Clinical Case Report

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New radiological findings and radiculomegaly in oculofaciocardiodental syndrome with a novel *BCOR* mutation

A case report

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Abstract

Rationale: Oculofaciocardiodental syndrome (OFCD) patients who show radiculomegaly are very rare. We treated a new OFCD patient orthodontically, and performed longitudinal observation for 30 years. New findings, termed calcified-dental-papillae (CDPs) beneath open-apices (OAs) of developing radiculomegalies, pulp-stone-like-calcifications (PSLCs) and the process of radiculomegaly development were observed. A novel mutation of *BCL-6 interacting corepressor* (*BCOR*) was identified. Cone-beam-computed-tomography (CBCT) images of the radiculomegalies clarified their morphology.

Patient concerns: A female patient and her parents were referred to orthodontic clinic for alignment of the teeth.

Diagnosis: A CDP that harbored bulbous-round-calcified-tissue in the dental papilla beneath the OA of a developing radiculomegaly was found radiographically. PSLCs were observed in the dental pulp. Genetic analysis revealed a novel mutation c.265G>A on Exon 4 and diagnosed as OFCD. CBCT images confirmed round-calcified-tissue and PSLC and that the length of an affected canine was 38.0 mm and calculated as +14.8SD. These novel findings were not observed in lateral incisors and molars.

Interventions: Observation was performed for 29 years and 3 months including orthodontic treatment for 2 years and 9 months.

Outcome: Longitudinal follow-up for 26 years and 7 months after the treatment revealed that the development of radiculomegaly every few months or years, CDPs beneath OAs and PSLCs were observed. CDPs, PSLCs, and OAs were associated with radiculomegaly. The patient and the affected teeth including aligned teeth showed no particular change after the completion of the radiculomegaly. CBCT images showed bulbous-calcified-tissue and PSLCs in the mature dental pulp associated with radiculomegaly.

Lessons: The radiographical findings of CDP, OA and PSLC help early diagnose of OFCD and have importance for initiating orthodontic treatment until radiculomegaly completion.

Abbreviations: *BCOR* = BCL-6 interacting corepressor, CBCT = Cone-beam-computed-tomography, CDP = calcified dental papilla, OA = open apex, OFCD = oculo-facio-cardio-dental syndrome, PS = Pulpstone, PSLC = pulp-stone-like-calcification.

Keywords: calcified-dental-papilla, oculofaciocardiodental syndrome (OFCD), open apex, pulpstone, radiculomegaly

1. Introduction

Abnormal tooth morphology and number, including hyperdontia, hypodontia, oligodontia, multiple roots, and taurodontia, are noticeable dental anomalies. A rare congenital tooth anomaly called radiculomegaly,[1] which is also called tooth gigantism or long root, is an important uncommon finding in patients with oculofaciocardiodental syndrome (OFCD).

OFCD is rare and only occurs in female individuals because of its X-linked inheritance pattern and embryonic lethality for male individuals.[1–3] OFCD was first reported by Hayward[4] as cuspid gigantism and incisor radiculomegaly in an 18-year-old female individual with congenital cataracts. Marashi and Gorlin[5] described 3 additional cases with radiculomegaly of a canine and open apex (OA) of an incisor. After some reports of radiculomegaly,[5–7] Marashi and Gorlin[8] confirmed the syndrome by reporting an additional case.

OFCD is considered a syndrome as it consistently presents with a specific group of symptoms. These include ocular anomalies such as congenital cataracts; a typical facial appearance including a narrow face, high nasal bridge, broadening of the nasal tip, cleft palate or submucosal cleft palate; cardiac anomalies such as atrial or ventricular septal defects; and specific dental characteristics including radiculomegaly of the canines, oligodontia, delayed

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Tooth numbering system: FDI two-digit notations were used in this report. Each tooth is shown by two-digit number consist of quadrant code and tooth code. Quadrant codes show that 1: upper right, 2: upper left, 3: lower left and 4: lower right permanent teeth. Tooth codes show that 1: central incisor, 2: lateral incisor, 3: canine, 4: first premolar, 5: second premolar, 6: first molar, 7: second molar and 8: third molar. Tooth number 34 indicate lower left first permanent premolar, as an example.

Informed written consent was obtained from the patient for publication of this case report and accompanying images.

The authors declare no conflict of interest in relation to this study.

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eruption, and retained deciduous teeth. Radiculomegaly of the canines develops until the teeth reach the cortical plate of the orbit or mandible.[7,9] Genetic analysis has revealed that mutation in the *BCL-6 corepressor gene* (*BCOR*) on chromosome Xp11.4 causes OFCD.[10]

OFCD is caused by heterozygous mutation in the *BCOR* gene[11] encoding the corepressor of the transcriptional repressor BCL-6.[10,12,13]*BCOR* is a transcriptional corepressor that was originally identified by its ability to interact with the site-specific transcriptional repressor BCL-6.[14]*BCOR* encodes a 1755 amino acid protein that affects transcriptional repression as part of a large DNA-binding complex.

To date, a number of cases of OFCD have been documented,[11] including after orthodontic treatment.[15,16] Moreover, we report novel important findings of an OFCD patient who has not been previously reported. Radiographic examination showed round pulp stone-like calcification (PSLC) in immature dental pulp and a calcified dental papilla (CDP), which was seen beneath the wide immature OA of a permanent dental root in the mixed dentition. We followed the PSLC, CDP, and OA of this case for 30 years radiographically, including the period of orthodontic treatment, until radiculomegaly developed. Moreover, we observed the development of radiculomegaly from the initiation of dental root morphogenesis in the mixed dentition until its completion in the permanent dentition, and revealed associations between PSLCs, CDPs, OAs, and radiculomegaly. The development of radiculomegaly has not previously been reported. Furthermore, we performed genetic analysis and confirmed an OFCD case with a novel *BCOR* mutation.

2. Case report

A female patient (Fig. 1A), aged 10 years and 10 months, and her parents were referred to our orthodontic clinic for alignment of the teeth, which showed spacing and crowding (Fig. 2A). She was an only child of nonconsanguineous Japanese parents. The mental development of both parents was normal. There was no history of rubella during pregnancy, family history of cataracts, birth defects, or genetically transmitted diseases. When her mother was 32 years and 7 months old, the patient was born vaginally 2 days earlier than a full-term spontaneous delivery, after an uneventful pregnancy. Her birth height and weight were 48 cm and 2890 g with standard deviations of –1.2 and –0.9, respectively, when compared with Japanese data. Hammer toe was found on left second toe. A preauricular tag was found on her left tragus. Medical examination by interview with the parents revealed that many dental caries was found during the deciduous dentition. She had bilateral congenital cataracts, with no operation having been performed, and an artificial eye had been placed on the left side (Fig. 1). She had a ventricular septal defect that had closed at 3 months without any treatment. No cleft of the lips, maxilla, hard and soft palates, or the uvula was noted on extra- and intraoral examination. The dental arches showed spacing of the teeth, anterior dental crowding, and an Angle's Class I malocclusion which sowed normal mesio-distal relationship between upper and lower first molars (Fig. 2A). Diastemas were observed both between the maxillary central incisors and the mandibular (Fig. 2A). The mesiodistal widths of 12 and 22 were measured at 5.0 and 6.2 mm with standard deviations of –4.4 and –1.7, respectively, when compared with the Japanese female mean data.[17]

The anterior teeth were aligned from 11 to 15 years of age. Impacted 23 was retracted and extruded. The last oral and facial photographs (Fig. 1C) and digital panoramic radiograph were taken at 40 years and 1 month.

To follow the development of dental root morphogenesis, panoramic and intraoral radiographs were taken every one to a few years until completion of orthodontic treatment. The PSLCs, CDPs, and OAs were observed radiographically for 30 years after the first examination. Panoramic radiographs were taken digitally after 32 years and 9 months. Cone-beam-computed-tomography (CBCT) images were taken at 37 and 40 years of age.

For further investigation, chromosomal and genetic analyses of the patient were also performed at 14 and 37 years of age, respectively.

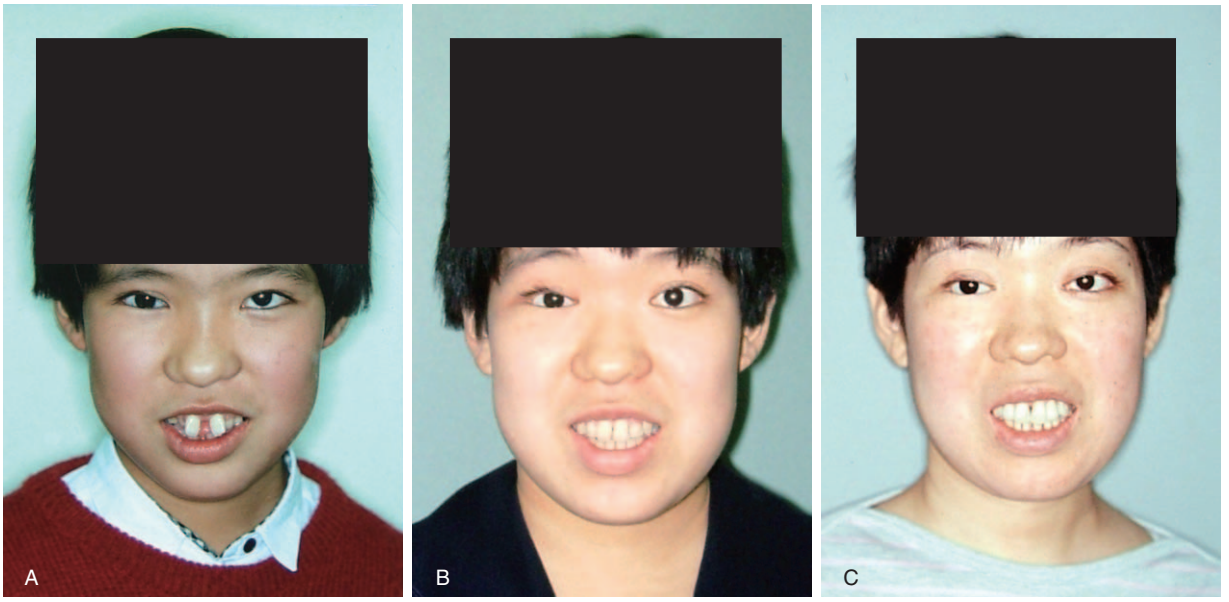

Figure 1. Facial photographs at 10 years and 10 months (A), 14 years and 9 months (B) and 40 years and 1 month (C) of age. The facial aspects are elongated, with broadening of the nasal tip, biprotrusive lips, and a thick lower lip.

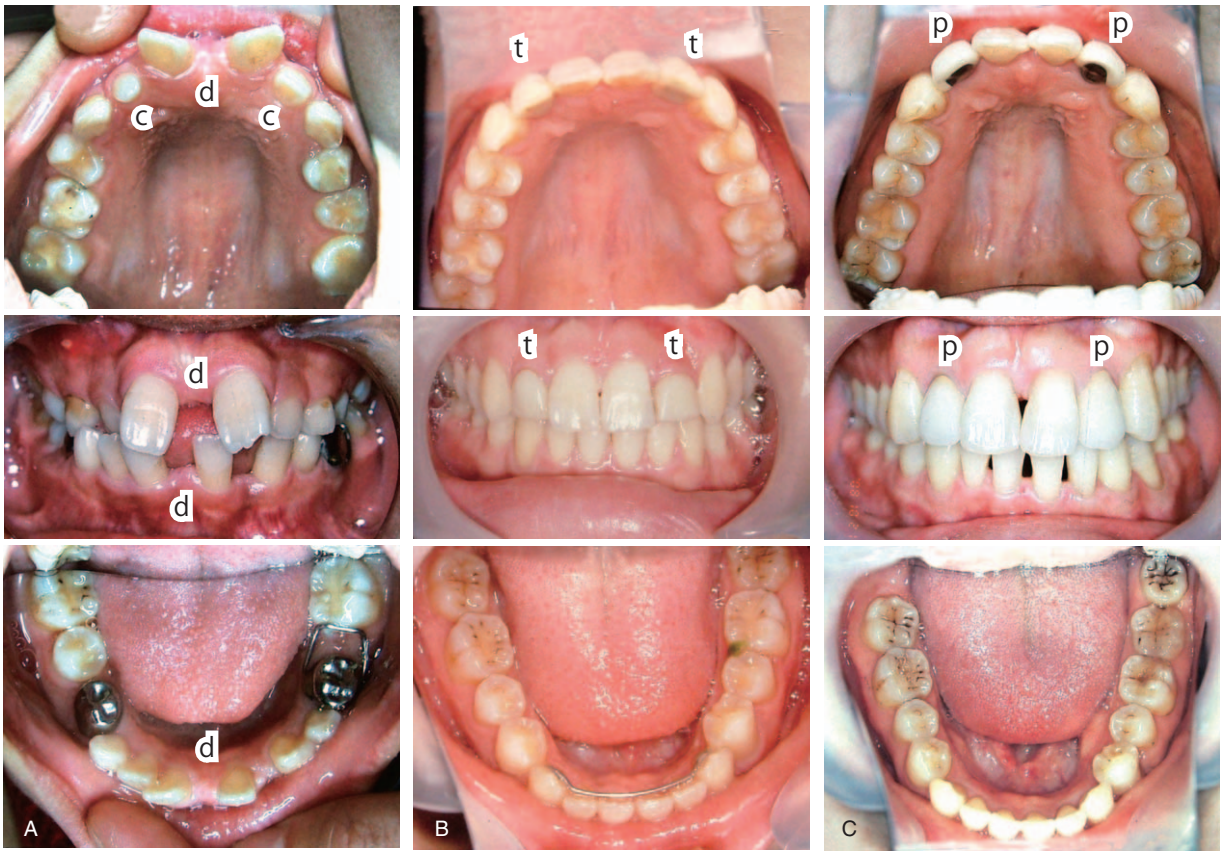

Figure 2. Oral photographs at 10 years and 10 months (A), 14 years and 9 months (B) and 40 years and 1 month (C) of age. (A) Angle's Class I malocclusion, spacing of the teeth, and anterior dental crowding are noted. Diastemas (d) were observed both between the maxillary central incisors and microdontia of the conical upper lateral incisors (c) can be seen. (B) The teeth are aligned after orthodontic treatment. The clinical crowns of 12 and 22 have been restored prosthodontically using provisional temporal crowns (t) and permanent crowns (p). c = conical upper lateral incisor, d = diasthema, t = provisional temporal crown, p = permanent crown.

Informed consents were obtained from the patient prior to any treatment procedure.

2.1. Clinical findings

Clinical examination revealed that the facial aspects were elongated, with broadening of the nasal tip (Fig. 1). The lips did not close normally, and were biprotrusive with a thick lower lip (Fig. 1). Orthodontic treatment was applied for 2 years and 9 months, and the teeth were aligned by 13 years and 9 months of age (Fig. 2B). After the treatment, 12 and 22 were restored prosthodontically, and photographs were taken at 40 years and 1 month (Fig. 2C). She was satisfied with her tooth alignment and occlusion aesthetically and functionally.

2.2. Radiographic findings

Serial panoramic and intraoral radiographs taken at 10 years and 10 months to 40 years and 1 month showed abnormal dental root maturation (Fig. 3). Some immature permanent teeth and tooth buds had PSLCs (Fig. 3A–H). The canines, central incisors, and first premolars had OAs (Fig. 3A–J). Round calcified tissue was found in some dental papillae beneath the OAs of permanent teeth (Fig. 3A–H). Tooth 34 had an OA that contained a very large CDP when compared with the tooth crown (Fig. 3A–G). CDPs that harbored large bulbous calcified tissue gradually appeared beneath the OAs of 13, 23, 33, 43, and 44 (Fig. 3A–I). The bulbous calcified tissue and PSLCs seemed to be gradually incorporated into the dental pulp cavity as the root apices of 13, 23, 24, 31, 32, 33, 34, 41, 43, 44, and 45 closed (Fig. 3C–L). Root apex formation of 34 was not completed by 19 years and 7 months of age (Fig. 3J). Elongated, thickened, clubbed, and bulbous calcified tissue- and PSLC-containing radiculomegalies were observed (Fig. 3K and L). At 32 years and 9 months, 34 years, and 37 years and 7 months, panoramic radiographs (data not shown) showed no significant change, as at 40 years and 1 month (Fig. 3L).

The Japanese mean apical completion ages[18] of the roots of central incisors, canines, and first premolars are 9–10, 12–15, and 12–13 years, respectively. The ages of completion of radiculomegaly in this case were prolonged until 14, 17, and 19 years, respectively.

2.3. Chromosomal and genetic analyses

Chromosomal analysis, which was performed when the patient was 14 years of age, showed 46, XX, which is consistent with a normal female individual. DNA analysis was performed at 37 years, and the results showed a mutation in Exon 4 of *BCOR* (data not shown). The mutation of the patient was detected using direct sequencing of Exons on *BCOR*. The novel mutation found on Exon 4 was c.265G>A, and a change in amino acid p.Val89Ile was also noted.

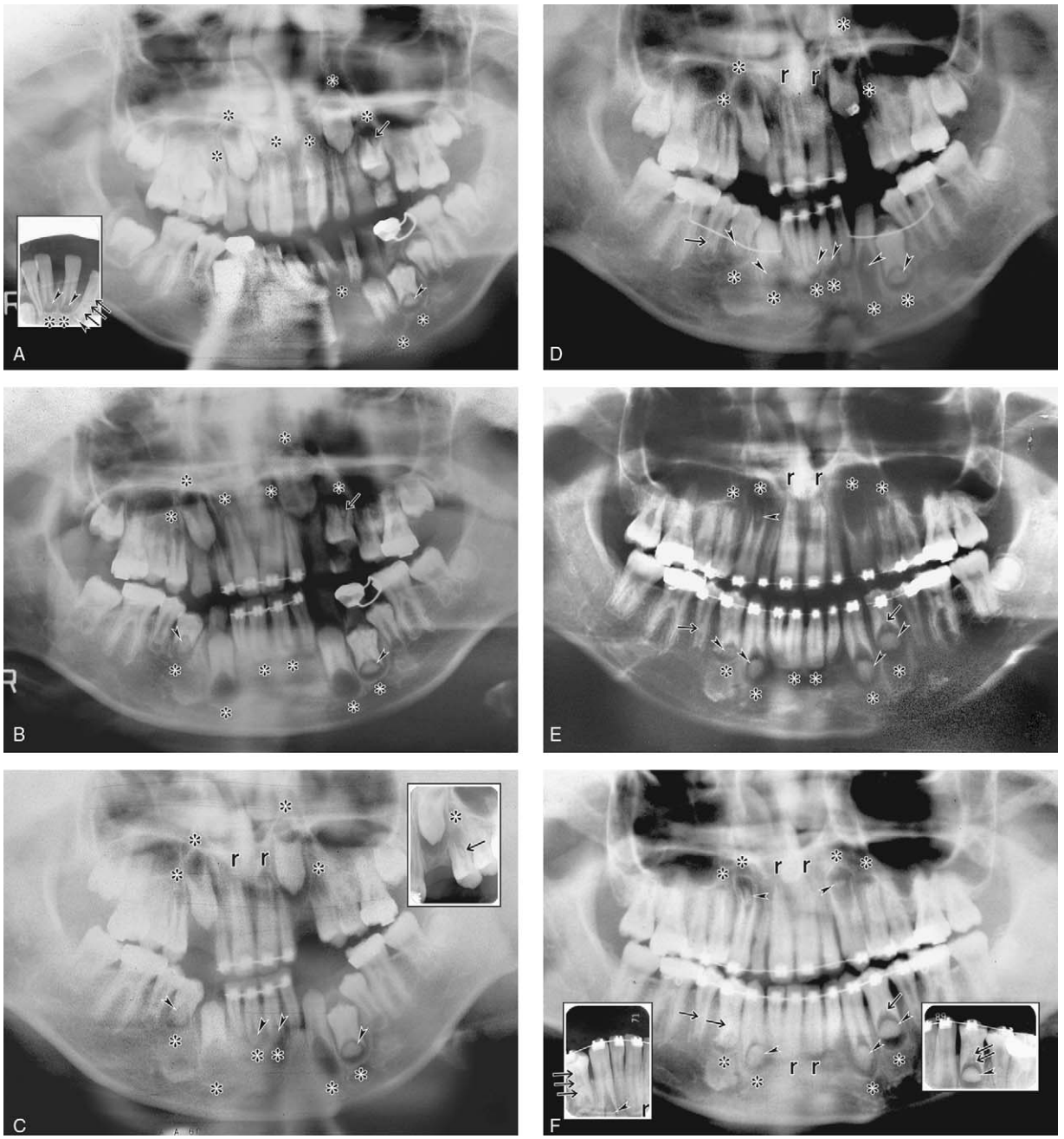

Figure 3. Panoramic and intraoral radiographs of the patient. (A) Mixed dentition when orthodontic treatment was initiated at 10 years and 10 months of age. CDPs containing round calcified tissue beneath the OAs of 31, 32, 34, and 41 (arrowheads). OAs of 11, 13, 14, 21, 23, 24, 31, 33, 34, and 41 (*), a PSLC in 24, and many PSLCs in 32 (arrows) are observed. 13, 15, 23, 24, 33, 34, 35, 43, and 44 are unerupted. (B) At 11 years and 5 months of age. The roots of 11, 13, 14, 21, 23, 24, 31, 33, 34, 41, 43, and 44 show OAs (*). CDPs (arrowheads) beneath the OAs of 34 and 44 are observed. The dental pulp of 24 contains a PSLC (arrow). (C) At 11 years and 10 months of age. All deciduous teeth have exfoliated. Bulbous or round calcified tissues are seen beneath the OAs of 31, 34, 41, and 44 (arrowheads). The roots of 13, 14, 23, 24, 31, 33, 34, 41, 43, and 44 show OAs (*). 11 and 21 show radiculomegaly (r). The dental pulp of 24 contains a PSLC (arrow). (D) At 12 years and 3 months of age. Round calcified tissues (arrowheads) appear in the dental papillae of 33 and 43. (E) At 13 years and 8 months of age. Hellman dental stage IV A. Round calcified tissue (arrowhead) in the dental papilla appears beneath the OA of 13. CDPs beneath the OAs of 33 and 43 are observed more clearly. PSLCs appear in the root pulp of 34 and 45 (arrows). (F) At 14 years and 2 months of age. Round calcified tissue (arrowhead) in the dental papilla of 23 begins to be visible. PSLCs are clearly observed in the root pulp of 34, 44, and 45 (arrows). The root apices of 31 and 41 are completed and 11, 21, 31, and 41 show radiculomegaly (r). (G) At 14 years and 9 months of age. Round calcified tissues in the dental papillae are seen in the root pulp of 13, 23, 33, 34 and 43 (arrowheads). Wide OAs can be seen in 13, 23, 33, 34, 43, and 44. PSLCs can be clearly observed in the root pulp of 34, 44, and 45 (arrows). (H) At 15 years and 6 months of age. The orthodontic appliance has been removed. Round calcified tissues are seen in the root pulp of 13, 23, 33, 34, and 43, which still display wide open apices. PSLC (arrow) is seen in the root pulp of 23. In the dental papilla of 34, newly formed round calcified tissue near Hertwig epithelial root sheath can be seen (arrowheads of 34). The roots of 13 and 23 curve distally. (I) At 17 years and 7 months of age. Some round calcified tissue and PSLCs can be clearly observed in the dental papillae and pulps of 34 and 44. 13, 23, 34, and 43 still show OAs. (J) At 19 years and 7 months of age. The root apices of 11, 13, 14, 21, 23, 24, 31, 33, 41, 43, and 44 have completed development and show radiculomegaly (r). The root apex of 34 still shows an OA (*). (K) At 28 years and 3 months of age. The root apices of 11, 13, 14, 21, 23, 24, 31, 33, 34, 41, 43, and 44 are completely developed and long thick radiculomegalies are observed (r). The root apices of 13 and 23 seem to penetrate the frontal processes of the maxilla. PSLCs and round calcified tissue-containing root pulp cavities are observed in 13, 23, 24, 33, 34, 43, 44, and 45. (L) At 40 years and 1 month of age. Radiographs were taken digitally. Significant changes were not observed after 32 years and 9 months of age. Teeth 12 and 22 were restored prosthodontically. arrows = PSLC, arrowheads = round calcified tissue, r = radiculomegaly, * = OA. CDP = calcified dental papilla, OA = open apex, PSLC = pulp-stone-like-calcification.

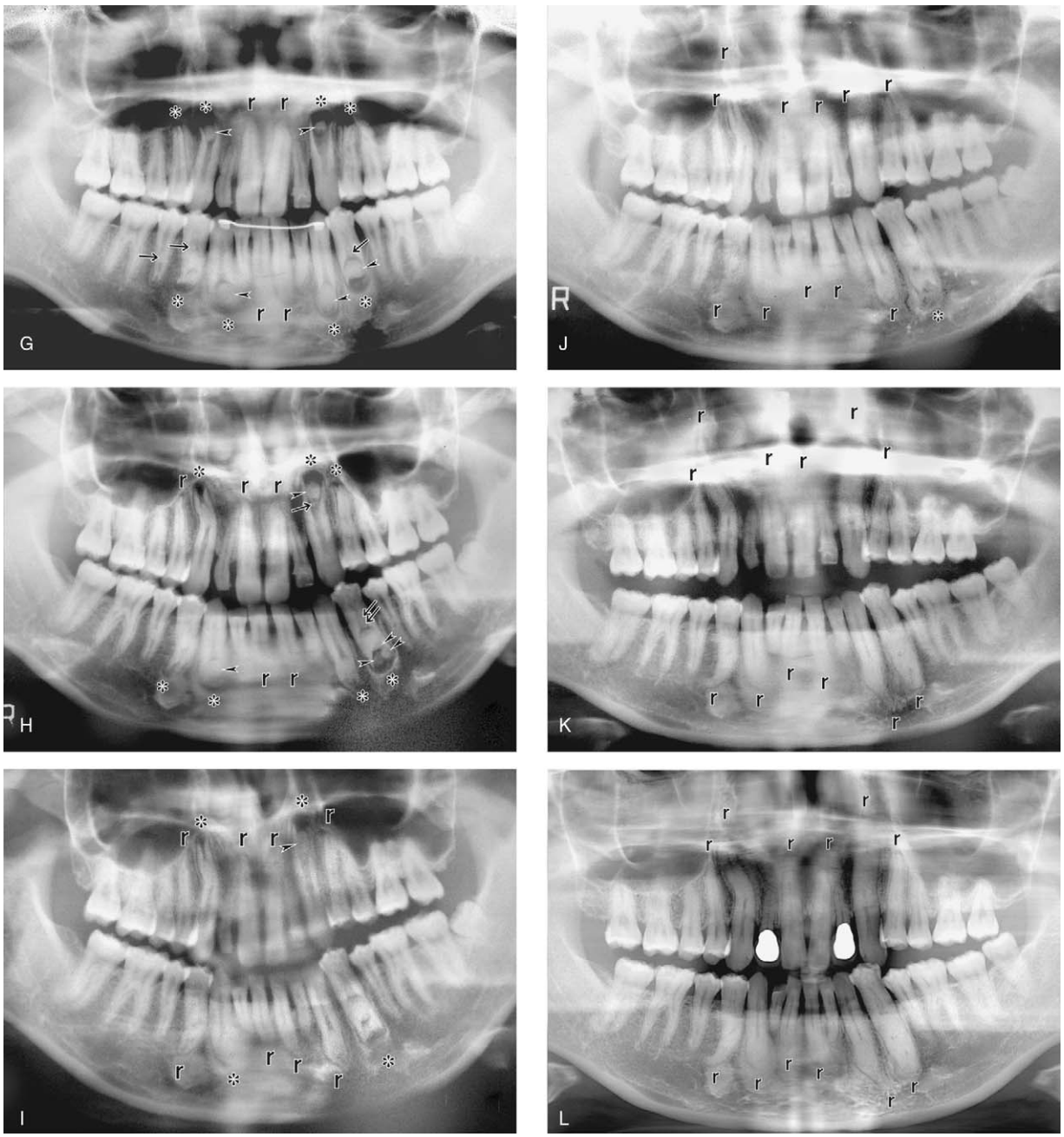

Figure 3. (Continued).

2.4. CBCT analysis

CBCT images of 13, 23, 33, 34, 43, and 44 showed radiculomegaly (Fig. 4). The roots of the maxillary canines were curved distolingually and their apices reached the cortical bone of the orbits (Fig. 4A and B). The labial cortical bone of the maxilla and mandible in the canine region was very thin (Fig. 4A–D). The root apices of 34 and 44 were curved labially and distally, and showed S- and J-shaped apices, respectively (Fig. 4C and E). The thickness of the 34 root was larger than its corresponding tooth crown (Fig. 4F). The bulbous calcified tissue that had been observed in the CDPs beneath the OAs of the developing root apices and PSLCs were observed inside the dental pulp of the canines, premolars, and incisors (Fig. 4).

We measured the lengths of 13, 23, 33, 43, 34, and 44 using CBCT images at 40 years and 1 month (Fig. 4), with results of 39.0, 44.8, 38.0 37.5, 35.9, and 31.0 mm and standard deviations of +7.2, +10.2, +14.8, +14.3, +15.8, and +10.5, respectively, when compared with the Japanese female mean tooth lengths.[17]

3. Discussion

Radiculomegaly is an important finding in OFCD.[7,9] Therefore, the diagnosis of OFCD could only be confirmed between 15 and 20 years of age, when the radiculomegaly becomes evident radiographically. In our case, the lengths of 23, 33, and 34, which showed radiculomegaly, continued to grow until 19 years of age. The Japanese mean completion age of the permanent dentition,

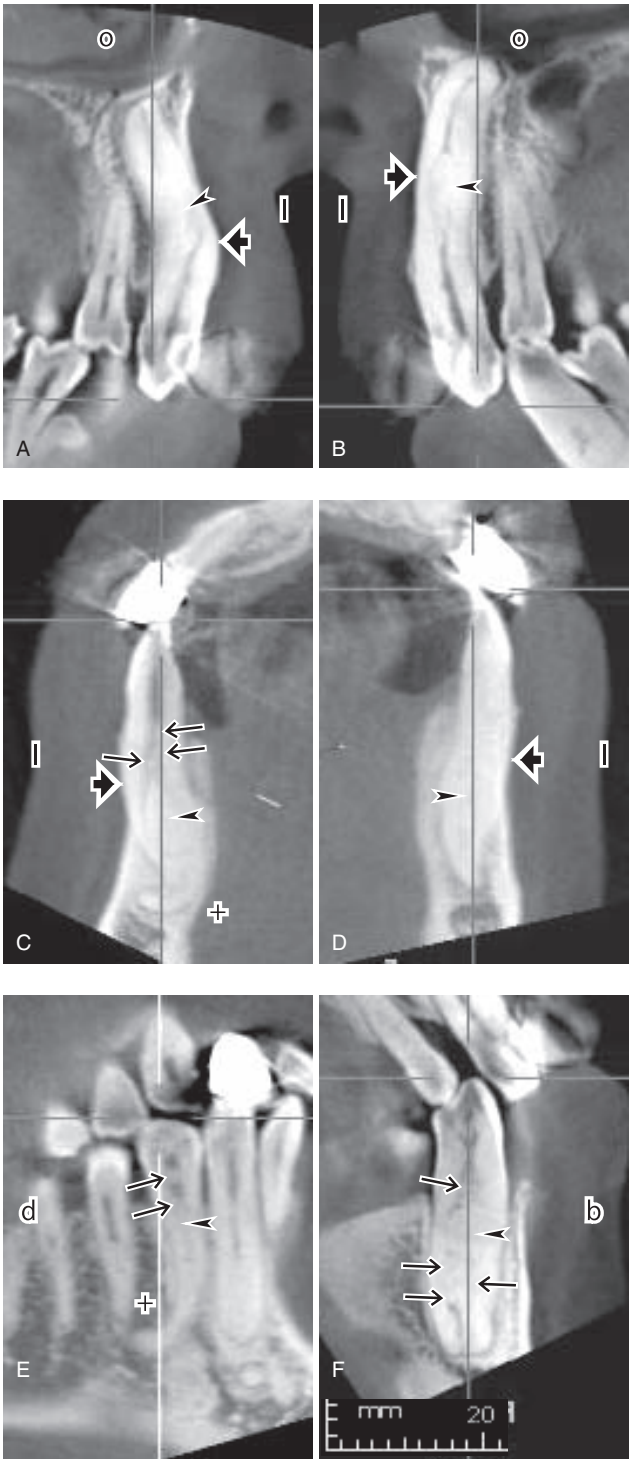

Figure 4. CBCT images of radiculomegalies. A to F show images of 13, 23, 43, 33, 44, and 34, respectively. S- and J-shaped curved roots are observed in 43 and 44 (C and E; +), respectively. Distolingually curved root apices of 13 and 23 reach the cortical bone of the orbits (A and B; o). The labial bone plates of the canines are very thin (A–D; thick arrows). PSLCs (C, E and F; arrows) and calcified tissue (A–F; arrowheads) that were observed in the CDP beneath the developing OA can be seen. Scale indicates 20 mm. arrows = PSLC, arrowheads = calcified tissue, b = buccal, d = distal, l = labial, o = orbit, thick arrows = thin labial bone, + = J-shaped curved root. CDP = calcified dental papilla, CBCT = Cone-beam-computed-tomography, OA = open apex, PSLC = pulp-stone-like-calcification.

termed Hellman dental stage III C, is 12 years.[17] In the present case, at the age of 12 years and 3 months, 13, 23, and 34 had not erupted as evident on panoramic radiography. Only a few photographs of OFCD cases have previously been presented; namely the surgical removal of radiculomegaly of a maxillary canine,[7] OAs of extracted affected teeth,[4,5,8] and an affected right mandibular canine.[19] In the present study, we suggested relationships between radiculomegaly, multi-PSLCs, CDPs, OAs and round calcified tissue, and showed the closure process of OAs.

Orthodontic movement of a tooth with radiculomegaly is difficult because of its long thick root. However, there are few case reports on the orthodontic treatment of OFCD patients[16,20] using an integrated orthodontic–prosthodontic approach[21] and orthognathic surgery.[15] Our case also involved alignment of the teeth orthodontically starting at 10 years of age after gingival fenestration to retract 23. We performed cephalometric analysis, which showed a large gonial angle and mandibular protrusion (data not shown) at 10 years of age as previous data has shown.[22]

The patient had many dental caries until Hellman dental stage III A. Caries control and tooth brushing instruction performed by a pedodontist, oral hygiene instruction avoided the need for endodontic dental pulp treatment.Endodontic treatment of a permanent tooth was not performed in our case despite the presence of many dental caries.

McGovern et al[23] reported OFCD in a mother and daughter, which highlighted the importance of hereditary transmission. In the present case, the patient's mother had no significant facial features consistent with OFCD, but the roots of her canines appeared slightly elongated (data not shown). Genetic analysis of the mother would determine whether the condition was hereditary.

Feberwee et al[11] reviewed and Danda et al[24] and Zhu et al[25] reported OFCD patients and corresponding sites of mutation in Exon on *BCOR*. Mutation of Exon 4, 5, 7, 8, 9, 10, 11, 12, 13 and deletion of Exon 2–15, 4–15, 9–15 were causative regions in the previous reports. The mutation on Exon 4 found in our OFCD patient was a novel, resulted to a translation into immature *BCOR*. Immature *BCOR* translated from *BCOR* with the mutation would have association with abnormal dentinogenesis of radiculomegaly.

BCOR expression in tooth primordial[26] and functional analysis of mesenchymal *BCOR* in tooth development using RNA interference showed the importance of *BCOR* for tooth development.[27] Using periodontal cells from an OFCD patient, BCOR expression was reduced in periodontal ligament cells.[28] *BCOR* mutation led to the upregulation of AP-2 in human mesenchymal stem cells and promoted osteo- and dentinogenesis.[29] The irregular PSLCs and CDPs might be the result of abnormal function of immature *BCOR*.

Dental morphogenesis is mediated by ecto-mesenchymal interactions, and its developing stage begins with epithelial thickening, followed by the bud, cap, and bell stages. The dental pulp and dentin are also induced by ecto-mesenchymal interactions, and they develop from the mesodermal dental papilla. After the tooth crown is formed in the bell stage by the ectodermal inner enamel epithelium, Hertwig epithelial root sheath, which contains outer and inner epithelia, proliferates in an apical direction and guides root morphogenesis. Odontoblasts are proliferated by the inner enamel epithelium and they secrete dentin to form the dental root. The dental pulp originates from

the mesenchymal dental papilla. The morphology of the tooth crowns did not show any significant abnormality in this case, except 12 and 22. With aging, pulp stones are sometimes found in the dental pulp of mature teeth, and they show laminated circular dentin histologically. PSLCs, CDPs, OAs, and radiculomegaly were associated with the mesodermal dental papilla, dentin, and pulp within the dental root.

A single round calcified tissue seen in a unilateral mandibular premolar of an asymptomatic 17-year-old male individual was reported by Piette.[30] The calcified material appeared localized, and the tooth showed normal crown morphology, including size, shape, and color, and the tooth responded normally to vitality testing. The calcified material that was surrounded by the periodontal ligament was attached to the apical portion of dentin and did not show enlargement or elongation of the root radiographically. Therefore, this case may not have been indicative of OFCD.

Canines, incisors, and premolars are the main teeth that show radiculomegaly in OFCD patients. The first molars, whose roots were completed before the affected roots were formed, the second molars, whose roots developed at approximately the same time as the affected roots, and the roots of 38, which formed after the affected roots completed development, were also unaffected. *BCOR* expression in the tooth primordium using *in situ* hybridization[26] and time-specific expression in a mouse developing molar tooth germ[27] suggest that the development of radiculomegaly is both tooth and time specific.

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Writing – review and editing: Joji Kato, Kazuhiko Kushima, and Fumikazu Kushima.

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