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The etiology of eruption disorders – further evidence of a ‘genetic paradigm’

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Abstract

The clinical spectrum of tooth eruption disorders includes both syndromic and non-syndromic problems ranging from delayed eruption to a complete failure of eruption. A defect in the differential apposition/resorption mechanism in alveolar bone can cause conditions such as tooth ankylosis, primary failure of eruption, failure of eruption due to inadequate arch length and canine impaction. As our knowledge of the molecular events underlying normal tooth eruption has increased, so too has our understanding of clinical eruption disorders. The recent finding that one gene, parathyroid hormone receptor 1 (*PTH1R*), is causative for familial cases of primary failure of eruption (PFE) suggests that other disturbances in tooth eruption may have a genetic etiology. In this report, we evaluated the current terminology (ankylosis, PFE, secondary retention, etc.) used to describe non-syndromic eruption disorders, in light of this genetic discovery. We observed that some individuals previously diagnosed with ankylosis were subsequently found to have alterations in the *PTH1R* gene, indicating the initial misdiagnosis of ankylosis and the necessary re-classification of PFE. We further investigated the relationship of the *PTH1R* gene, using a network pathway analysis, to determine its connectivity to previously identified genes that are critical to normal tooth eruption. We found that *PTH1R* acts in a pathway with genes such as *PTHrP* that have been shown to be important in bone remodeling, hence eruption, in a rat model. Thus, recent advances in our understanding of normal and abnormal tooth eruption should allow us in the future to develop a clinical nomenclature system based more on the molecular genetic cause of the eruption failures versus the clinical appearance of the various eruption disorders.

Introduction

In the human dentition, normal eruption includes the axial movement of a tooth from its non-functional, developmental position in alveolar bone to a functional position of occlusion (1).

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Recent molecular studies have revealed more precisely that eruption is a tightly coordinated process, regulated by a series of signaling events between the dental follicle and the osteoblast and osteoclast cells found in the alveolar bone (2). A disruption in this process can occur as part of a syndrome or as a non-syndromic disorder (isolated or familial), ranging from delayed eruption (3) to a complete failure of eruption (4). Unfortunately, the delineation between eruption disorders is often based on ambiguous clinical characteristics. For the clinical orthodontist, an accurate and timely diagnosis of an eruption disorder is of tremendous value since it can facilitate correct management of the orthodontic problem (5–6). Until the recent reports of mutations in the parathyroid hormone receptor 1 (*PTH1R*) gene (7–8), non-syndromic eruption disturbances [i.e. ankylosis, secondary retention, primary retention and primary failure of eruption (PFE)] proved difficult to distinguish from one another. The confirmation of a genetic etiology for PFE will certainly simplify its diagnosis, but could also point to a genetic cause for other eruption disturbances. We hypothesize that the clinical spectrum of eruption disturbances, including delayed eruption, ankylosis, PFE, and select instances of impacted teeth, could share a genetic versus an acquired etiology.

Diagnosis of Eruption Problems

The *PTH1R* gene is not likely responsible for all eruption disorders, but given recent research, it is reasonable to suspect a genetic etiology for eruption disturbances that do not involve a physical obstruction, such as, mechanical failure of eruption or lateral tongue pressure. Viewing eruption disorders from a genetic perspective not only shifts the focus to the biologic basis of eruption, but also provides the foundation for a standardized clinical diagnosis and unified terminology. Instead of the often redundant and non-standardized descriptions used currently, eruption disturbances can now be thought of in broad etiologic categories rather than narrowly defined morphological characteristics (9). These categories should include 1) biologic dysfunction such as primary failure of eruption and primary retention, and 2) physical obstruction such as mechanical failure, cysts and lateral tongue pressure. Impacted teeth might belong to either category, depending upon the location of the impacted tooth, for example, palatal or buccal canine impaction. While palatally impacted canines are hypothesized to be both multifactorial and genetic in origin (10–13), teeth can also become impacted secondary to an obstruction of the eruption pathway, such as crowded dental arches. Likewise, though ‘secondary retention,’ defined as a cessation of tooth eruption after its emergence into the oral cavity in the absence of a physical barrier, has an unknown etiology, it has been suggested that this condition could be due to a physiologic, mechanical or genetic disturbances (14–15).

Secondary retention has been characterized in the literature as a clinical condition that includes submergence, reimpaction, reinclusion, and ankylosis (15–16). Ankylosis, the most commonly diagnosed of this group, refers to the fusion of a tooth to bone in the absence of a periodontal ligament. It can be thought of as a mechanical eruption failure, primarily because it can occur secondary to trauma (17) or from lateral tongue pressure (18). It is also true that ankylosis can occur secondarily from orthodontic forces applied to a tooth with a defective eruption mechanism as in PFE (4). The diagnosis of ankylosis can be made radiographically by the absence of a periodontal ligament space and based on the absence of physiologic mobility and the sharp solid sound on percussion of the tooth (17). However, the determination of an absent periodontal ligament space can be often misinterpreted on a radiograph, making the diagnosis of ankylosis somewhat subjective. In this case, ankylosis/secondary retention can be difficult to distinguish from PFE. Such a misdiagnosis has been seen in cases previously identified as ankylosis that were subsequently diagnosed as PFE based on the positive identification of a mutation in the *PTH1R* gene (8). The recent identification of a gene associated with PFE clarifies the current terminology used to describe eruption failure, and also contributes to our understanding of the specific biologic mechanism underlying eruption.

Phenotypic Variation of Eruption Failure

Previous findings in our laboratory have noted the high degree of variability in the clinical presentation of PFE (19,9). Specifically, our phenotypic evaluation of eruption failure in a large cohort revealed that there are two distinguishable types of PFE that may be related to the timing of onset. The first (Type I) is marked by a progressive open bite from the anterior to the posterior of the dental arches. For Type I, we speculate that the eruption defect, which we now know is genetically controlled, was expressed at the same developmental time for all affected teeth. The second type (Type II) also presents as a progressive open bite from the anterior to the posterior, however, there is also a more varied expression of eruption failure in more than one quadrant and greater although inadequate eruption of a second molar. It was originally hypothesized that in Type II, the timing of onset might be related to the stage of root development. While the exact reason for this clinical variation is unknown, in light of the recent *PTH1R* finding, we speculate that the predominant ‘molar’ phenotype that we observe may be the result of a coordinated series of molecular events that act in a temporally- and spatially-specific manner such that posterior rather than anterior alveolar bone is affected. The details of this molecular genetic pathway are not entirely known, but future *in silico* and *in vivo* studies have great potential for determining the phenotype:genotype correlation.

The range of clinical variability observed in PFE is also evident in affected individuals who present with a failure in both intraosseous and supraosseous eruption (Figure 1 A–B). It is not uncommon for medical genetic disorders to show *variable expressivity*, ie, the observation of individuals with the same disorder who do not have the same phenotype. Hence, such a clinically heterogeneous presentation is best explained by its genetic etiology. The clinical presentation of both intraosseous and supraosseous eruption failure in one individual suggests that eruption failure cannot be categorized solely on this clinical distinction, but should instead be based on whether the eruption failure is due to a physical or biologic defect in the eruption process.

The Biologic Basis of Tooth Eruption

The identification of a causative gene in human eruption failure warrants that we consider the biologic basis of normal tooth eruption very carefully. Much of our understanding of the cellular and molecular events surrounding tooth eruption has improved tremendously over the past two decades (2). Specifically, the role of the dental follicle has emerged as a central mediator of tooth eruption (20–22) and has since been shown to provide the environment and chemoattractants for monocytes to differentiate into osteoclasts, facilitating the bone resorption necessary for normal tooth eruption. Cahill and Marks demonstrated the critical role of the follicle in experiments where a metal object was substituted for a tooth in the dental follicle (20). Evidenced by the successful eruption of the follicle containing a metal object, it was concluded that the follicle was necessary and sufficient for eruption.

More recently, studies using the rat molar illustrate the importance of key cytokines and diffusible growth factors in tooth eruption. Wise and collaborators suggest that specific growth factors and cytokines produce the ‘motive force’ that propels the tooth into the oral cavity (23–24). Specifically, stellate reticulum cells found in the dental follicle are observed to secrete parathyroid hormone related peptide (*PTHrP*), which induces over expression of colony stimulating factor-1 (*CSF1*) and receptor activator of NF-kappaB ligand (*RANKL*) responsible for osteoclastogenesis (23). A concomitant over expression of bone morphogenic protein (*BMP2*), which leads to osteogenesis occurs at the apical end of dental follicle (23) in a chronological and spatial fashion (25). While these experiments in rats reveal that the amount and duration of bone growth occurring at the apical base of the tooth is necessary and sufficient to propel the tooth into the occlusal cavity (24), it remains unclear what role, if any, root

development or crown mineralization might play in the eruption process. It is already known that genes involved in mineralization, e.g., amelogenin (*AMELX*) and ameloblastin (*AMBN*), may act in concert with those involved in osteoclastogenesis, such as *RANKL*, *CSF1*, *C-Fos*, (26). Our analysis of two genes involved in tooth mineralization (*AMLEX* and *AMBN*) did not reveal any functional mutations in a small PFE cohort, but it remains entirely possible that defects in genes primarily responsible for mineralization may act to suppress *RANKL* and prevent tooth eruption (27). The respective roles of these genes in PFE and their connection to each other warrant further investigation.

Network Pathway Analysis of *PTH1R*

To further investigate the link between the *PTH1R* gene and the molecular basis of tooth eruption, we generated a simple network (Figure 2) using Ingenuity Pathways Analysis (Ingenuity® Systems, www.ingenuity.com). This network recapitulates the expected link between *PTH1R* and *PTHrP* (also parathyroid-like hormone, *PTHrP*), which is secreted in the stellate reticulum and responsible for the induction of *CSF1* and *RANKL*. We reason that this provides significant evidence of the link between *PTH1R*, PFE and the mediators of eruption necessary for normal bone remodeling; it is also consistent with the hypothesis that a critical target of the genetic defect in PFE is the alveolar bone. Hence, we believe that genes essential to the bone remodeling process are high-priority candidates for evaluation. However, the question remains how a genetic defect in *PTH1R* acts to cause eruption failure since the pathway for the erupting tooth appears to be cleared by bone resorption (Figure 1B). The single canonical pathway associated with the simple network introduced above (constructed around the focal genes/proteins *PTH1R* and *PTHrP*) is the vitamin D receptor – retinoid X receptor (VDR/RXR) activation pathway. Primarily affecting cell signaling, molecular transport, as well as vitamin and mineral metabolism (28–29), the VDR/RXR activation pathway plays a key role in balancing bone formation with bone resorption – i.e., remodeling (30–31). In addition to influencing calcium homeostasis in general, these focal genes and this pathway have been shown to affect number, quality, and function of both osteoclasts and osteoblasts (32–33); and the volume, thickness, and density of trabecular bone (34–35). Consequently, one might hypothesize that some variants in one of these two focal genes – e.g., *PTH1R* – could disrupt the balance between bone resorption, necessary to establish the passageway for an erupting tooth, and bone formation, necessary to rebuild bone through which the tooth has transited, thus contributing to PFE.

The simple network we have constructed illuminates only a small portion of a single canonical pathway. Clearly there are many additional genes and/or proteins both in that pathway and in other canonical pathways (36) that can interact directly or indirectly with *PTH1R* and other actors in VDR/RXR activation. Further, there are many “environmental” factors – with e.g., cell-, tissue- and developmental stage-specific effects – that also may influence the contributions of these genes to PFE. Accordingly, there are still substantial gaps remaining in our understanding of tooth eruption. Studies that evaluate additional candidate genes and investigate the role of environmental factors, such as trauma or orthodontic forces, will be essential to completely understand the normal eruption process.

Conclusion

The diagnostic distinction between isolated ankylosis, secondary retention and PFE is important in the context of whether teeth distal to the more commonly unerupted first molar are normal or abnormal. If the determination is made that PFE is the culprit, based on a familial inheritance or positive identification of a mutation in *PTH1R* (likely additional genes in the not-so-distant future), then affected teeth would be abnormal and unresponsive to orthodontic treatment. However, if it is determined that ankylosis is the correct diagnosis; the remaining

teeth will be responsive to orthodontic treatment following extraction of the ankylosed tooth. The fact that both PFE and ankylosis are characterized by preferentially affecting molars and premolars raises another important diagnostic question - do these disorders belong to the same spectrum? One premise is that when ankylosis cannot be linked to a physical or mechanical cause and a genetic etiology is discovered, then PFE is the more likely diagnosis. This critical step in the diagnostic regime allows the clinician to follow two different treatment courses including 1) if PFE can be confirmed, avoiding orthodontic treatment to attempt movement of affected teeth prevents a waste of effort by the doctor and the patient because the teeth will not respond, and 2) if a first molar fails to erupt and the fate of the second molar is not yet known, early extraction of the first molar allows the second molar to drift mesially *if* it is normal, and does no harm if it is not. And so, with the significant advances in our understanding of the cellular and genetic control of the eruption process, it may soon be important that we re-consider our current clinically- and morphologically-based nomenclature of eruption disorders to shift to one that is more biologically and genetically-based.

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Figure 1.

(A) Clinical presentation of PFE in an individual with a lateral posterior open bite, characterized by supraosseous eruption failure and as shown in the lower right posterior quadrant of the panoramic radiograph (B) intraosseous eruption failure of the lower right second molar. The radiograph also well demonstrates the failure of the second molar to erupt despite a clear eruption pathway.

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Figure 2.

The gene identifiers for *PTH* and *PTH1R* were uploaded into the application, Ingenuity Pathway Analysis. Each gene identifier was mapped to its corresponding gene object in the Ingenuity Pathways Knowledge Base. These genes, called focus genes, were overlaid onto a global molecular network developed from information contained in the Ingenuity Pathways Knowledge Base. Networks of these focus genes were then algorithmically generated based on their connectivity. NOTE: *PTHLH* in the diagram above is another gene name for *PTHrP*.