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Dental abnormalities observed in the oculo-facio-cardio-dental (OFCD) syndrome present in two Czech families bearing novel *de novo* *BCOR* pathogenic variants

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Abstract

Background The oculo-facio-cardio-dental syndrome (OFCD) is an ultra-rare multiple congenital anomaly. This report describes clinical findings emphasising dental phenotype in five, molecularly confirmed, female cases from two Czech families.

Case presentation Dental examinations were carried out. An orthopantomogram was taken in three patients, and all patients' intraoral cavities and teeth were photographed. Exome sequencing was performed in both probands. Results were validated by Sanger DNA sequencing which was also used to follow segregation of the variants in first-degree relatives. Dental abnormalities and congenital cataracts were present in all five cases, whilst other signs were variable and included facial dysmorphism, microphthalmia, and cardiac and skeletal abnormalities. Two individuals had cleft lip and/or cleft palate. Radiculomegaly occurred in three patients with permanent teeth and was diagnosed on orthopantomograms. Two patients had agenesis of permanent teeth. Malocclusion was also present in two patients due to crowding and a Class III malocclusion and mandibular overjet. *De novo* novel pathogenic variants in the *BCOR* gene were identified; c.2382del p.(Lys795Argfs*12) and c.3914dup p.(Gln1306Alafs*20) and co-segregated with the disease in each family.

Conclusions The OFCD syndrome has a unique dental phenotype and dentists should be aware of signs of this ultra-rare genetic disorder. All patients with congenital cataracts and dental abnormalities, including those without a family history, should be referred for genetic testing and indicated to specialised dental care.

Keywords *BCOR*, Dental anomalies, Congenital cataract, Novel pathogenic variants, OFCD syndrome, Syndromic microphthalmia-2 radiculomegaly

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Background

The oculo-facio-cardio-dental (OFCD) syndrome (OMIM #300166; ORPHA 2712; synonym: microphthalmia, syndromic-2) is an ultra-rare disease characterised by ocular abnormalities (comprising congenital cataract, microphthalmia, eyelid ptosis); facial dysmorphia (long narrow face, high nasal bridge, nose with cartilages separated at the tip, long philtrum, and clefts of the hard/soft palate); heart disease (ventricular and atrial septal defects, mitral valve prolapse) and a distinct dental phenotype [1–4].

Dental abnormalities in patients with the OFCD syndrome were first reported by Hayward in 1980 [5] describing a case with cuspid gigantism associated with congenital cataracts. Subsequent reports on the dental phenotype presented delayed primary/secondary dentition, persistent primary dentition with multiple unerupted teeth, duplicated teeth, hypodontia, oligodontia and fusion of teeth, palatal abnormalities, including cleft palate, high-arched palate, and bifid uvula [6–9]. However, the elongation of canine roots is a constant pathognomonic sign, since these roots continue to grow until they reach the orbit and lower parts of the mandible body. In vitro experiments, provided evidence that dental mesenchymal stem cells of patients with OFCD syndrome have an enhanced potential for dentin formation [1].

Skeletal anomalies, e.g. syndactyly of the second and third toes, hammer-type flexion of the second and fourth toes, radioulnar synostosis, and vertebral and rib anomalies, have also been reported [4, 9, 10]. Other rare phenotypic features include defective organ lateralisation (involving dextrocardia, asplenia and intestinal malrotation), hearing impairment, intellectual disability and/or delayed psychomotor development [8–10].

The OFCD syndrome is an X-linked dominant trait, caused by pathogenic variants in the *BCOR* gene (OMIM *300485) [11, 12]. The encoded BCOR protein functions as a corepressor for BCL6, a POZ/zinc finger transcriptional repressor, required for the germinal centre formation and may also influence cell apoptosis [13]. As OFCD syndrome affects only females it is presumed to be prenatally lethal in males [11, 14].

This study reports on the early dental signs and treatment options in five cases drawn from two families with genetically confirmed OFCD syndrome. Herein, we also underscore the need for increased awareness of rare genetic disorders such as OFCD syndrome in clinical dentistry.

Methods

Patients and clinical examination

Five females from two families of Czech origin diagnosed with the OFCD syndrome (aged 3–49 years) were longitudinally followed at the Department of Stomatology, Motol University Hospital, 2nd Faculty of Medicine Charles University, Prague. The study followed the recommendations of the American Dental Association (ADA) [15]. Panoramic radiographs of the oral cavity (OPG - orthopantomogram) were performed and intraoral/extraoral photographs were taken.

Genetic testing

Genomic DNA was extracted from venous blood using a Gentra Puregene™ blood kit (Qiagen, Hilden; Germany) or from saliva samples using Oragene™ OG-300 kit (DNA Genotek; Canada).

Exome sequencing was performed in both probands (Fig. 1) aged 45 and 30 years. Sequencing libraries were generated using a SureSelect Human All Exon V6 (Agilent Technologies, Santa Clara, CA, USA) and massively

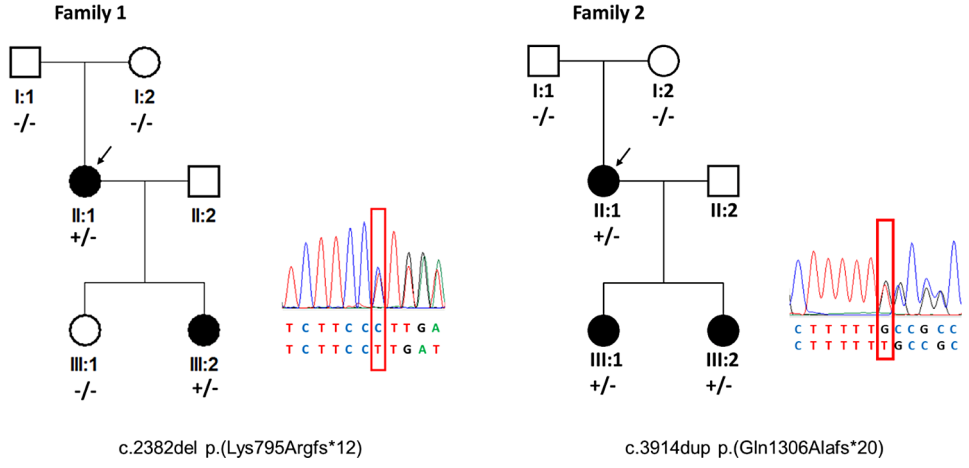

Fig. 1 Genetic testing in two Czech families with OFCD syndrome. Two novel loss-of-function variants were identified in the *BCOR* gene. NM_001123385.2 was taken as a reference sequence; probands are indicated by arrows; +/- = pathogenic variant present, -/- = pathogenic variant absent

parallel sequencing was performed on the NovaSeq 6000 platform (Illumina, San Diego CA; USA) as recommended by the manufacturer.

Sequence reads were aligned against the hg19 version of the human genome, using the Burrows-Wheeler Aligner (http://bio-bwa.sourceforge.net). Variant calling was performed with the Genome Analysis Toolkit (version 4.4.0.0; http://gatk.broadinstitute.org/hc/en-us). Rare variants (i.e. with a minor allele frequency ≤ 0.001 as per gnomAD v4.0.0; gnomad.broadinstitute.org), and in-house variant frequency data drawn from 2,132 individuals of Czech origin available through various massively parallel sequencing projects carried out by the National Centre for Medical Genomics (ncmg.cz/en) in genes known to be associated with cataract development as per Cat-Map (cat-map.wustl.edu/), were prioritised for further assessment. Targeted Sanger DNA sequencing utilised a set of primers 1 F 5′-TTCGTGGAAGTC ACTGATGC-3′, 1R 5′- CCGTCCAGAGTTTGTGAC CT-3′ and 2 F 5′- CTTCTTCGTCTGCACACAGC-3′, 2R 5′- GTCTCTGGGTCCTGAGCAAC-3′ confirmed the presence of the suspected *BCOR* disease-causing (pathogenic) variants in proband′s first-degree relatives. Standard paternity and maternity testing were performed as previously described [16]. The pathogenic potential of the selected variants was evaluated according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) recommendations [17] using the Varsome Clinical portal (clinical.varsome.com).

Results

Clinical findings and molecular genetic analysis

All five patients with OFCD syndrome had typical dental and ocular abnormalities, while some of them also exhibited cardiac and skeletal signs. The observed phenotypic features in all subjects included in the study are summarised in Table 1.

Exome sequencing revealed two novel loss-of-function variants in the *BCOR* gene (reference sequence NM_001123385.2); c.2382del p.(Lys795Argfs*12) in family 1 and c.3914dup p.(Gln1306Alafs*20) in family 2 (Fig. 1). These pathogenic variants co-segregated with the disease phenotype in all affected cases and were not found in unaffected parents confirming their *de novo* occurrence. Variants were classified as pathogenic (Class 5) based on the following ACMG/AMP criteria: PVS1_Very Strong (null variant in a gene where loss-of-function is a known mechanism of disease), PS2_Strong (*de novo*, both maternity and paternity confirmed),

Table 1 Clinical findings in five cases with genetically confirmed OFCD syndrome

Individual ID	F1-II:1	F1-III:2	F2-II:1	F2-III:1	F2-III:2
Age at dental examination	49 years	13 years	33 years	5 years	3 years
Facial features	Broad nasal root, broad nasal tip with septate nasal cartilage	Long narrow face, deep-set eyes, broad nasal root, epicanthal folds, broad nasal tip with septated nasal cartilage, laterally curved and thick eyebrows, long philtrum, dysplastic anteverted ears	Ptosis, broad nasal tip with septated nasal cartilage	N	Broad forehead, deep set eyes, broad nasal root, epicanthal folds, broad nasal tip, smooth philtrum, anteverted dysplastic ears
Cleft	N	Hard and soft cleft palate	N	N	Hard and soft cleft palate
Dental anomalies	Agenesis of 12, 45	Agenesis of 35, 31, 41, 45	N	N	Class III malocclusion with mandibular overjet
Radiculo-megaly	14, 13, 11, 23, 33, 41, 43	11, 21, 33, 32, 42, 43	13, 23, 33, 41, 31, 43, 44	Cannot be determined	Cannot be determined
Crown malformation	Cone-shaped tooth 22	N	N	N	N
Ocular anomalies	BE CC, surgery at 4 y in BE, strabismus, secondary glaucoma in BE	BE CC - surgery at 3 m in LE, 3.5 m in RE, LE microphthalmia, LE secondary glaucoma, LE amblyopia, LE ptosis	BE CC - surgery before 4 m	BE CC - surgery at 2 m in RE, 3 m in LE, RE secondary glaucoma	BE CC - surgery at 1.5 m in RE, RE microphthalmia
Cardiac anomalies	N	Atrial septal defect, patent ductus arteriosus	N	Atrial septal defect	Atrial septal defect
Failure to thrive	N	Y	N	N	Y
Skeletal anomalies	N	Right syndactyly of toes 2–3, hammer toe	N	N	N
Intellectual disability	N	N	N	N	N
Other	Primary lymphedema of lower limbs, bronchial asthma	Bronchial asthma, mild conductive bilateral hearing loss	N	Gastro-esophageal reflux	Gastroesophageal reflux

Legend: CC = congenital cataract, F1 = family 1, F2 = family 2, BE = both eyes, RE = right eye, LE = left eye, y = year, Y = yes, N = no, m = months

PP1_Supporting (co-segregation with the disease) and PM2_Moderate (absent in population databases), PP4_Supporting (phenotype or family history is specific for a disease with a single genetic aetiology).

Dental examinations

Individual II:1 from family 1 with permanent dentition

The female patient was referred for dental assessment at the age of 49 years. Typical features of OFCD syndrome-associated facial dysmorphism were noted. Intraoral (Fig. 2A-E) photographs showed permanent dentition with a dental implant as a substitution of 36, and fixed retainers in the frontal area which were placed due to hypermobile teeth caused by periodontitis, also visible on the OPG radiograph (Fig. 2F). OPG also documented radiculomegaly of 14, 13, 11, 23, 33, 41, 43. Other dental anomalies included the agenesis of 12, 45, and 22 with an atypical crown shape.

Individual III:2 from family 1 with mixed dentition

The female patient was examined at the age of 13 years but her dental age was closer to that observed in 10-year-old children. Teeth 15, 14, 13, 23, 24, 25, 34 still had not erupted. This observation corroborated that the eruption of her teeth was markedly delayed. Intraoral examination revealed mixed dentition with the agenesis of 35, 31, 41, 45 and cheilognathopalatoschisis (Fig. 3B). In addition, the removable orthodontic appliance for expansion (Fig. 3A) and fixed partial appliance in the lower frontal area (Fig. 3C-F) were present. In the OPG (Fig. 3H), the agenesis of 35, and 45 was noted. Radiculomegaly of 11, 21, 33, 32, 42, 43 with widely open apices and incomplete root formation were also detected. Intraoral radiographs (Fig. 3G, I) detected interdental caries represented by an initial carious lesion distally on 75. When she was 4 years old multiple extractions of deciduous teeth were performed in general anaesthesia due to strong caries-related destruction.

In addition to dental abnormalities, she had a long narrow face with facial asymmetry, left eye ptosis and hazy cornea as a result of eye surgery and secondary glaucoma. The patient also suffered from an atrial septal defect, patent ductus arteriosus, and bronchial asthma. Further examination revealed unilateral syndactyly of toes 2 and 3, and mild conductive hearing loss (Table 1).

Individual II:1 from family 2 with permanent dentition

Intraoral photographs (Fig. 4A-E) and OPG were taken in a younger female adult patient (aged 33 years) with a history of bilateral congenital cataracts. Prominent radiculomegaly of 14, 13, 23, 33, 31, 41, 43, 44, were observed on the OPG radiograph (Fig. 4F). Talon cusps were present on 21, 22 (Fig. 4D). Interestingly, she did not have cardiac signs of OFCD.

Individual III:1 from family 2 with primary dentition

The patient was referred for dental examination at the age of 5 years together with her mother and younger sister. Congenital cataracts were noted soon after birth. Intraoral photographs (Fig. 5A-E) showed full primary dentition with a median diastema in the upper arch. The crown of 81 was considerably wider than 71. Her mother reported a delayed eruption of deciduous teeth. The OPG image could not be taken due to her young age. She has an atrial septal defect and gastroesophageal reflux disease.

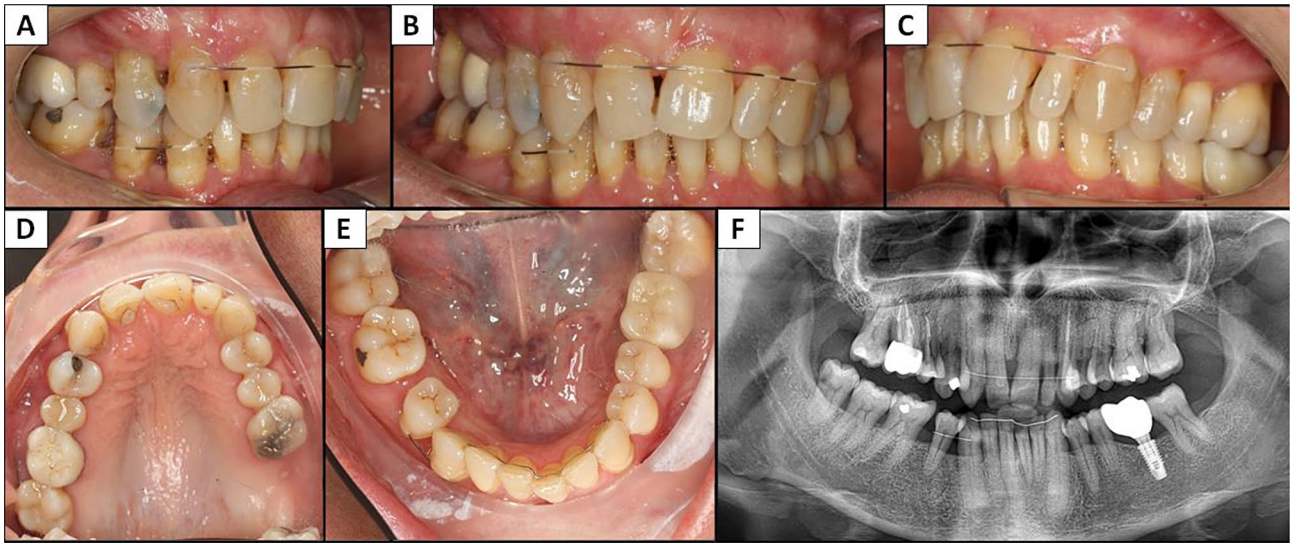

Fig. 2 Intraoral photographs and panoramic radiograph of case F1-II:1. (**A**) View from the right, (**B**) front and (**C**) left side, (**D**) the upper and (**E**) lower jaw shows teeth affected by periodontitis, (**F**) Panoramic radiograph documenting teeth with radiculomegaly 14, 13, 11, 23, 33, 41, 43, dental implant loco 36

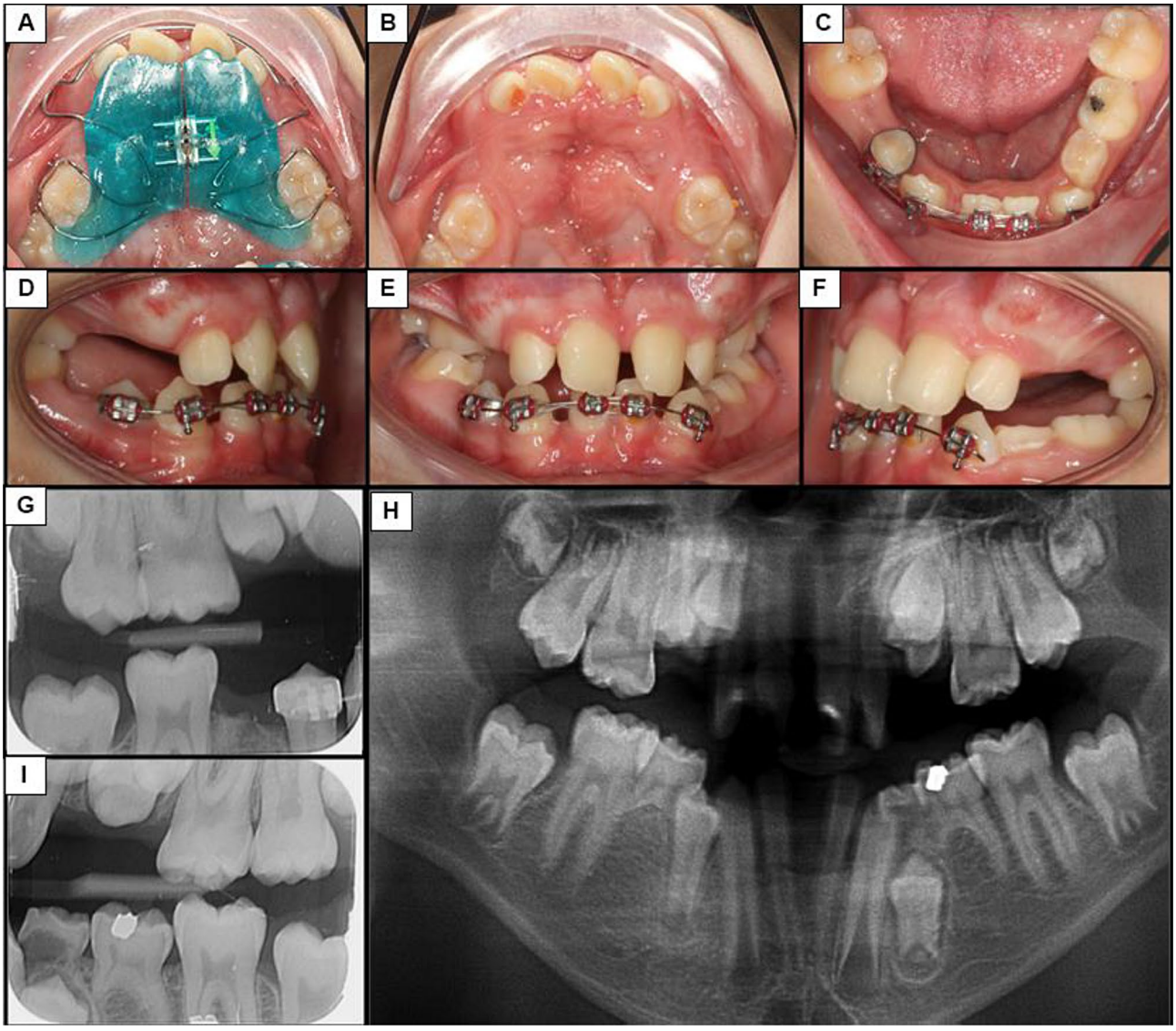

Fig. 3 Intraoral photographs, panoramic and intraoral radiographs of case F1-III:2. (**A**) Orthodontic removable appliance for expansion, (**B**) the upper jaw and palatal cleft, (**C**) the lower jaw, (**D**) view from the right, (**E**) front and (**F**) left side, **H**) panoramic radiograph shows mixed dentition with radiculomegaly affecting teeth 11, 21, 33, 32, 42, 43, (**G**) right bitewing radiograph, (**I**) left bitewing radiograph

Individual III:2 from family 2 with primary dentition

The 3-year-old patient had a history of bilateral congenital cataracts which were detected by prenatal ultrasound examination in the 32nd week of gestation. Intraoral examination (Fig. 6A-E) revealed a full primary dentition with Class III malocclusion with mandibular overjet and cleft of the hard and soft palate. She also had a congenital atrial septal defect and gastroesophageal reflux.

Discussion

We report clinical findings with a special focus on dental examinations in five Czech subjects with OFCD syndrome caused by two novel truncating pathogenic variants in *BCOR* c.2382del p.(Lys795Argfs*12) and c.3914dup p.(Gln1306Alafs*20). Although the number of disease-causing variants identified in *BCOR* has been increasing in recent years with the wide availability of genetic testing less than 100 have been reported worldwide [18].

All patients suffered from congenital cataracts and dental and/or occlusal anomalies, while other typical clinical signs typical for OFCD were variably present. As congenital cataracts are part of many other rare genetic syndromes dental abnormalities represent the most specific features for dentistry-aided diagnosis of the OFCD syndrome. From the stomatology point of view elongation of canine roots occasionally also first premolars or incisors [19, 20], represents the key radiodiagnostic feature of the syndrome [1, 4, 19, 21, 22]. Hypodontia, delayed

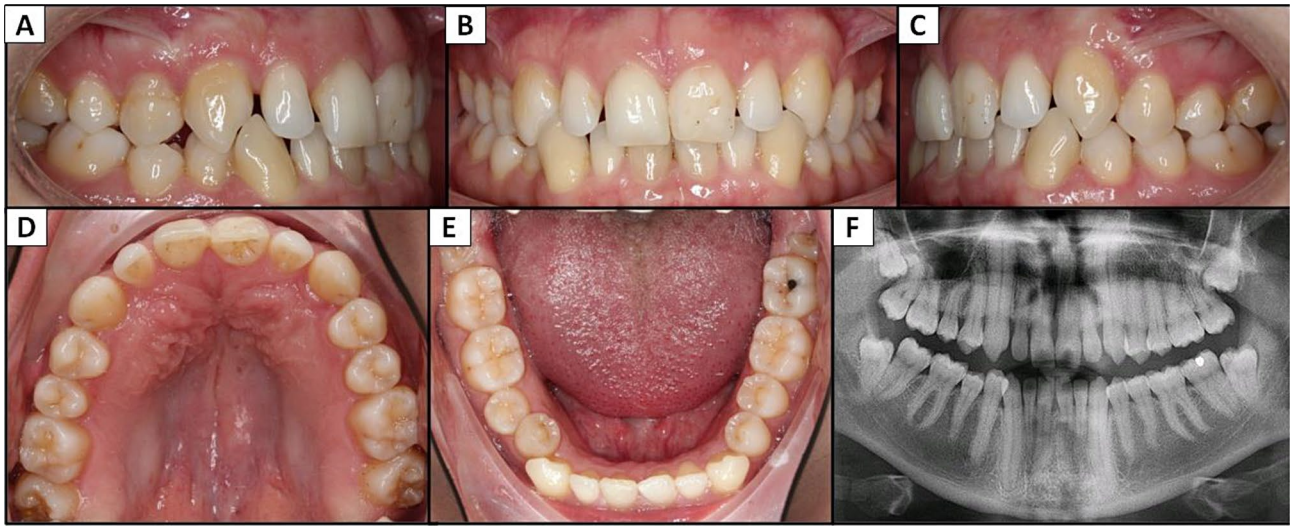

Fig. 4 Intraoral photographs and panoramic radiograph of case F2-II:1.(**A**) View from the right, (**B**) front and (**C**) left side, (**D**) the upper and (**E**) lower jaw, (**F**) panoramic radiograph shows complete permanent dentition with radiculomegaly of teeth 14, 13, 23, 33, 31, 41, 43, 44; dental talon cusps are present on picture D)

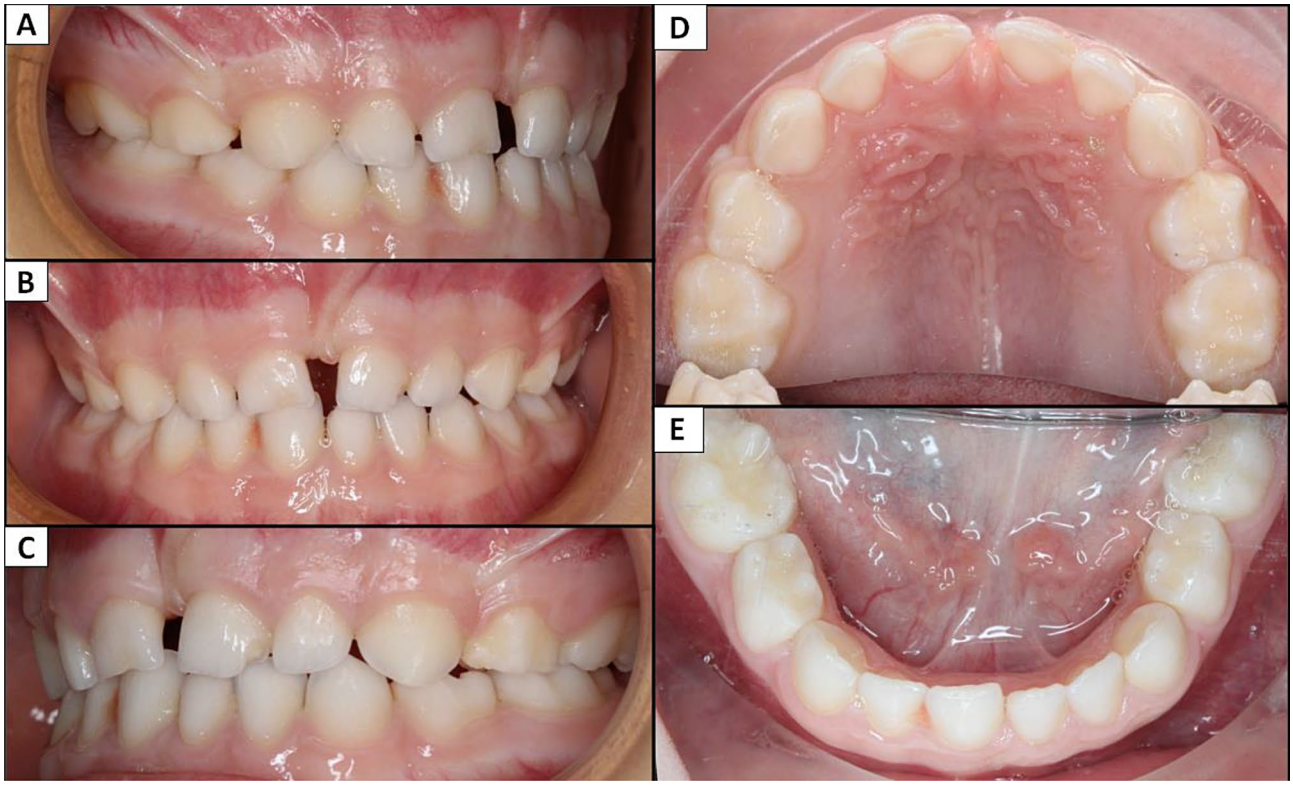

Fig. 5 Intraoral photographs of case F2-III:1. (**A**) View from the right, (**B**) front and (**C**) left side, (**D**) the upper and (**E**) lower jaw

permanent dentition and cleft palate are also variably present [2, 6, 7, 9, 14].

Although dental and occlusal anomalies, particularly radiculomegaly of the permanent canines, have already been described in OFCD, here we report omitted findings in patients with primary dentition. Delayed eruption of deciduous teeth in patient III:1 from family 2 and Class III malocclusion with mandibular overjet and cleft of the hard and soft palate in patient III:2 from family 2 were noted, which however are not specific for the diagnosis of OFCD syndrome. Our observations indicate that there is intrafamilial and interfamilial variability in the clinical course of the syndrome where symptoms also develop in an age-specific manner.

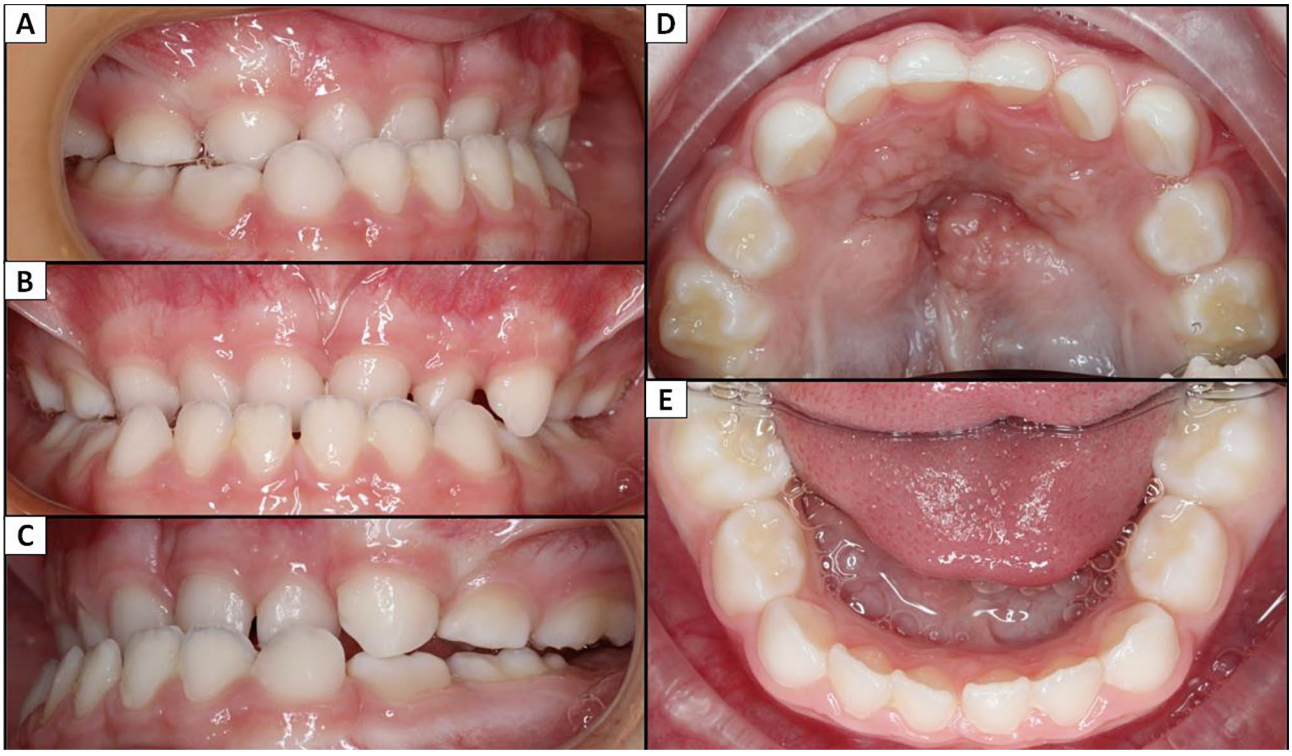

Fig. 6 Intraoral photographs of case F2-III:2. (**A**) View from the right, (**B**) front and (**C**) left side, (**D**) the upper jaw, signs of palatal cleft and (**E**) lower jaw

Patient management in the OFCD syndrome requires the cooperation of multiple medical specialists. For the dental treatment alone, the team should consist of a general dentist, a prosthodontist, an oral and maxillofacial surgeon, an implantologist and an orthodontist. Root gigantism may complicate orthodontic as well as endodontic treatment and tooth extractions. However, implant insertion is not a contraindication in radiculomegaly since we can augment the underlying bone with bone autotransplant and/or with a bioceramic material (ASTRA TECH Implants System E.V; Austria). Their long-term retention could be assessed only in the 49-year-old mother (Individual II:1 from family 1) where the implant was inserted 10 years prior to our examination and there were no complications. Furthermore, an early diagnosis and improved prevention of dental caries is important in these cases.

From the genetic point of view, it is important that a considerable number of sporadic patients with congenital cataracts harbor *de novo* mutations transmitted as an X-linked or autosomal dominant trait including pathogenic variants in *BCOR* as observed also in this study. Genetic testing which ought to be initiated based on suggestive dental findings could have a significant diagnostic value. Establishing the molecular diagnosis of the severe syndromic disease has profound implications for clinical management and preconception/reproductive counseling. It also substantially shortens the diagnostic Odyssea representing an additional stress for affected families. Finally, this study also highlights the need for raising awareness about rare genetic disorders, such as the OFCD syndrome, in general dental practice.

Conclusions

In conclusion, dentists should consider this ultra-rare genetic disorder in cases with radiculomegaly. All patients with congenital cataracts and dental abnormalities, including those without a family history of OFCD syndrome, should be referred to genetic testing followed by multidisciplinary care.

Abbreviations

ACMG/AMP	American Mollege of Medical Genetics and Genomics/ American Association of Molecular Pathology
ADA	American Dental Association
BCOR	BCL6 corepressor
BE	Both eyes
CC	Congenital cataract
LE	Left eye
OFCD	Oculo-facio-cardio-dental
OMIM	Online Mendelian Inheritance in Man
OPG	Orthopantomogram
ORPHA	Orphanet nomenclature of rare diseases
RE	Right eye

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Author contributions
MB – patients' dental treatment, methodology; MH – clinical geneticist, phenotyping, data interpretation; AN – visualization, orthodontic therapy; LD –molecular genetic analysis, contributed to manuscript drafting; MM – conceptualization; formal analysis, data interpretation; PL – ascertained and examined individuals included in the study, obtained funding for molecular genetic analysis, drafted the manuscript; TD –patients' dental treatment, methodology, data interpretation, preparation of the manuscript.All authors have read and agreed to the final version of the manuscript.

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Data availability
The datasets used and analysed during the current study are available from the corresponding authors upon request. The variants described in manuscipt were submitted to ClinVar database (Accession: VCV003242408.1 and VCV003242269.1).

Declarations

Ethics approval
The study was approved by the relevant Institutional Review Boards of General University Hospital in Prague (reference no. 65/16) and Motol University Hospital (reference no. EK-973IGA 1.12/11). The research followed the provisions of Art. 28–29 of the Act 373/2011 Coll., and followed the World Medical Association "Declaration of Helsinki" principles. All patients or their legal guardians and available unaffected first-degree relatives signed informed consent before participating in the study.

Consent to publish
Our institutional informed consent comprises a point where the patient. agrees with the publication of clinical data, including radiographs and intraoral photographs. However, patients did not agree with the publication of facial photographs.

Competing interests
The authors declare no competing interests.

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