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Abnormal dental phenotypes in GAPO syndrome: A descriptive study with a new *ANTXR1* variant & insights on teeth eruption

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ABSTRACT

Objective: GAPO syndrome is usually diagnosed clinically owing to its characteristic features of growth retardation, alopecia, pseudoanodontia, and ophthalmic anomalies. Pseudoanodontia describes the failure of eruption of the two sets of teeth in these patients. Thus, the abnormal dental phenotype is the emergence of a set or part of a set of dentitions.
Purpose: This study reports the physical, oro-dental, and molecular findings of two new sibs with GAPO syndrome and provides a description of the dental phenotype of one of the patients reported before.
Materials & Methods: The patients were subjected to full medical history taking and three generations-pedigree construction. They were phenotyped according to the elements of morphology: Standard terminology series. After parental consents were acquired, molecular analysis was carried out for the two sibs (Patient 1 & 2).
Results: These included a new gene variant associated with erupted teeth in GAPO syndrome and new clinical features. A new classification for the terminologies of eruption disturbances was suggested.
Conclusion: The study asserts the importance of oro-dental examination and follow-ups as dental updates may occur in these cases.

1. Introduction

GAPO syndrome is an autosomal recessive disorder caused by mutations in the *ANTXR1* gene located on chromosome 2p13.3. According to Tipton and Gorlin, 1984, the first to describe this syndrome were Anderson and Pindborg in 1947. Since then, almost 62 patients with autosomal inheritance have been described worldwide (Falcone et al., 2023).

GAPO syndrome is usually diagnosed clinically owing to its characteristic features of growth retardation, alopecia, pseudoanodontia, and ophthalmic anomalies that constitute the acronym GAPO (Troxell et al., 2018).

Pseudoanodontia describes the failure of eruption of the two sets of teeth. The deciduous and the permanents fail to erupt due to ankylosis in GAPO syndrome. Thus, the abnormal dental phenotype is the emergence of a set or part of a set of dentitions (Bacon et al., 1999).

This study reports the physical, oro-dental, and molecular findings of two new sibs with GAPO syndrome and provides a detailed description of the dental phenotype of one of the patients reported before by Abdel-Hamid et al. (2019).

2. Materials and methods

The studied patients were clinically evaluated both physically and oro-dentally. First, they were subjected to full medical history taking and three generations-pedigree construction. Then, they were phenotyped according to the elements of morphology: standard terminology series (Allanson et al., 2009; Biesecker et al., 2022; de La Dure-Molla et al., 2019). Additionally, panoramic radiographs were acquired from the two sibs (patients 1 and 2).

2.1. Molecular testing

Genomic DNA was extracted from peripheral blood lymphocytes of

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patients 1 and 2 and their parents. DNA was extracted using a standard extraction procedure. The 18 coding exons and exon/intron boundaries of the *ANTXR1* gene were amplified using primers designed by Exon-Primer SOFTWARE. PCR products were purified using the Exo-SAP PCR Clean-up kit (Fermentas, Germany) and sequenced in both directions using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) and analyzed on the ABI Prism 3500 Genetic Analyzer (Applied Biosystems) according to the manufacturer's instructions. The sequence data of the *ANTXR1* gene was compared with the reference genomic and cDNA sequence of the gene (NM_032208.3). The identified variant was inspected in dbSNP141, Exome Variant Server, 1000 Genomes, and gnomAD databases. Furthermore, the effect of mutations was predicted using Polyphen2, MutationTaster, SIFT, and CADD software.

3. Results

3.1. Patients 1 and 2

These were two sibs from a consanguineous marriage. One was 15 years old, and the other was 8. They presented to the clinic because the eldest retained deciduous teeth. The eldest showed dysmorphic facies with thick lips and hypertelorism. Both had mild puffiness of the eyelids, depressed nasal bridge, hyperextensibility of the joints, broad forehead, and frontal bossing. In addition, both had sparse eyebrows and hair, but the eldest began to lose her hair in an androgenic-like manner. Eye examinations for both revealed the eldest to have optic atrophy (Fig. 1).

On oral examination, the eldest had her full set of primary dentitions that showed no clinical signs of shedding, whether it be looseness or eruption of the successors posterior to the deciduous teeth. The ridge appeared thick and rather lobulated with mandibular prognathism in the elder patient. The younger had her upper canines and first molars and the lower anterior teeth only. Both had a highly attached upper labial frena and microdontia of the erupted deciduous teeth with subsequent spacing. According to the dental history of both sibs, there was a delay in the eruption of teeth, particularly in the first and second deciduous upper incisors of the eldest (Fig. 2).

Radiographically, patient 1 showed absent second lower premolars and obliterated pulp chamber of the lower first molars. Eruption in both cases seemed to halt irrespective of the root length. In patient 2, the lower right second deciduous molar was in a dental crypt with almost full roots. Both had molars with taurodontism.

It is worth noting that both were performing well at school. Yet, their condition affected both girls psychologically, particularly the delayed eruption of the upper incisors of the younger sibling, which made her very conscious about her look.

3.2. Patient 3

A 7-year-old male patient presented to the clinic to seek management and rehabilitation. The patient's chief complaint was the absence of teeth since birth. The patient was, as aforementioned, previously

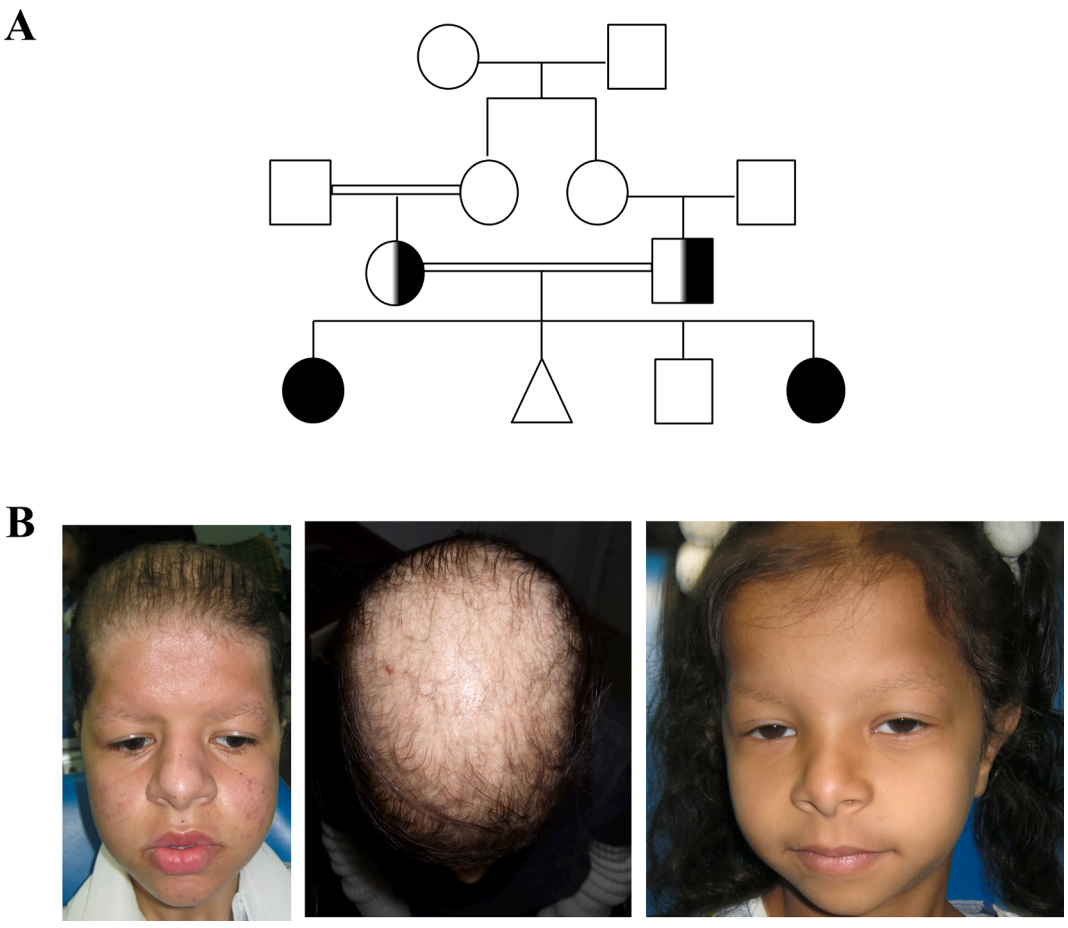

Fig. 1. (A) Pedigree of the family of cases 1 and 2 showing autosomal recessive inheritance due to consanguinity. Consanguinity is represented by a double line, the couple had 2 affected females represented by fully shaded circles, and a son represented by a clear square and a stillbirth represented by a triangle. The pedigree shows that the parents are carriers which is represented by half-shaded figures. (B) Clinical features presented in cases 1 and 2 include; dysmorphic facies with thick lips and hypertelorism. Mild puffiness of the eyelids, depressed nasal bridge, broad forehead, and frontal bossing. Sparse eyebrows and loss of hair in an androgenic-like manner.

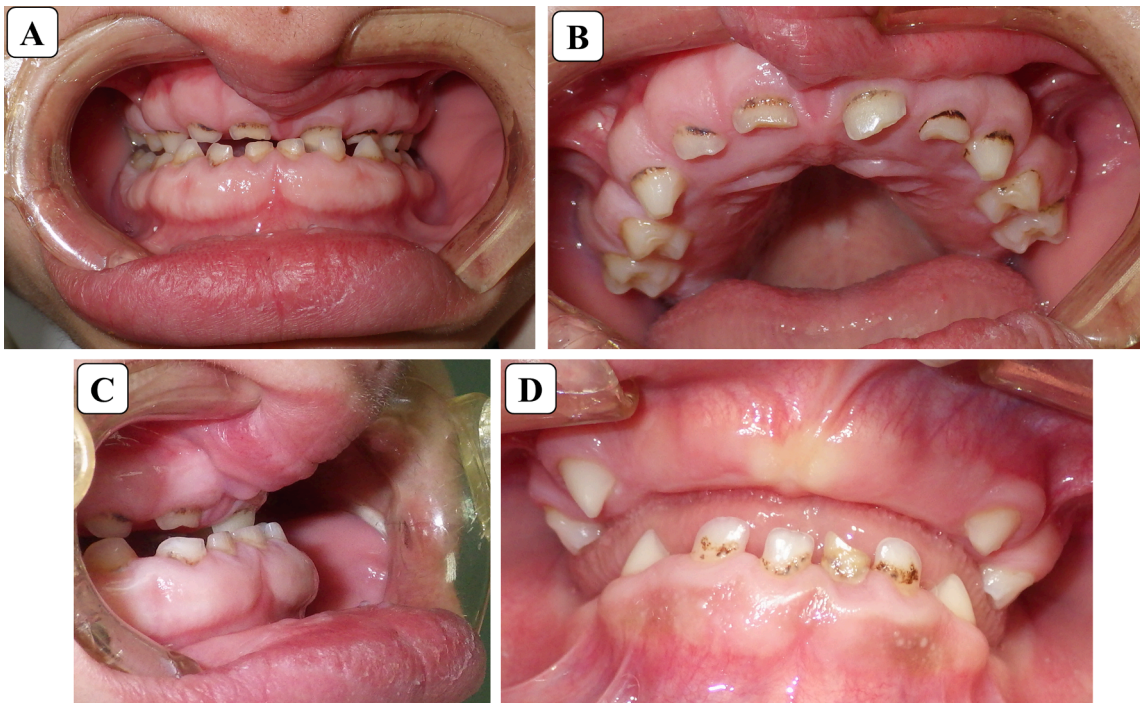

Fig. 2. Oral manifestations: in cases 1 and 2: (A) Microdontia and spacing (B) thick and lobulated ridge (C) mandibular prognathism, in case 1. (D) delayed eruption of upper anterior deciduous teeth in case 2.

diagnosed with GAPO syndrome and published by Abdel-Hamid et al., 2019 (Patient 2, who carried the c.12_30dup, p.I11Gfs*40 variant). In the report, the patient had normal height and weight, alopecia since birth, pseudoanodontia, and eye affection. Craniofacially, he had delayed closure of fontanelle, broad forehead, frontal bossing, puffiness around the eyelids, broad forehead, depressed nasal bridge, thick lips, thick alveolar ridges, and a long philtrum. On examining the patient orodentally, there was an eruption of two teeth: one emerging cusp tip on the right side and one emergent crown on the left side (Fig. 3). It is worth noting that the proband was scheduled for a panoramic radiograph;

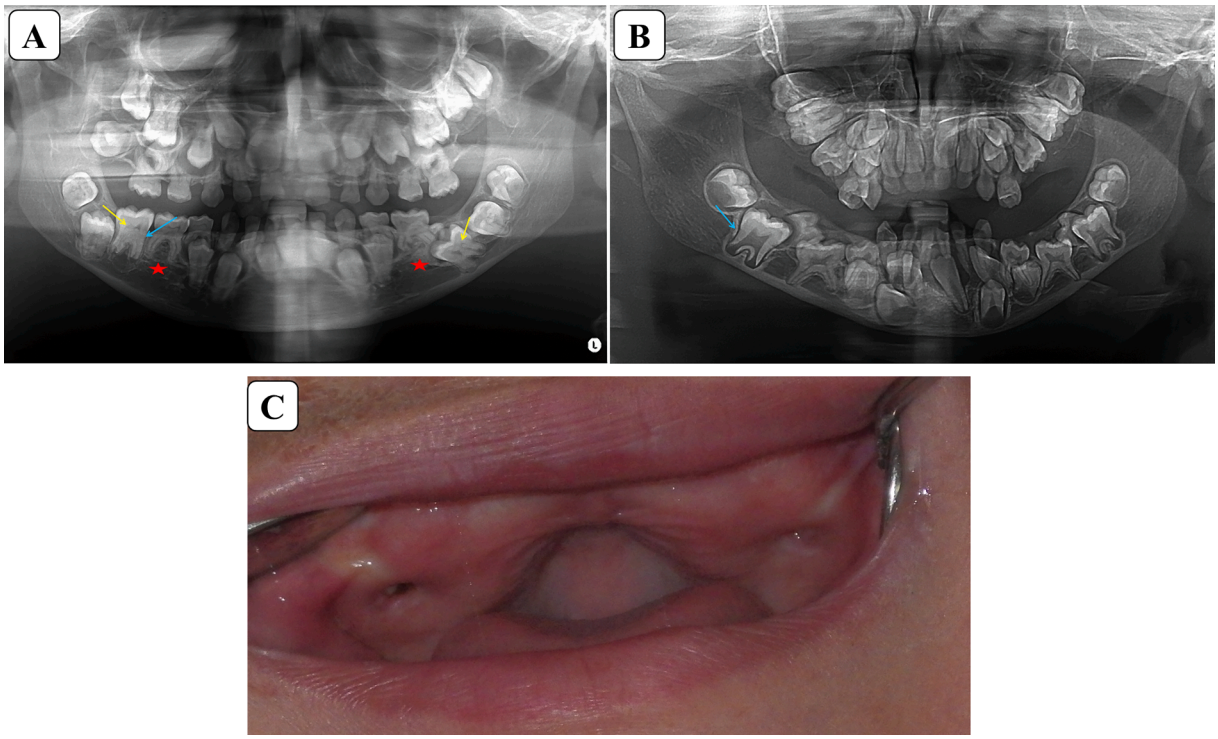

Fig. 3. (A) Panoramic radiograph of case 1 shows; absent second lower premolars (Red stars), Obliterated pulp chamber of the lower first molars (yellow arrows) with taurodontism (blue arrow) (B) Panoramic radiograph of patient 2 shows; the lower right second deciduous molar with almost full roots, and molars with taurodontism (blue arrow). (C) Eruption of two teeth in patient 3: an emerging cusp tip on the right side and another emergent crown on the left side. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

unfortunately, he passed away in an accident.

3.3. Molecular results

Mutational analysis of the *ANTXR1* gene revealed a missense variant in exon 9 of the gene, c.664G > A (p. Glu222Lys). The c.664G > A (p. Glu222Lys) in the two sibs was homozygous and heterozygous in both parents (Fig. 4A). The variant affected a highly conserved amino acid residue (Fig. 4B) and was not found in public genetic databases. Further, it was predicted by different bioinformatic tools to be deleterious (Supp Table 1).

4. Discussion

4.1. Stages of eruption

Broadly speaking, teeth eruption occurs through 3 stages: root formation, bone resorption, and gingival clearance, respectively. After emergence, the tooth continues to erupt until it reaches the occlusal plane and then comes to adult equilibrium. Abnormalities of eruption can be grouped into pre-emergence problems and post-emergence ones (Proffit and Frazier-Bowers, 2009). To our knowledge, this is the second report of GAPO patients with erupted teeth. In patient 3, a post-eruption problem was added to the pseudoanodontia (Bacon et al., 1999).

4.2. Classifications and terminologies

According to Raghoebar et al., 1991, the causes of eruption disturbances at the pre-emergent stage could be classified into local and general factors. General factors are those caused by genetic disorders and affect several teeth, while local ones affect a few teeth only. This classification is rather obsolete because genetic disorders can cause local factors, as in GAPO patients who suffer pseudoanodontia due to ankylosis (Bacon et al., 1999). Additionally, *PTH1R* gene mutations, which cause the condition known as primary failure of eruption (PFE), can be localized to one or two teeth (Yamaguchi et al., 2022).

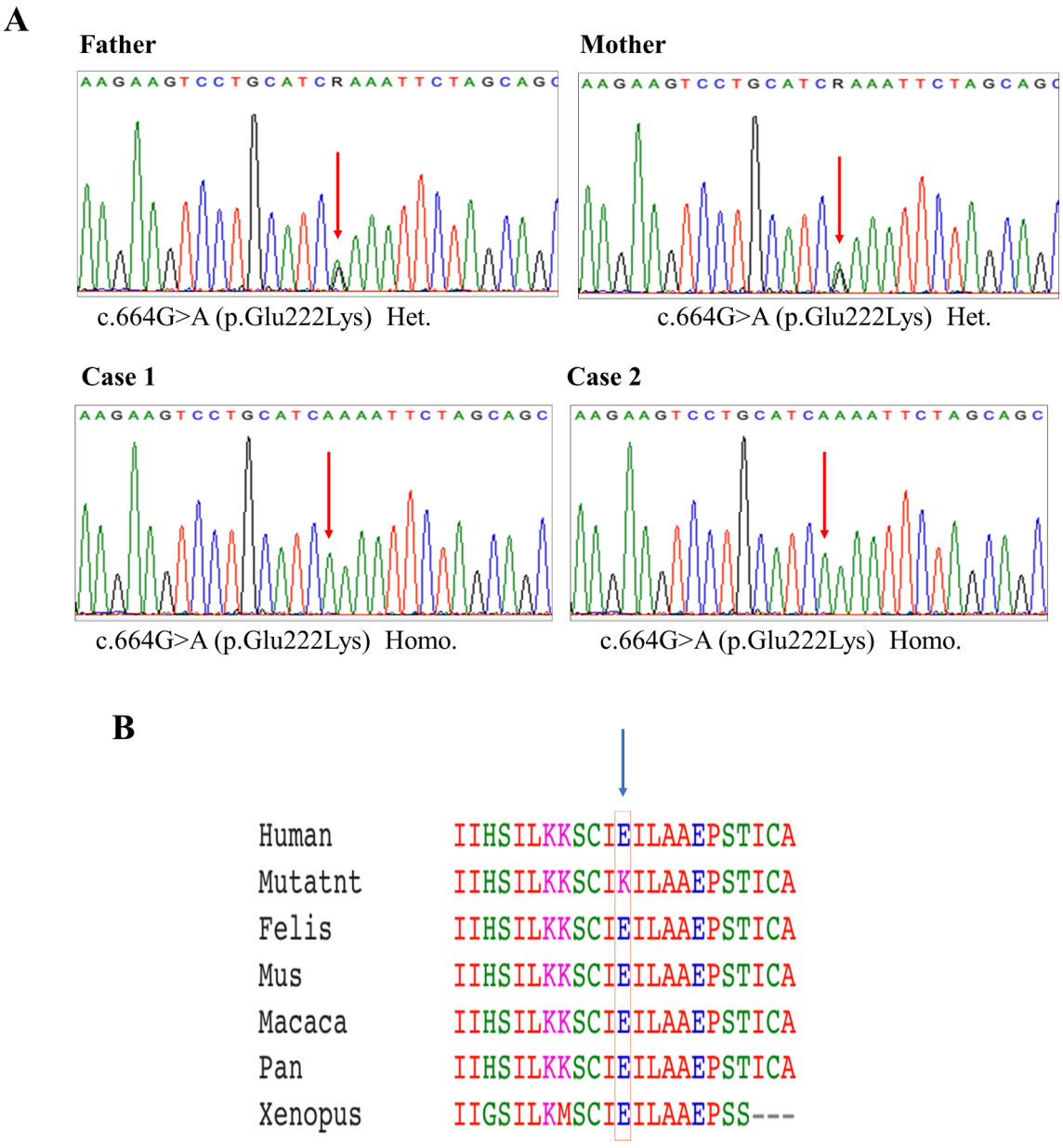

Fig. 4. (A) Portion of the sequencing electropherograms showing the new missense variant identified in our study. The arrow indicates the site of the variant. (B) The conservation of p.Glu222 residue across different species.

Another way to classify abnormalities of eruption is to identify the local causes, which are either mechanical obstruction or lack of eruptive forces. Mechanical obstruction could be another tooth. Mechanical obstruction causes what is known as impactions if in the pre-emergence state. Post-emergence mechanical hindrance is called secondary retention. It is referred to as infra-occlusion. Ankylosis is a post-emergence mechanical hindrance. On the other hand, the lack of eruptive forces before tooth emergence causes primary retention. There is no obvious cause for the cessation of eruption in primary retention, and the tooth has passed the 2-year mark with no eruption. As mentioned, the lack of eruptive force after eruption is usually due to *PTH1R* gene mutations and causes PFE (Janssen et al., 2014; Proffit and Frazier-Bowers, 2009; Raghoebar et al., 1991).

This second classification is mainly for non-syndromic cases. It cannot be applied for GAPO syndrome patients who suffer from ankylosis in an obvious pre-emergent abnormality; thus, a new classification is warranted that would include both syndromic and non-syndromic cases and help categorization that would hopefully aid in dental management (Frazier-Bowers et al., 2010).

The suggested classification will first add ankylosis to pre-emergence mechanical obstruction and second have a term that explains the post-emergence failure of eruption other than PFE by using infra-occlusion in this category instead of a mechanical hindrance, for instance, or submerged teeth (Table 1).

Patient 3 showed localized secondary retention since the teeth erupted, and there was clearance of both the bone and the gingiva, but it is ankylosed. This condition raises the question of possible bone resorption and the absence of gingival clearance in other published GAPO cases. Patients 1 and 2, on the other hand, showed delayed eruption and retained deciduous teeth.

4.3. The genetics of eruption

While the terminologies are set, it is often difficult to distinguish one from the other clinically. There is growing evidence that they may have common pathways since there are cases that showed ankylosis with PFE, and attempting to treat PFE causes ankylosis of the affected teeth (Awad et al., 2022; Frazier-Bowers et al., 2010).

Eruption disturbances and ankylosis of teeth are seen in *CLCN7*-related autosomal recessive osteopetrosis. The decreased blood supply to the jaws and ankylosis of teeth often cause osteomyelitis of the jaws in these patients, which was described in a GAPO patient. Sclerosing of the cranial base and mastoid has been reported in GAPO syndrome, which is evidence of probable bone alterations due to *ANTXR1* gene mutations (Puranik et al., 2018; Sobacchi et al., 2013).

4.4. The new molecular variant

So far, 15 pathogenic variants have been reported in the *ANTXR1* gene in patients with GAPO syndrome (Abdel-Hamid et al., 2019; Smigiel et al., 2019; Yildiz et al., 2022). Most reported cases were from populations with high rates of consanguineous marriages, like Egypt and Turkey. Given the reported variants, there were no common variants or hot-spot regions. However, a nonsense variant c.262C > T (p. Arg88Ter) was reported before in two unrelated families (Stránecký et al. 2013). In addition, Abdel-Hamid et al. (2019) described five different *ANTXR1* variants in five unrelated Egyptian families, and four of them were clustered in exon 1. In the current study, we identified a new missense variant (c.664G > A, p. Glu222Lys) in exon 9 of the gene.

To our knowledge, this is the first variant to be reported in this exon. Generally, only three missense variants were described in the literature: c.1150 G > A (p. Gly384Ser) (Bayram et al., 2014), c.410A > T (p. Gln137Leu) (Salas-Alanis et al., 2016), and c.949 T > C (p. Cys317Arg) (Yildiz et al., 2022). Our new variant and the c.949 T > C (p. Cys317Arg) are in the anthrax receptor extracellular domain, which is essential for protein function.

Table 1
Classifications of eruption disturbances.

	Established classification	New suggested classification (Syndromic and non-syndromic)
Mechanical obstruction	• Pre-emergence: Impaction • Post-emergence: Secondary retention (Infra-occlusion or Ankylosis)	• Pre-emergence: a) Impactions b) Ankylosis • Post-emergence: Secondary retention (Ankylosis)
Lack of eruptive force	• Pre-emergence: Primary retention • Post-emergence: Primary failure of eruption (PTH1R gene)	• Pre-emergence: Primary retention • Post-emergence: Infra-occlusion (Submerged teeth)

4.5. Other phenotypic variations

In this study, we added pulp chamber obliteration and taurodontism to the dental phenotype of GAPO syndrome. Apart from the dental phenotype, patient 2 showed prognathism of the lower jaw, which was documented twice before (Demirgüneş et al., 2009; Bacon et al.,1999). Tooth agenesis was reported in a case that had a biallelic *ANTXR1* variant. The patient did not have GAPO syndrome. Tooth agenesis has not been reported in GAPO patients before, probably due to the lack of panoramas in previous reports (Dinckan et al., 2018). Another feature was the androgen-like alopecia as opposed to the complete alopecia normally observed in these patients. This condition was observed in another case where telogen hair loss was observed (Ahmed and Gritli, 2019).

5. Conclusion

This report raises the number of GAPO patients reported from Egypt to 13. It adds to the literature another variant that causes the deciduous teeth to erupt normally in the oral cavity and cause alopecia later in life. In addition, it points to the fact that another reported variant could have a role in teeth eruption and gingival clearance. It raises other research questions as to whether the cases reported in the past had partial emergence of teeth and lacked the clearance of gingiva or not. Moreover, taurodontism and pulp chamber obliteration are added to the dental phenotype. The report asserts the importance of oro-dental follow-ups in these cases.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sdentj.2024.07.001.

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