFE include small segmental osteotomies and prosthetic restoration of the occlusion.[3,6] However, no treatment or limited esthetic treatment is often the best option because orthodontic treatment with a continuous archwire, even after extracting the most severely affected teeth, results in exacerbation of the lateral open bite by intrusion of the adjacent teeth and, frequently, ankylosis of the affected teeth.[3-5] This is in contrast to ankylosis, which can be successfully treated by extraction of the ankylosed tooth and subsequent orthodontic movement of all other teeth. Thus, misdiagnosis of PFE and treatment with a continuous archwire can actually lead to an inferior occlusal result, providing a significant disservice to the patient.

It is expected that the uncertainty surrounding an eruption-disorder diagnosis will diminish with the increasing application of genetic analysis in this field. Unlike the limited clinical indicators discussed above, genetic analysis of specific genes offers an objective measure of the presence of pathology. Recent studies have shown that a genetic mutation in the *PTH1R* gene (associated with bone homeostasis) is also associated with PFE. The mutation is present in multiple members of some families who exhibit PFE.[5,7-9] It has previously been reported that 10% to 40% of PFE cases are familial,[3,6,9,10] and we expect that this estimate will increase as more is learned about the genetic makeup of patients diagnosed with PFE. The potential for a genetic diagnosis of PFE or other dental disorder is a huge step forward in establishing a definitive and objective diagnosis of PFE in patients with clinical characteristics of the disorder. Although genetic "testing" is not currently available for use in clinical practice for most dental disorders, it is in the early phases of development in the diagnosis of PFE and could be a chairside diagnostic test in the future. Logical first steps in developing this diagnostic rubric are to document and then associate the clinical features of PFE with the associated genetic mutations.

In this study, we sought to take advantage of a unique data set to establish the clinical diagnostic criteria that distinguish PFE from other eruption disorders, particularly ankylosis. The combination of objective genetic information and clinical data from affected persons can be used to establish a genotype-phenotype correlation for PFE and, by extension, an objective diagnosis: ie, determined by associating clinical (phenotypic) features with genetic (genotypic) analysis. We therefore compared clinical features identified in the genetically characterized sample to a broader data set of patients diagnosed with PFE based on clinical parameters only. The resultant developmental and morphologic features identified in patients with obvious clinical characteristics of PFE and harboring a genetic mutation in *PTH1R* will represent a hallmark of the condition, giving clinicians greater diagnostic certainty and subsequent improved clinical management.

MATERIAL AND METHODS

A data set of 64 patients with eruption disorders was collected at the University of North Carolina over several years. This group consisted of patients of the Graduate Orthodontic Clinic, Faculty Practice, and various private practices (sent for consultation and recommendations from faculty at the University of North Carolina). After phenotypic review using radiographs or clinical photos, we placed these patients into 3 categories: those definitively diagnosed with PFE through genetic analysis that showed a mutation in *PTH1R* (n = 11; genetic PFE cohort), patients diagnosed with PFE based on clinical records alone (n = 47; clinical PFE cohort), and patients diagnosed with ankylosis based on clinical criteria (n = 6; clinical ankylosis cohort). All records were evaluated by the 3 authors, and agreement in diagnosis and feature identification was confirmed for all subjects. Those in the ankylosis cohort had a confirmed history of trauma or were treated with extraction of the affected tooth or teeth and had successful orthodontic treatment of the remaining teeth. All other subjects were diagnosed with PFE based on clinician acumen, history of unsuccessful orthodontic treatment, or genetic analysis.

Of the 58 subjects diagnosed with PFE, 27 underwent genetic (mutational) analysis (previously described); a mutation or polymorphism in *PTH1R* was identified in 11 patients, and an unclassified nonfunctional single nucleotide polymorphism in *PTH1R* was identified in the remaining 16. These 11 subjects comprised the genetic PFE cohort, and those with single nucleotide polymorphisms were grouped into the clinical PFE

cohort. Mutational analysis was performed as follows: DNA was extracted and purified from salivary samples (Oragene; DNA Genotek, Toronto, Ontario, Canada). All coding regions of *PTH1R* (exons 3-16) were amplified and sequenced using previously described primer sets.[8] Splice junctions were included in the sequencing results using primer sets designed to delineate regions that included a minimum of 25 bases on the intron sequence, in addition to the exon sequences. The amplification of sequences was performed with HotStart polymerase chain reaction MasterMix (GE Healthcare Life Sciences, Piscataway, NJ) under the following conditions: 10 minutes at 95°C activation or premelt, followed by 35 cycles of 30 seconds at 94°C melt, 30 seconds at 60°C anneal, and 3 minutes at 72°C extension. The polymerase chain reaction products were purified with Exosapit (Affymetrix, Santa Clara, Calif) and sequenced at the University of North Carolina's genome analysis core facility. All sequences were compared with a wild type of *PTH1R* (accession NM_000316.2) from GenBank release GRCh37 using the BLAST algorithm.

Clinical (phenotypic) information was reviewed for all 3 cohorts to assess the subjects' clinical features. The records assessed included a minimum of a panoramic radiograph for every patient, and cephalometric radiographs, intraoral periapical radiographs, and clinical photographs were used when available. The following information was gathered for the 3 cohorts: (1) unilateral or bilateral presentation of infraoccluded teeth; (2) arch involved (affected teeth in the maxilla, mandible, or both); (3) teeth with infraocclusion (at least 1 premolar, first molar, and second molar); (4) location of affected teeth in the alveolar ridge (supracrestal or infracrestal), and third molars were excluded from evaluation, as were second molars in young patients who would not be expected to have second molars erupted according to normal dental eruption timing; (5) presence or absence of root anomalies, including descriptions; (6) presence or absence of any other abnormal or noteworthy findings, including specific descriptions; and (7) record types provided.

Additionally, the following information was included when available and applicable: (1) PFE type I or II (determined by the degree of eruption of the second molars, as discussed below); (2) age; and (3) Class III dental or skeletal relationship (determined by high-quality clinical photos or cephalometric radiographs that clearly showed the skeletal Class III relationship; patients lacking these records were classified as indeterminable).

For the clinical and genetic PFE cohorts, the classification of PFE was recorded as type I or II as previously described in the literature.[7,10] These types are distinguished based on the timing of onset and the presentation. Briefly, type I PFE is characterized by a progressive posterior open bite, in which all teeth distal to the most mesial infraoccluded tooth are affected and do not erupt into occlusion. Those with type II PFE exhibit greater eruption potential, although still inadequate, for the more distal teeth, such as second molars. Comparison of the eruption disorders based on the 3 cohorts was completed to identify similar and distinguishing characteristics. The genetic PFE cohort provides an objective basis to classify the associated clinical features. Therefore, the following comparisons were made: clinical features of the genetic PFE cohort with the clinical PFE and clinical ankylosis cohorts based on the attributes listed above.

RESULTS

Twenty-four of the 58 PFE patients had age information available. The average age of the patients in this data set for which age was recorded was 12 years 9 months (range, 6 years 2 months-18 years 4 months).

Previously identified mutations in the *PTH1R* gene in addition to a novel mutation in *PTH1R* (1092delG, which results in a frameshift and premature termination of the *PTH1R* protein) formed the basis of the genetic cohort. This novel mutation, associated with the clinical finding of infraoccluded deciduous teeth, was discovered in a small nuclear family (n = 2). The index case was a boy, 7 years 9 months of age, with PFE affection of the permanent and deciduous teeth in the form of a right lateral posterior open bite and a mild Class III skeletal malocclusion (Fig 1).

We evaluated a subset of patients with eruption failure that included both clinical and genetic data to establish a genotype-phenotype correlation. The Table summarizes the numbers and percentages of patients in our entire sample (n = 64) who had various clinical features. Specifically, the genetic cohort (n = 11) was examined for clinical characteristics of PFE. Since the subjects in the genetic cohort had a confirmed mutation in *PTH1R*, the hallmark features consistent with PFE are outlined based on this data set. Our phenotypic analysis primarily using radiographs and clinical photographs showed the following.

Six of the 11 patients in the genetic cohort had affected teeth unilaterally, and 5 had bilateral infraoccluded teeth. Most patients (10 of 11; 90.2%) had infraoccluded teeth in both the maxilla and the mandible. One patient had affected teeth in the mandible only. At least 1 premolar was affected in 8 of the 11 (72.7%) patients, and at least 1 second molar was severely affected in 7 of the 11 (63.6%) patients.

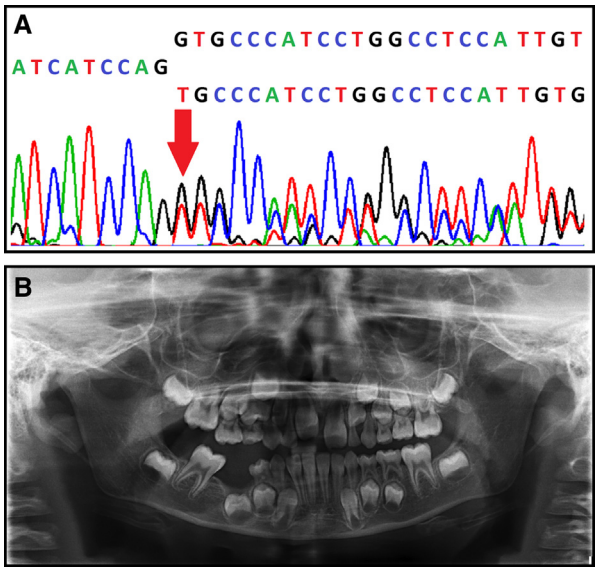

Fig 1. A, Chromatogram demonstrates a familial 1092 G deletion in the *PTH1R* gene linked to infraocclusion of deciduous teeth in an affected child; **B,** panoramic radiograph illustrating involvement of both deciduous and permanent teeth in a patient with a 1092 G deletion in *PTH1R*.

This, however, might be an underestimation because of the early dental age of some patients, prohibiting the second molar's eruption potential from being truly evaluated. Of particular significance is the finding that all patients had an affected first permanent molar. One subject in the mixed dentition had all deciduous molars on the right side affected. The affected teeth in each dental quadrant were adjacent to one another.

In the genetic PFE cohort, all patients had a supracrestal presentation of the affected teeth. Supracrestal was defined by a completely cleared eruption pathway, with no alveolar bone occlusal to the affected tooth. No patient in this group had exclusively infracrestal affected teeth, although 2 had an ectopically placed second molar that remained infracrestal (excluding the second and third molars when age and developmental status precluded their eruption). Furthermore, 4 of the 11 subjects had characteristics of type I PFE, in which the second molar was at least as severely affected as the first permanent molar. Six of the 11 had type II PFE, in which the second molar retained more eruptive capability than the first molar, although still remaining infraoccluded. One subject was indeterminable because of an early dental developmental age without eruption of the second molar at the time of records.

We also investigated the presence or absence of simultaneous notable dental features. Class III malocclusion or skeletal patterns were noted in 7 of the 11 (64%) patients. One patient did not have adequate records to judge the Angle classification or skeletal pattern. Dilacerated roots were observed in 1 patient. Finally, 4 of these 11 (36%) patients had at least 1 other dental anomaly, including impacted teeth (n = 3) and infraoccluded, overretained deciduous teeth (n = 2). Figures 2 and 3 give an example of a patient in the genetic cohort illustrating many hallmark features of PFE.

In the clinical PFE cohort (n = 47), most of the patients that we reviewed exhibited PFE bilaterally (26 of 47; 55%). Of the remaining subjects with unilateral presentation, 10 were only on the left, and 11 were only on the right. PFE most often presents as infraoccluded teeth in both arches (33 of 47; 70%). In our sample, however, 5 patients had features of PFE only in the mandibular arch, and 9 had affected teeth only in the maxillary arch. Essentially, all affected teeth were supracrestal, despite being infraoccluded (40 of 47; 85%). As previously noted, we excluded the second and third molars when age and developmental status precluded their eruption. Importantly, the first molar was always supracrestal, demonstrating either a notable clear eruption pathway through the bone or, most often, supragingivally yet below the plane of occlusion.

At least 1 first permanent molar was affected in 43 of 47 subjects (91%) in the clinical PFE cohort. Furthermore, a second permanent molar (31 or 66%) and at least 1 premolar (30; 64%) were frequently affected. In all 10 patients in the mixed dentition, at least 1 deciduous tooth was affected. Teeth as far anterior as the canine were affected in many patients, and all affected teeth in each quadrant were adjacent to one another. Twenty-five of 47 (53%) of the clinical PFE patients had PFE type I, and 13 (28%) patients exhibited PFE type II. For the remaining 9 subjects, the classification of PFE was indeterminable, primarily because of inadequate dental development or dental age at the time of records.

Other dental features noted in the clinical PFE cohort included alterations in root morphology, notably blunted or dilacerated roots (n = 10; 21%) and a remarkable prevalence of cosegregating dental anomalies such as missing teeth (3 second premolars, 1 maxillary lateral incisor), delayed eruption of multiple teeth (n = 6), impacted teeth (n = 7), and transposition of 2 teeth (n = 2). A high prevalence of Class III malocclusion was also noted in this cohort, with 11 of the 47 (23%) patients demonstrating a Class III dental, and often skeletal, relationship. The classification could not be determined for 21 patients because of inadequate records.

Table. Descriptive characteristics of the 3 cohorts

	PFE (genetic) (n = 11)		*PFE (clinical) (n = 47)*		*Ankylosis (n = 6)*	
	n	*%*	*n*	*%*	*n*	*%*
Symmetry						
Unilateral	6	54.5	21	44.7	5	83.3
Bilateral	5	45.5	26	55.3	1	16.7
Arch involved						
Maxilla	0	0.0	9	19.1	2	33.3
Mandible	1	9.1	5	10.6	4	66.7
Both	10	90.9	33	70.2	0	0.0
Teeth involved						
At least 1 premolar	8	72.7	30	63.8	0	0.0
First permanent molar	11	100.0	43	91.5	6	100.0
Second permanent molar	7	63.6	31	66.0	0	0.0
Location in alveolar ridge						
Supracrestal	11	100.0	40	85.1	5	83.3
Infracrestal	0	0.0	2	4.3	1	16.7
Both	0	0.0	5	10.6	0	0.0
PFE classification						
Type I	4	36.4	25	53.2	NA	NA
Type II	6	54.5	13	27.7	NA	NA
Indeterminable	1	9.1	9	19.1	NA	NA
Mutation type						
Intronic–substitution	4	36.3	NA	NA	NA	NA
Coding–substitution	2	18.2	NA	NA	NA	NA
Coding–insertion (frameshift)	3	27.3	NA	NA	NA	NA
Coding–deletion (frameshift)	2	18.2	NA	NA	NA	NA
Coding–nonfunctional SNP	0	0.0	16	34.0	NA	NA
Angle Class III	7	63.6	11	23.4	3	50.0
Dilacerated or blunted roots	1	9.1	10	21.3	2	33.3
Other dental anomaly	4	36.4	16	34.0	2	33.3

The first cohort was a group of PFE patients who underwent genetic analysis to confirm that they harbor a mutation in *PTH1R*; the second is a group of patients diagnosed with PFE through clinical assessment; the third is a small group of patients diagnosed with ankylosis through clinical assessment.
NA, Not applicable; *SNP*, single nucleotide polymorphism.

The clinical ankylosis cohort (n = 6) had a mean age of 10 years 1 month. Most cases were unilateral, with only 1 subject having bilaterally affected teeth. Additionally, the affected teeth were confined to 1 arch in every patient. The affected tooth or teeth were in the maxilla in 2 patients and in the mandible in 4 patients. All affected teeth were first permanent molars. With the exception of 1 subject with bilateral presentation (affecting both maxillary first permanent molars), all others had 1 affected tooth. Similarly to the teeth affected by PFE, all but 1 tooth in this group were supracrestal. Other dental features also prevalent in this patient cohort included Class III malocclusion (n = 3), missing second premolars (n = 2), blunted roots (n = 1), and ectopic canines (n = 1).

DISCUSSION

The available information and technology that can be used for accurate diagnosis of eruption disorders are severely lacking, hindering the ability of clinicians to make the best treatment decisions for their patients. Although definitive and objective diagnosis through genetic analysis might one day be the gold standard, the research on this front is in the nascent stages of development. However, with rapid progress being made in "personalized medicine," the clinical applicability of genetic testing for practicing orthodontists is likely soon. The establishment of definitive clinical criteria to aid in the diagnosis of eruption disorders is critical now.

In this study, we evaluated the clinical phenotype of patients in a genetic PFE cohort with a functional mutation in the *PTH1R* gene. Previous studies have shown that PFE is a progressive lateral open bite unable to be eliminated through orthodontic traction and often has an associated familial mutation in the *PTH1R* gene.[3-5,7,8,10,11] The genotype-phenotype correlation presented here was based on the genetic cohort and showed that specific phenotypic characteristics are the hallmarks of PFE, since all affected patients possess these features. These include involvement of the first

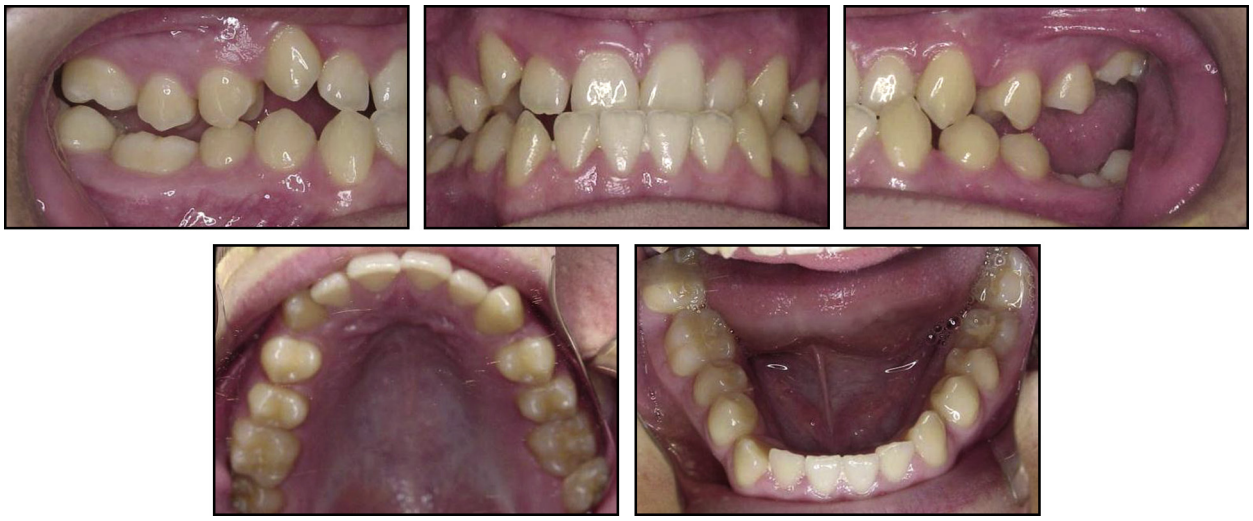

Fig 2. Clinical photos of a patient in the genetic cohort.

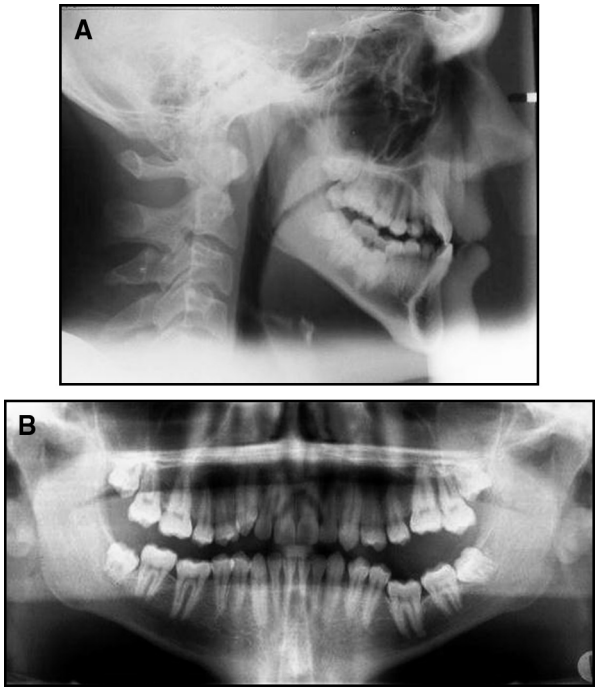

Fig 3. A, Cephalometric radiograph demonstrating a Class III skeletal and dental pattern; **B,** panoramic radiograph demonstrating type II PFE with posterior open bite on the left side in the affected patient in which the second molar has maintained more eruptive potential than the first molar, and the mandibular right first permanent molar is also affected.

permanent molar and supracrestal presentation of the affected teeth. Although a posterior lateral open bite is a diagnostic feature of PFE, there are alternative documented causes of a lateral open bite, such as mechanical failure of eruption (ie, unleveled curve of Spee or lateral tongue thrust) or a skeletal discrepancy (particularly a progressive mandibular asymmetry).[12] These patients can typically be successfully treated with orthodontic mechanics or orthognathic surgery. Therefore, these causes of a lateral open bite must be ruled out before consideration of a PFE diagnosis. After eliminating the likelihood of mechanical failure of eruption or a skeletal discrepancy, a lateral open bite remains a key diagnostic feature of PFE. Nonetheless, a comparison between patients with a mutation in the *PTH1R* gene and those who have not yet been genetically assessed provides an additional objective measure (infraoccluded first molar) that can be applied to the clinical diagnostic regimen.

Moreover, through our genetic analysis procedure, we found that the presence of a familial 1092delG mutation in *PTH1R* is associated with affection of the deciduous teeth. This novel functional mutation has been found in 2 family members, one of whom is currently in the mixed dentition. This finding is the first report of a *PTH1R* mutation and affection of deciduous teeth.

Since this was a retrospective study, we could not complete the genetic analysis of every subject. This is a potential limitation of the study because it resulted in fewer patients (11) with a confirmed mutation in *PTH1R*. However, when the genetic and clinical PFE cohorts were compared, no striking variations were noted between their clinical features. Thus, we contend that the genetic and clinical PFE cohorts for practical purposes can be analyzed as 1 group, since the absence

of a mutation in *PTH1R* does not rule out PFE, but a mutation confirms a diagnosis of PFE. The absence of a *PTH1R* mutation in these patients with clinical PFE underscores the fact that at least 1 other gene is probably responsible for PFE. Additionally, of the patients who underwent genetic analysis, 16 harbored nonfunctional single nucleotide polymorphisms whose role in the eruption disorder is uncertain at this time. We therefore concluded that PFE is a complex disorder that is most likely the outcome of genetic alterations in many genes and disturbances in various molecular pathways.

The most striking feature of PFE in our genetic cohort was that the first permanent molar was always involved. This hallmark feature was also seen in the clinical PFE cohort in most patients. Collectively, when the genetic and clinical PFE cohorts were combined, the first permanent molar was affected 93% of the time. Other hallmark clinical features associated with a mutation in *PTH1R*, as well as those diagnosed clinically, are frequent involvement of the second premolar and the second molar, multiple adjacent teeth affected, supracrestal presentation of the infraoccluded teeth, bilateral presentation in most cases, involvement of teeth in both the maxilla and the mandible, frequent Class III malocclusion, and a high prevalence of concurrent dental anomalies. This, therefore, provides the basis for a genotype-phenotype correlation that can be applied to the diagnosis of patients with eruption disorders who do not have genetic data available. Our characterization of common PFE findings is consistent with previous reports.[3-7,10,11] Evidence of substantial variability among PFE patients, and particularly variability among quadrants in a patient, suggests a combination of environmental and epigenetic factors influencing PFE presentation as well as a patterning effect whereby spatial and temporal controls (ie, combinatorial code) of molecular pathways lead to a varied phenotype.[13]

We also sought to identify clinical features that can be used to distinguish between PFE and ankylosis. It is likely that there was an ascertainment bias favoring PFE over ankylosis in our sample, since many PFE patients were sent for our consultation and because our database was initially established to identify probable PFE cases. Our analysis showed that features common to PFE and ankylosis include supracrestal presentation of the affected teeth and involvement of the first permanent molar. We speculate that first molar involvement in both disorders is due to molecular timing of defects in the eruption mechanism (ie, temporal and spatial specificity favors the first erupting permanent tooth in a posterior quadrant). However, there are distinctions between the clinical appearance of PFE and ankylosis in these cohorts that can be used to distinguish the 2 disorders. For ankylosis, the affected tooth was confined to only 1 arch in every case; this is strikingly different from PFE, in which 74% of the patients had features in both arches. Bilateral presentation of affected teeth was apparent in 53% of the PFE subjects, with multiple adjacent teeth typically affected and infraoccluded; only 1 patient with ankylosis (17%) exhibited bilateral presentation, and a maximum of 1 affected tooth was noted per quadrant. Taken together, we have applied our phenotype-genotype analysis in a clinical decision tree (Fig 4) to provide the clinician a systematic tool to aid in the diagnosis of eruption disorders.

It was notable that many PFE and ankylosis patients exhibited other concurrent dental anomalies. This might support a hypothesis that ankylosis is also under intricate genetic control and could result from a variation of the misdirected molecular pathway that leads to PFE. Dental anomaly patterns have been studied by Shalish et al,[14] who concluded that patients with infraoccluded deciduous teeth (most of which continued to normal eruption of the premolars) were 2 to 7 times more likely to exhibit another dental anomaly compared with reference samples. They noted a significant correlation between infraocclusion of at least 1 deciduous tooth and increased occurrence of tooth agenesis, microdontia of the maxillary lateral incisors, palatally displaced canines, and distal angulation of the mandibular second premolars. Hypodontia in eruption disorders has been reported as a particularly common finding.[6,14] These anomalies appear to be under genetic control and might result from disturbances in the same or intertwined genetic and molecular pathways. Studying them as a group could reveal information about other connected dental anomalies and disclose that they are all manifestations of the same spectrum of eruption disturbances.

Even though the numbers reported could underrepresent the prevalence of Class III patterns in our cohorts (many patients lacked adequate records to determine the skeletal pattern), 31% of the PFE subjects exhibited a Class III relationship; this is much higher than the reported prevalence of this malocclusions in American children (<1%) and in the Japanese population (at its highest, 3%-5%).[15] As a result of the high association between PFE and Class III patterns, one can speculate that there is a generalized disturbance in bone metabolism and turnover that not only inhibits normal eruption of teeth and development of the alveolar bone, but also precludes proper forward and downward growth of the entire maxilla. Since a strong genetic component to Class III skeletal relationships

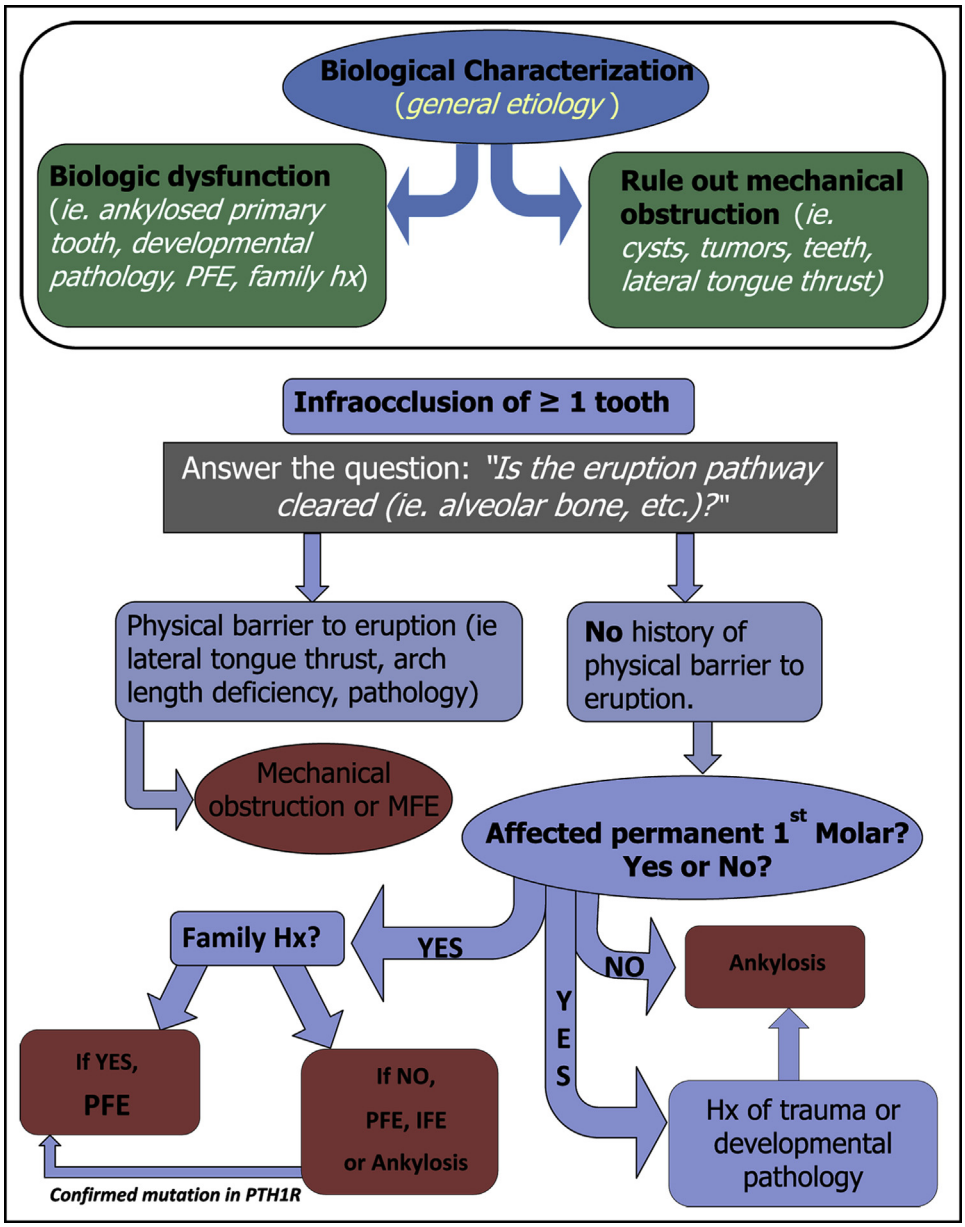

Fig 4. Decision tree provided as a tool for clinicians to aid in an objective and systematic diagnosis of eruption disorders. This decision tree also assumes that dental development is sufficient to analyze the eruption potential of the first permanent molar. *MFE*, Mechanical failure of eruption; *PFE*, primary failure of eruption; *IFE*, idiopathic failure of eruption.

has been demonstrated in previous research, there appears to be an overlapping genetic component to dental and skeletal disturbances that remains to be elucidated.[16] This important connection could shed light on the normal eruption process, the genetic influence on eruption disturbances, and the interaction between molecular pathways that orchestrate the complex process of dental eruption.

CONCLUSIONS

Definitive diagnosis of PFE is currently made through the identification of a mutation in the *PTH1R* gene, which has been shown in this study to be largely consistent with the diagnosis of PFE based on clinical parameters. Hence, the use of our genetic PFE cohort establishes 2 clinical parameters that will guide our diagnosis of PFE: involvement of the first permanent

molar and supracrestal presentation of affected teeth, in which the eruption pathway is completely clear of obstruction and clear of alveolar bone occlusal to the tooth. Other hallmark clinical features that, if present, can help support a diagnosis of PFE are involvement of the second premolar and the second molar, multiple adjacent teeth affected, bilateral presentation, involvement of teeth in both arches, Class III malocclusion, and concurrent dental anomalies. Although the only means of establishing a definitive PFE diagnosis at this time is the identification of a mutation in *PTH1R*, clinical diagnostic criteria are essential for many reasons. The lack of a mutation in *PTH1R* does not preclude a PFE diagnosis. Most likely, other mutations are linked to variations of PFE that remain to be identified through ongoing research. Additionally, genetic analysis is not readily available to practicing clinicians who must make important treatment decisions based on clinical diagnoses. The hallmark features of PFE identified here through the establishment of a genotype-phenotype correlation can give clinicians a means of making a confident and evidence-supported PFE diagnosis. However, it also raises speculation about how confidently PFE can be differentiated from ankylosis. The features in 100% of our PFE patients were also common in patients with ankylosis. Pragmatically, our results suggest that the 2 might sometimes be clinically indistinguishable without knowledge of prior trauma, ability to radiographically or otherwise identify an intact periodontal ligament space, evaluating treatment response, or obtaining genetic information for the patient. However, we attempted to highlight some features that can be helpful in clinically differentiating between PFE and ankylosis based on the information available at this time. Referencing the hallmark features of PFE outlined here, along with the characteristics specific to ankylosis, will aid clinicians in providing the most confident diagnoses to patients and offering the most appropriate and comprehensive treatment plan options.

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