Hydrolysis fibromatosis syndrome: a case presenting with gingival enlargement as the only clinical manifestation and a report of two new mutations in the ANTXR2 gene

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Abstract

Background: Hyaline fibromatosis syndrome (HFS) is a rare autosomal recessive disorder caused by mutations in the gene for anthrax toxin receptor-2 (ANTXR2). The clinical features of HFS include skin thickening with nodules, papules and plaques, gingival enlargement, joint stiffness and contractures, and systemic manifestations. Notably, in all patients with HFS reported in the literature, gingival enlargement has never occurred alone.

Case presentation: A case of a child with gingival enlargement as the only clinical manifestation, who was later diagnosed with HFS, is described. In this case, the absence of skin and joint lesions and other characteristic clinical presentations gave rise to a diagnostic problem. This uncommon condition was clinically indistinguishable from other diseases or conditions that presented with diffuse gingival enlargement. A definitive diagnosis of HFS was reached through genetic analysis. Trio whole exome sequencing revealed compound heterozygous mutations of ANTXR2 in this patient and two new mutations were reported.

Conclusions: The findings of this case serve as an important reminder to clinicians. When dental practitioners encounter gingival manifestations of HFS without accompanied skin or joint involvement, there is a need to pay attention to the differential diagnosis and increase awareness of HFS.

Keywords: Hyaline fibromatosis syndrome, Gingival enlargement, Differential diagnosis, Case report

Background

Hyaline fibromatosis syndrome (HFS; MIM# 228600) is a rare autosomal recessive disorder of the connective tissue caused by mutations in the gene for anthrax toxin receptor-2 (ANTXR2), also known as capillary morphogenesis protein 2, located on chromosome 4q21 [1–3]. HFS is characterized by an abnormal deposition of hyaline-like material in the skin, mucosa, joints and internal organs. The clinical features of HFS include skin thickening with nodules, papules and plaques, gingival enlargement, painful joint stiffness and contractures, and occasional systemic involvement.

The severity of HFS varies between the mild form with limited skin involvement and the severe form with an earlier age of onset, visceral involvement, and early lethality [4–6]. A grading system of HFS was proposed by Nofal et al. [4] and modified by Denadai et al. [5], which classifies HFS into grade 1 or mild (skin and/or gingival involvement), grade 2 or moderate (joint and/or bone involvement), grade 3 or severe (internal organ

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involvement with or without clinical manifestations), and grade 4 or lethal (severe clinical decompensation).

Generally, most patients with HFS develop subcutaneous nodules and gingival enlargement. However, only a few patients reported in the literature presented with sole cutaneous and mucosal manifestations and were classified as having grade 1 or mild HFS. Importantly, all patients with grade 1 HFS reported had characteristic skin lesions [2–4, 7–14]. In this paper, we present a case of HFS with gingival enlargement as the initial and sole manifestation in the absence of subcutaneous nodules. This unique situation, which would lead to difficulties in the differential diagnosis between HFS and other diseases characterized by gingival fibromatosis, requires special attention among dental practitioners. In addition, two new mutations in the \textit{ANTXR2} gene were reported.

**Case presentation**

A 6-year-old boy had a history of gingival overgrowth, which had been present since the boy’s first tooth erupted at 6 months of age. The painless overgrowth of the gingiva progressed slowly causing no discomfort up to the age of 6 years, when the esthetic appearance also became intolerable. No other complaints were noted. The child was systemically healthy and was the only child of two healthy non-consanguineous parents. Similar findings or a history of such findings were not identified in either the parents or their relatives.

Oral cavity examination showed severe gingival enlargement involving both the mandibular and maxillary arches and was particularly prominent over the anterior regions (Fig. 1). The patient’s gingivae seemed to have slight redness and mild edema, with absence of normal stippling. The oral hygiene was poor due to the formation of pseudopockets containing large amounts of dental plaque and a small amount of calculus. As a result, the marginal gingiva was slightly inflamed. Apart from gingival enlargement, other mucosal lesions such as submucosal deposits or thickening, were not observed. Radiographical examination revealed no periodontal bone destruction.

The routine hematological and biochemical test results were unremarkable and initial phase therapy was administered. The gingival enlargement was not alleviated after the gingival inflammation was controlled. Gingivectomy was performed, and the wound healing was uneventful.

![Fig. 1](image-url) Intraoral view of the 6-year-old boy at the first appointment. Note the severe gingival enlargement
Tissue specimens obtained during gingivectomy were sent for histopathologic examination. Hematoxylin–eosin (HE) staining revealed a hyperplastic epithelium, mild inflammatory cell infiltration, proliferation of the capillary layer, and an increase in the amount of fibrous tissue (Fig. 2A, B). This result did not indicate a definitive diagnosis. Meanwhile, recurrence of gingival enlargement occurred 1 week after the gingivectomy. Since this child presented with gingival enlargement as the only clinical manifestation and showed no other systemic involvement, the diagnosis proved difficult. Hence, genetic tests were performed.

Trio whole exome sequencing (WES) of DNA isolated from peripheral blood was performed at the Chi-gene Translational Medicine Research Center Co. Ltd. (Beijing, China). Detailed methods of genetic tests are provided in the supplementary information (Additional file 1). Genetic analysis revealed compound heterozygous mutations of \textit{ANTXR2} in this patient: c.524G > A (p.Cys175Tyr) in exon 6 and loss of exons 1 and 2. The patient’s father had a heterozygous \textit{ANTXR2} mutation, loss of exons 1 and 2, and his mother had a heterozygous \textit{ANTXR2} mutation, c.524G > A (Fig. 3). The mutation in exon 6 of \textit{ANTXR2} was further verified via Sanger sequencing, and the loss of exons 1 and 2 in \textit{ANTXR2} was further verified by quantifying the copies of exons 1 and 2 via quantitative real-time polymerase chain reaction assays (Fig. 3).

Genetic analysis confirmed the diagnosis of HFS. Therefore, further physical, radiographic, and histopathologic examinations were performed after a literature review. No skin lesions or joint contractures were observed. Skeletal radiography showed no abnormalities of the bilateral distal humeri, radii, ulnae, carpal bones, metacarpals, distal femurs, tibiae, fibulae, metatarsi, and phalanges. The gingival-specimen sections were stained with periodic acid Schiff (PAS) and Congo red. Deposits of an amorphous, homogeneous, and PAS-positive hyaline substance were found in the

![Fig. 2](image)

Fig. 2  Histopathologic image from a gingiva biopsy showing (A, B) hyperplastic epithelium, mild inflammatory cell infiltration, proliferation of the capillary layer, and increase in fibrous tissue (hematoxylin–eosin stain). (C, D) deposits of an amorphous, homogeneous, and PAS-positive hyaline substance in the lamina propria and perivascular spaces (periodic acid Schiff stain)

![Fig. 3](image)

Fig. 3  Mutation analyses for the anthrax toxin receptor 2 gene in the family members of the patient. A The c.524G > A mutation in exon 6 was observed in the patient and his mother. B Real-time polymerase chain reaction assay of the \textit{ANTXR2} normalized by the human albumin gene showed the relative amounts of exons 1 and 2 in family members. The father and the patient had partial gene deletions involving both exons 1 and 2.
Fig. 3  (See legend on previous page.)
### Table 1  Differential diagnoses of generalized gingival overgrowth in children

| Disease                              | Features                                                                                     | Inheritance             | Chromosomal region/gene locus |
|--------------------------------------|----------------------------------------------------------------------------------------------|--------------------------|------------------------------|
| Gingivitis                           | The inflammatory response to a local irritant can lead to chronic hyperplastic gingivitis. Gingival enlargement is usually limited to areas affected by the irritant | Autosomal dominant       | 17q11.2                      |
| Drug-induced gingival overgrowth [21] | Intake of anticonvulsants, immunosuppressants, calcium channel blockers, or other drugs implicated in the occurrence of gingival overgrowth | Autosomal recessive      | 1q32.2, 8p21.3, 1q21.3       |
| Gingival overgrowth associated with systemic diseases | Anemia, neutropenia, thrombocytopenia, easy fatigability, fever, bone pain, spontaneous gingival bleeding, gingival enlargement, petechial hemorrhages, mucosal pallor, herpetic infections, candidiasis, and oral ulceration | Autosomal recessive      | 7p22.3                      |
| Leukemia [22]                        | Anemia, neutropenia, thrombocytopenia, easy fatigability, fever, bone pain, spontaneous gingival bleeding, gingival enlargement, petechial hemorrhages, mucosal pallor, herpetic infections, candidiasis, and oral ulceration | Autosomal recessive      | 7p22.3                      |
| Vitamin C deficiency [23]            | Vitamin C deficiency is defined as a serum ascorbic acid level < 2 μg/mL. Clinical manifestations of scurvy include anemia, myalgia, bone pain, swelling, gingival enlargement, poor wound healing, and spontaneous bleeding | Autosomal recessive      | 1q32.2, 8p21.3, 1q21.3       |
| Crohn’s disease [24]                 | Crohn’s disease is a chronic gastrointestinal inflammatory disease. Clinical manifestations include abdominal pain, diarrhea, nausea, vomiting, and weight loss. Oral manifestations include mucosal tags; swelling of the lips, cheeks, and gingiva; and cobblestone appearance of the mucosa | Autosomal recessive      | 1q32.2, 8p21.3, 1q21.3       |
| Genetic diseases and syndromes       |                                                                                              |                          |                              |
| Neurofibromatosis, type I (MIM 162200) [25] | Café-au-lait macules, axillary and inguinal freckling, neurofibromas, plexiform neurofibroma, optic pathway gliomas, sphenoid wing dysplasia or long-bone dysplasia, and Lisch nodules | Autosomal dominant       | 17q11.2                      |
| Hereditary gingival fibromatosis (MIM 135300, 605544, 609955 et al.) [26–28] | Benign, slow-growing, non-hemorrhagic, fibrous hyperplasia of the maxillary and mandibular gingiva | Autosomal dominant       | 2p22.1, 5q13-q22, 2p23.3-p22.3 et al |
| Congenital generalized hypertrichosis with or without gingival hyperplasia (MIM 135400) [29, 30] | Hypertrichosis, gingival hyperplasia, dysmorphic and coarse facies | Autosomal dominant, autosomal recessive | 17q24.2-q24.3 |
| Mucolipidosis (MIM 252500, 252600) [31] | Short stature, skeletal abnormalities, cardiomegaly, developmental delay, and gingival hyperplasia | Autosomal recessive      | 1q23.2                      |
| Winchester syndrome (MIM 277950) [32] | Generalized osteoporosis, multicentric osteolysis, and progressive joint destruction | Autosomal recessive      | 14q11.2                      |
| Zimmermann-Laband syndrome (MIM 135500, 616455, 618658) [33–35] | Gingival fibromatosis, hypo/aplastic nails and distal phalanges, hepatosplenomegaly, hypertrichosis, joint hypermobility, and abnormalities of the cartilage of the nose and/or ears | Autosomal dominant       | 1q23.2, 8p21.3, 1q21.3       |
| Frank-ter Haar syndrome (MIM 249420) [36] | Thick skin, osteolysis, gingival hypertrophy, craniofacial anomalies, skeletal dysplasia, and cardiac defects | Autosomal recessive      | 5q35.1                      |
| Amelogenesis imperfecta, type IG (MIM 204690) [37] | Generalized thin hypoplastic or absent enamel in the primary and permanent teeth, pulp stones, delayed tooth eruption, root dilacerations of impacted teeth, gingival hyperplasia, and nephrocalcinosis | Autosomal recessive      | 17q24.2                      |
| Raine syndrome (MIM 259775) [38]     | Generalized osteosclerosis, craniofacial dysplasia, thoracic hypoplasia, and gingival hyperplasia | Autosomal recessive      | 7p22.3                      |
lamina propria and perivascular spaces (Fig. 2C, D). The hyaline substance could not be stained with Congo red.

Based on the clinical presentation and genetic analysis results, the child was diagnosed with HFS of grade 1. A treatment plan, including regular periodontal debridement, oral hygiene motivation, and gingivectomy when necessary was proposed. As HFS is a progressive disease, and manifestations tend to be additive over time, the child was referred to a pediatrician for regular follow-up considering the possibility of systemic involvement in the future.

**Discussion and conclusions**

Skin lesions such as subcutaneous nodules, papules, and plaques are the most common feature of HFS. These lesions typically occur in the scalp, ears, neck, face, hands, and feet. Additional features include gingival enlargement, joint stiffness and contractures, osteopenia, and osteoporosis. The severer form of HFS, which was previously referred as infantile systemic hyalinosis, shows internal organ involvement with or without systemic manifestations and can be lethal [5, 6]. The diagnosis of HFS is usually based on typical clinical manifestations combined with histopathologic characteristics, such as hyaline-like material in tissues. When HFS is suspected, sequencing of all exons and flanking sequences of the *ANTXR2* gene on chromosome 4q21 should be performed to genetically confirm the diagnosis. Diseases that should be considered in the differential diagnosis of diffuse gingival enlargement are listed in Table 1. As the gingiva did not show much inflammation and the gingival enlargement was not relieved after periodontal debridement in this patient, the diagnosis of chronic gingivitis could be easily excluded. Moreover, drug-induced gingival enlargement, leukemia, vitamin C deficiency, and Crohn’s disease were not considered as candidate diagnoses because the medical history and blood tests of the child were both unremarkable. Among the genetic diseases, hereditary gingival fibromatosis was first considered because of the increase of fibrous tissue observed with HE staining. However, the gingiva of this patient was not as firm and dense as that of patients with hereditary gingival fibromatosis. Ultimately, we had to resort to genetic testing to help arrive at a diagnosis.

This patient was diagnosed with grade 1 HFS according to the grading system of HFS [5]. Genetic analysis showed compound heterozygous mutations of *ANTXR2* in this child: c.524G > A in exon 6 and loss of exons 1 and 2. To the best of our knowledge, these two mutations have not been previously identified. Loss of exons 1 and 2 could result in deletion of 75 amino acids in the vWA domain and significant change in the protein sequence, while c.524G > A in exon 6 might result in amino acid change in the coding protein at position 175 (p.Cys175Tyr). According to the previous references [6, 15], missense mutations in the vWA domain, other missense mutation in exons 1–11, and mutations leading to premature stop codons (frameshift and splicing mutations) were associated with the severe form of HFS, while missense mutations in exons 13–17 were associated with the mild form of the disease. However, in this case, the genotype could not explain the mild phenotype of the patient. It appears that genotypes are not sufficient to account for all clinical variations. This phenomenon has also been observed in other case reports [3, 4].

### Table 1 (continued)

| Disease                                      | Features                                                                 | Inheritance            | Chromosomal region/gene locus |
|----------------------------------------------|--------------------------------------------------------------------------|------------------------|------------------------------|
| Gingival fibromatosis with progressive deafness (MIM 135550) [39] | Gingival fibromatosis associated with progressive neural hearing loss  | Autosomal dominant /   | /                            |
| Gingival fibromatosis with distinctive facies (MIM 228560) [40]   | Gingival fibromatosis, macrocephaly, bushy eyebrows, synophrys, hypertelorism, downslanting palpebral fissures, flattened nasal bridge, hypoplastic nares, cupid-bow mouth, and highly arched palate | Autosomal recessive /   | /                            |
| Ramon syndrome (MIM 266270) [41, 42]         | Gingival fibromatosis, cherubism, short stature, mental deficiency, hypertichosis, juvenile rheumatoid arthritis, and epilepsy | Autosomal recessive /   | /                            |
| Rutherfurd syndrome (MIM 180900) [43, 44]    | Failure of eruption of teeth, gingival hyperplasia, dense corneal opacities | Autosomal dominant /   | /                            |

When characteristic skin or joint lesions are present, HFS is not difficult to diagnose. However, given that gingival enlargement may be the initial and only manifestation in a case of HFS, and the hyaline-like material in gingiva may be hardly distinguishable from collagen fiber bundles in the HE stained section, as we reported in the present study, the differential diagnosis between HFS and other gingival fibromatosis diseases is both difficult and important.
Therefore, in addition to the gene itself, there may be other factors, such as modifier genes and environmental elements, that can influence the HFS phenotype. Further research is required to elucidate this phenomenon.

To date, there is no effective treatment for HFS, and supportive care is the mainstay of treatment [6]. Lesions may require recurrent excision and tend to worsen during adolescence [5, 18]. Fortunately, some studies have shown the potential of personalized treatment such as proteasome-inhibitor administration [19] and therapies that inhibit the nonsense-mediated mRNA decay pathway [20], when the different molecular consequences of ANTXR2 mutations are considered.

In conclusion, to the best of our knowledge, this was the first case of HFS solely presenting with gingival manifestations. It is possible that there have been similar cases which, however, remain undiagnosed, have not been reported. The findings of this case serve as an important reminder to clinicians. When dental practitioners encounter gingival manifestations of HFS without skin or joint involvement, there is a need to pay attention to the differential diagnosis and increase awareness of HFS.

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**Authors’ contributions**
DD took charge of patient treatment and follow-up, and revised the article. YL contributed to literature review and drafted the article. XZ, YD and YX provided helpful guidance on the diagnosis and management of the patient. All authors read and approved the final manuscript.

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**Availability of data and materials**
All data generated or analysed during this study are included in this published article.

**Declarations**

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Written informed consent was obtained from the patient’s parents for publication of this case report and any accompanying images.

**Competing interests**
The authors declare that they have no competing interests.

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**References**

1. Rahman N, Dunstan M, Teare MD, Hanks S, Edkins SJ, Hughes J, et al. The gene for juvenile hyaline fibromatosis maps to chromosome 4q21. Am J Hum Genet. 2002;71(4):975–80.
2. Dowling O, Difeo A, Ramirez MC, Tukel T, Narla G, Bonafe L, et al. Mutations in capillary morphogenesis gene-2 result in the allelic disorders juvenile hyaline fibromatosis and infantile systemic hyalinosis. Am J Hum Genet. 2003;73(4):957–66.
3. Hanks S, Adams S, Douglas J, Arbour L, Atherton DJ, Balci S, et al. Mutations in the gene encoding capillary morphogenesis protein 2 cause juvenile hyaline fibromatosis and infantile systemic hyalinosis. Am J Hum Genet. 2003;73(4):791–800.
4. Nofal A, Sanad M, Assaf M, Nofal E, Nassar A, Almokadem S, et al. Juvenile hyaline fibromatosis and infantile systemic hyalinosis: a unifying term and a proposed grading system. J Am Acad Dermatol. 2009;61(4):695–700.
5. Denadai R, Raposo-Amaral CE, Bertola D, Kim C, Alonso N, Hart T, et al. Identification of 2 novel ANTXR2 mutations in patients with hyaline fibromatosis syndrome and proposal of a modified grading system. Am J Med Genet A. 2012;158a(4):732–42.
6. Casas-Alba D, Martinez-Monseny A, Pino-Ramirez RM, Alisa L, Castejon E, Navarro-Villarrubi S, et al. Hyaline fibromatosis syndrome: clinical-update and phenotype-genotype correlations. Hum Mutat. 2018;39(12):1752–63.
7. Chitale AR, Murthy AK, Maniar JK. Juvenile hyaline fibromatosis. Ultrasound Pathol. 1987;11(S–6):771–5.
8. Scibba JJ, Niebloom T. Juvenile hyaline fibromatosis (Murray–Purdie–Drescher syndrome): oral and systemic findings in siblings. Oral Surg Oral Med Oral Pathol. 1986;62(4):397–409.
9. Jacyk WK, Wentzel LF. Juvenile hyaline fibromatosis in two South African black children. Int J Dermatol. 1996;35(10):740–2.
10. Ko CJ, Barr RJ. Calciospherules associated with juvenile hyaline fibromatosis. Am J Dermatopathol. 2003;25(1):53–62.
11. Kalgaonkar PS, Wade M, Warke C, Makhecha M, Khare M. Juvenile hyaline fibromatosis—a rare autosomal recessive disease. J Clin Diagn Res. 2017;11(7):Sd04-sd6.
12. Rashmi MV, Geetha JP, Srinivas Arava NM, Kondadaswamy CR. Juvenile Hyaline Fibromatosis (JHF): a rare case with recurrence. J Clin Diagn Res. 2014;8(2):161–2.
13. Momin YA, Bharambe BM, D’Costa G. Juvenile hyaline fibromatosis: a rare lesion. Indian J Pathol Microbiol. 2011;54(4):838–9.
14. Krishnamurthy J, Dalal BS, Sunila, Gubanna MV. Juvenile hyaline fibromatosis. Indian J Dermatol. 2011;56(6):731–3.
15. Dequeut J, Lausch E, Superti-Furga A, van der Goot FG. The dark sides of capillary morphogenesis gene 2. EMBO J. 2012;31(1):3–13.
16. Haidar Z, Temanni R, Chouery E, Jithesh P, Liu W, Al-Ali R, et al. Diagnosis implications of the whole genome sequencing in a large Lebanese family with hyaline fibromatosis syndrome. BMC Genet. 2017;18(1):3.
17. Gao Y, Bai J, Wang J, Liu X. Two novel mutations in the ANTXR2 gene in a Chinese patient suffering from hyaline fibromatosis syndrome: a case report. Mol Med Rep. 2018;18(4):4004–8.
18. El-Maayyah M, Jerjes W, Shah P, Upile T, Murphy C, Ayliffe P. Gingival hyperplasia associated with juvenile hyaline fibromatosis: a case report and review of the literature. J Oral Maxillofac Surg. 2010;68(10):2604–8.

19. Dequequet J, Lauuch E, Guex N, Abrami L, Salvi S, Lakkaraju A, et al. Hyaline fibromatosis syndrome inducing mutations in the ectodomain of anthrax toxin receptor 2 can be rescued by proteasome inhibitors. EMBO Mol Med. 2011;3(4):208–21.

20. Yan SE, Lemmim T, Salvi S, Lauuch E, Superti-Furga A, Rokicki D, et al. In-depth analysis of hyaline fibromatosis syndrome frameshift mutations at the same site reveal the necessity of personalized therapy. Hum Mutat. 2013;34(7):1005–17.

21. Bondon-Guitton E, Bagheri H, Montastruc J-L. Drug-induced gingival overgrowth: a study in the French Pharmacovigilance Database. J Clin Periodontol. 2012;39(6):513–8.

22. Fernandes KS, Galliottini M, Castro T, Amato MF, Lago JS, Braz-Silva PH. Gingival leukemic infiltration as the first manifestation of acute myeloid leukemia. Spec Care Dentist. 2018;38(3):160–2.

23. Léger D. Scurvy: reemergence of nutritional deficiencies. Can Fam Physician. 2012;58(9):199–203.

24. Monroe CL, Dahiya S, Gutmann DH. Dissecting clinical heterogeneity in autosomal dominant hereditary gingival fibromatosis, GINGF3, maps to chromosome 2p22.3-p23.3. Clin Genet. 2005;68(3):239–44.

25. Sheth J, Bhavsar R, Gandhi A, Sheth F, Pancholi D. A case of Raine syndrome presenting with facial dysmorphism and review of literature. BMC Med Genet. 2018;19(1):76.

26. Skrzat A, Olczak-Kowalczyk D, Turska-Szybka A. Crohn’s disease should be considered in children with inflammatory oral lesions. Acta Paediatr. 2017;106(2):199–203.

27. Hart TC, Pallos D, Bowden DW, Bolyard J, Pettenati MJ, Cortelli JR. Genetic linkage of hereditary gingival fibromatosis to chromosome 17q24.2–q24.3 in congenital generalized hypertrichosis terminalis with or without gingival hyperplasia. Am J Hum Genet. 1998;62(4):876–83.

28. Jones G, Wilroy RS Jr, McHaney V. Familial gingival fibromatosis associated with progressive deafness in five generations of a family. Birth Defects Orig Artic Ser. 1977;13(3b):195–201.

29. Kortüm F, Caputo V, Bauer CK, Stella L, Ciolfi A, Alawi M, et al. Mutations in KCNG1 and ATP6V1B2 cause Zimmermann-Laband syndrome. Nat Genet. 2015;47(6):661–7.

30. Bauer CK, Schneeberger PE, Kortüm F, Altmüller J, Santos-Simarro F, Baker L, et al. Gain-of-function mutations in KCNQ3 encoding the small-conductance Ca2+-activated K+ channel SK3 cause Zimmermann-Laband syndrome. Am J Hum Genet. 2019;104(6):1139–57.

31. Wilson GR, Sunley J, Smith KR, Pope K, Bromhead CJ, Fitzpatrick E, et al. Mutations in SH3PXD2B cause Borrone dermato-cardio-skeletal syndrome. Eur J Hum Genet. 2014;22(6):741–7.

32. de la Dure-Molla M, Quentric M, Yamaguti PM, Acevedo A-C, Mighell AJ, Vikkula M, et al. Pathognomonic oral profile of Enamel Renal Syndrome (ERS) caused by recessive FAM20A mutations. Orphanet J Rare Dis. 2014;9:84.

33. Rutherfurd ME. Three generations of inherited dental defect. Br Med J. 1931;2(3678):9–11.

34. Pina-Neto JM, Moreno AE, Silva LR, Velludo MA, Petean EB, Ribeiro MV, et al. Cherubism, gingival fibromatosis, epilepsy, and mental deficiency (Ramon syndrome) with juvenile rheumatoid arthritis. Am J Med Genet. 1986;25(3):433–41.

35. Rutterford ME. Three generations of inherited dental defect. Br Med J. 1931;2(3678):9–11.

36. Higgins JE, Clayton-Smith J. Rutterford syndrome revisited: intellectual disability is not a feature. Clin Dysmorphol. 2015;24(3):125–7.