• Letter to the Editor •

A novel frameshift mutation in the *BCOR* gene is associated with oculo-facio-cardio-dental syndrome: a case report

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Dear Editor,

Oculo-facio-cardio-dental (OFCD) syndrome is a rare X chromosome-linked dominant genetic disease with multiple system and site abnormalities. The typical traits shown in this disease are: 1) eye abnormalities, notably congenital cataracts, microphthalmia, and secondary glaucoma; 2) facial deformities, in particular long and narrow face, high nasal bridge, nasal tip cartilage division, and cleft palate; 3) heart abnormalities, including atrial septal defect, interventricular septum defect, patent ductus arteriosus, tetralogy of Fallot, mitral valve prolapse, tricuspid valve insufficiency, and aortic valve stenosis; 4) dental abnormalities, notably malocclusion of teeth; pulpal and periapical diseases; oligodontia, macrodontia, delayed tooth eruption, and radiculomegaly; 5) limb abnormalities, including short metacarpal bone, syndactyly, and hammer toe; 6) other system abnormalities, such as hearing impairment and delay in growth and development[1-3].

Genetic analysis of OFCD syndrome indicates that it is caused by mutations in the B-cell lymphoma 6 corepressor (*BCOR*). The *BCOR* gene is located on Xp11.4 and is known to have truncation, missense, frameshift, and deletion mutations, all of which produce premature termination codons, leading to different phenotypes of OFCD syndrome[2]. OFCD syndrome caused by this gene is the result of X chromosome-linked dominant inheritance, and all patients are heterozygous mutant females. A complete lack of this protein is fatal to male patients[4]. Mutations in the *BCOR* gene are rare and are manifested in daughters of mothers carrying the mutation.

In the present study, we identified a new frameshift mutation (p.Cys1080fs) in exon 6 of the *BCOR* gene, discovered in a Chinese mother and daughter through whole genome sequencing (WGS) technology. The results of this study extend the description of *BCOR* gene mutation points and provide a reference for genetic screening of patients with OFCD syndrome.

The study was approved by the Institutional Ethics Committee of Sichuan Academy of Medical Sciences and Sichuan People's Hospital (2022, No.330). Informed consent was obtained from all individuals (FM1, FM2, and FM3) after we explained the nature of the study.

CASE REPORTS

Case 1 The proband (daughter, family member 1; FM1) is 4 years old and was born at full term. The proband's mother (family member 2; FM2) and father (family member 3; FM3) are in good health and are not close relatives. FM1 was born with a weight of 3.9 kg, a birth height of 50 cm, and a head circumference of 35 cm.

At 2 months of age of FM1, a physical examination revealed congenital cataracts in both eyes. At age of 14mo, an examination revealed a 33-cm corneal reflection and a right eye deviation of 30°-35°, which was diagnosed as perceptual esotropia (Figure 1A1). Consequently, FM1 underwent bilateral cataract phacoemulsification and anterior vitrectomy.

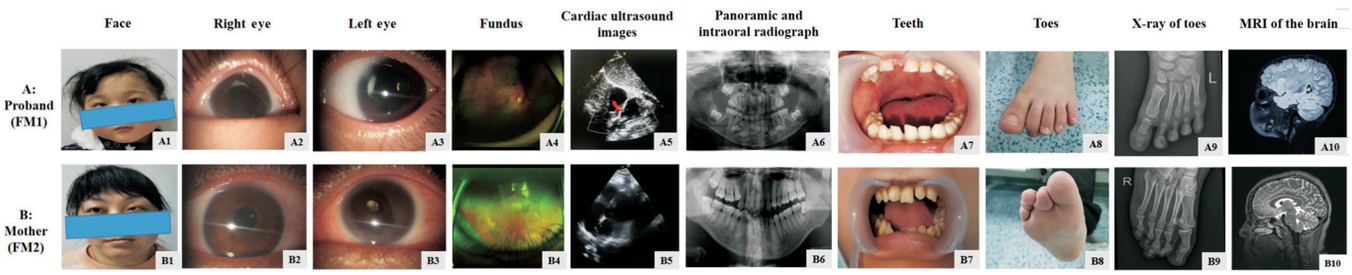

Figure 1 Clinical phenotypic characteristics of OFCD syndrome A: The proband (FM1). A1: Facial feature; A2, A3: Anterior segment of the right and left eyes of FM1 with intraocular lens implantation under slit lamp; A4: Fundus of left eye, showing scattered pigmentation; A5: Ultrasound image of the FM1's heart; A6: Panoramic and intraoral radiograph; A7: Oral cavity, indicating significant developmental abnormalities in the teeth; A8, A9: Photos and X-rays of the right toes, with the second toe increased curvature suggestive of hammertoe; A10: MRI of brain, which shows obvious focal demyelinating lesions in the frontal lobe. B: The proband's mother (FM2). B1: Facial feature; B2, B3: Slit lamp examination of anterior segment of both eyes with no obvious abnormalities in the right eye and congenital cataract in the left eye; B4: Fundus of right eye, showing scattered pigmentation; B5: Ultrasound image of the FM2's heart; B6: Panoramic and intraoral radiograph; B7: Oral cavity showing obvious developmental abnormalities in the teeth; B8, B9: Photos and X-rays of left toes, with the second and third toes increased curvature suggestive of hammertoes; B10: MRI of brain indicating completely normal. OFCD: Oculo-facio-cardio-dental; MRI: Magnetic resonance imaging.

At the age of 2.5y, bilateral intraocular lens implantation was performed. The postoperative visual acuity was counting fingers (CF) at 20 cm in the right eye and 0.25 in the left eye. After long-term amblyopia training, the proband's vision improved. At 4 years of age, visual acuity of FM1 was 0.02 in the right eye and 0.5 in the left eye. The right corneal diameter was approximately 9 mm, with evident nystagmus, and the left corneal diameter was 11 mm (Figure 1A2, 1A3). Fundus examination revealed scattered pigmentation in both eyes (Figure 1A4). The diagnosis included a number of vision deficits: right microphthalmia, right nystagmus, bilateral intraocular lens eyes, bilateral amblyopia, and bilateral retinal pigmentation.

In addition, regular physical examinations indicated that FM1 developed relatively slowly compared to children of the same age. Before the age of 2y, the child had limited communication skills—a small vocabulary, limited vocal expression with respect to her environment, and limited social skills—all of which led to a diagnosis of comprehensive developmental delay. At 4 years of age, language and other aspects of development in the proband were comparable to those of children of the same age. From the age of 3y 7mo to 4y, FM1 experienced recurrent secretory otitis media in both ears; however, hearing was not impaired.

FM1's face was unique: they have a round face, high forehead, wide nose, and pointed chin (Figure 1A1). We comprehensively examined FM1 based on eye symptoms and facial features. Cardiac ultrasonic indicated mild tricuspid valve regurgitation, 2.0 mm regurgitation beam, mill mitral regurgitation, and patent foramen ovale. Two layers of the membrane were pushed open by 2.0 mm, and the atrium-level fine bundle was shunted left to right (Figure 1A5). The oral examination showed slow tooth development, uneven dentition, and malocclusion. Delayed dentition, which is manifested as the 52nd and 82nd deciduous teeth not being erupted. Congenital loss of the 15th, 25th, 35th, and 45th (FDI notation) permanent teeth (Figure 1A6, 1A7). In terms of deformities in the feet, the second distal phalanx of both feet showed curvature suggestive of hammertoes (Figure 1A8, 1A9).

Magnetic resonance imaging (MRI) of FM1's brain showed that focal demyelinating lesions in the left and right frontal and parietal lobes may have occurred (Figure 1A10). Based on the above, the diagnosis is OFCD syndrome.

Case 2 FM2 is 32 years old and has a congenital cataract, microphthalmia, and esotropia in the left eye. She has not been treated and is blind in the left eye, with no cataracts in the right eye (Figure 1B1, 1B2, and 1B3). The fundus examination found scattered pigmentation in the right eye, while the left eye was unable to view the fundus owing to cataracts (Figure 1B4). FM2 has a round, asymmetrical face, high forehead, wide nose tip, and crooked mouth corners (Figure 1B1). Color Doppler echocardiography revealed congenital heart disease (atrial septal defect, left atrial enlargement, and tricuspid valve insufficiency; Figure 1B5). Oral examination revealed malocclusion and dysplasia of the right tooth: the nerve root of the first premolar of the right mandible was swollen, and the right maxillary premolar was missing (Figure 1B6, 1B7). The toe flat film revealed bilateral distal phalanges of second and third, showed curvature suggestive of hammertoes (Figure 1B8, 1B9). MRI of brain showed that the brain is completely normal (Figure 1B10). FM2 underwent atrial septal occlusion surgery, and exhibited good postoperative recovery. Based on the above, the diagnosis is OFCD syndrome.

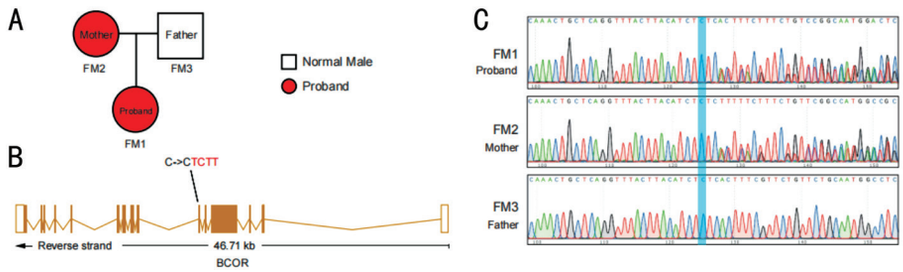

Figure 2 Whole genome sequencing A: Genetic pedigree of the family; B: The location of the frameshift on the transcript of *BCOR*; Boxes represent exons, and lines represent introns; C: Sanger sequencing results of the three samples. Different colors of the base peaks represent the different bases (green: A, red: T, blue: C, and black: G). The blue bar marks the last base C before insertion. Sanger sequencing results; the low transparence blue rectangle marks the site of chrX: 40070977. *BCOR*: B-cell lymphoma 6 corepressor.

WGS and Variants Calling DNA samples of all family members (FM1, FM2, and FM3) were extracted from throat swabs and further sequenced using an external HiSeqX sequencer (Illumina Inc., USA). We obtained 30× raw data points to perform the downstream workflow. After quality control, clean data were aligned to the hg38 human reference genome using the Genome Analysis Toolkit with burrows-wheeler aligner version 0.7.12, Plink v1.90b6.24, and Ensembl Variant Effect Predictor (VEP) for variant calling and annotation. Common Insertion and deletion (INDEL) and single nucleotide variant (SNV) were excluded from the gnomAD v3. 1, Asian dataset. Only those variants with "HIGH" or "MODERATE" annotations in the VEP results, rare occurrence (MAF<0.01) in the Asian population, and matched to the genetic relationship of the family were considered candidate mutation sites.

RESULTS

Novel High Impact INDEL of *BCOR* may Related to OFCD Syndrome We performed WGS on the all family members (FM1, FM2, and FM3; Figure 2A). In the data, all three samples were more than 30×, and the coverage was more than 90% (Table 1). We identified 7 195 331 INDELs or SNVs. Of these, 512 614 sites were rare in Asian populations. In those rare sites, there are 239 sites annotated as "HIGH" impact and 1734 as "MODERATE" impact by VEP. After screening, we found a frameshift variant (NC_000023.11:g.40070977_40070978insTCTT, NP_001116855.1:p.Cys1080fs) located in the 6th exon of *BCOR* on Xp11.4 (Figure 2B), which results in truncated BCOR protein; this variant appeared only in the FM1 and her mother FM2, indicating a typical X-dominant inheritance pattern.

We confirmed the high impact variant data in all three Binary Alignment Map format files; only FM1 and FM2 possessed almost half of the variant reads (Figure 3), suggesting that they were heterozygotes, whereas the reads of FM3 were all matched to the reference. Sanger Sequencing was performed to verify next generation sequencing results. As the cause of the insertion of "TCTT" and subsequent frameshift, the sequences of FM1 and FM2 are nearly all heterozygous after chrX:40070977. However, FM3 is normal; that is, the same as the next generation sequencing results (Figure 2C).

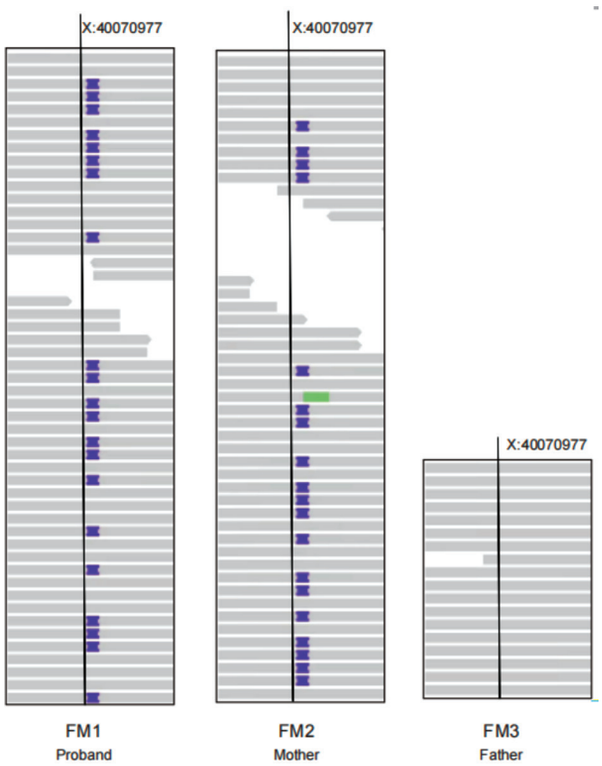

Figure 3 Visualization of the frameshift site in the Binary Alignment Map file using Integrative Genomics Viewer software The black line indicates site ChrX:40070977, and the purple symbol indicates an insertion.

Table 1 Whole genome sequencing: sequencing depth and genomic coverage

Members	Average depth	Coverage (%)
FM1	31.43	90.83
FM2	36.87	90.89
FM3	31.67	91.52

FM: Family member.

DISCUSSION

Here, we describe a mother-daughter case of OFCD syndrome, in which both subjects present with the typical clinical features of OFCD syndrome. OFCD syndrome is a very rare hereditary disease that mainly manifests in the eyes, face, heart, and teeth.

In this article, FM1 showed significant overall developmental delay in early childhood, but gradually improved in later stages and caught up with peers, which is consistent with the results observed by researchers such as Redwood *et al*[5]. FM1 presents with recurrent secretory otitis media, but no hearing impairment or obvious ear structural abnormalities. Previous studies report that only 9% of patients have mild conductive or sensorineural hearing loss[6]. Although certain researchers believe that the most characteristic diagnostic symptom of OFCD syndrome, is dental abnormalities, particularly abnormal dental root development[7]. However, during infancy, the teeth have not yet erupted, complicating the diagnosis of OFCD syndrome through the appearance of abnormal teeth.

In this study, congenital cataracts first appeared in FM1 in both eyes with right microphthalmia. The first appearance in FM2 was a congenital cataract in the left eye. Therefore, eye abnormalities are the first symptoms in infants and young children[4,7]. Meanwhile, according to previously published reports, the *BCOR* gene abnormalities account for almost all cases of OFCD syndrome. Animal experiments, using zebrafish and African clawed frog (*Xenopus laevis*), have shown that knockout of the *BCOR* gene results in dysplasia of the eyes, teeth, heart, bones, neural tubes, and other organs. BCOR protein expression has been detected in the lens, optic nerve, retina, and other eye tissues[8-9]. Therefore, at the genetic level, eye abnormalities are a typical manifestation of OFCD syndrome[8]. As the child grows, abnormalities in the face, teeth, heart, bone, and other dysplasias may be present, which should be viewed as signs of OFCD syndrome.

Recent reports on OFCD syndrome have focused on genetic testing. Most patients with OFCD syndrome have insertion-deletion mutations in the *BCOR* gene that produce termination codons in advance[6]. Unlike the patients in previous reports, the subject of our study and her mother underwent gene exon sequencing; as a result, it was discovered that the mutation site was exon 6 of the *BCOR* gene and there was a new frameshift mutation (p.Cys1080fs) that leads to the production of termination codons and truncated proteins. The *BCOR* gene base sequence of the FM3 is consistent with that in the gene library, so it can be considered that this case is a typical X-chromosome dominant inheritance: the mutated genes of the FM1 and FM2 are the same, and the first symptom is congenital cataract. The health and condition of the FM1 and FM2 in terms of vision, teeth, heart, ear, and other aspects are not completely the same. Differences in the phenotypic symptoms of OFCD are due to individual differences in the proportion of key X-chromosome histiocytes with *BCOR* mutation transcriptional activity[2]. In previous studies, it has been reported that patients with OFCD syndrome develop secondary glaucoma after cataract surgery. Although the FM1 and FM2 in this case had not yet developed glaucoma, it is recommended that long-term ophthalmic follow-up, early diagnosis, and early treatment should be performed for patients with OFCD syndrome.

In summary, this is the first case of both mother and daughter suffering from OFCD syndrome caused by a frameshift mutation (p.Cys1080fs) in *BCOR*. OFCD syndrome is a genetic disease involving multiple systems and organs, and eye abnormalities can be detected at early stages of the disease. Therefore, before tooth abnormalities are detected, eye abnormalities can serve as potential clinical predictors of OFCD syndrome[10]. This case confirms the important role played by ophthalmologists in managing the care of complex OFCD syndrome patients, and ophthalmologists are likely to be the first to meet and diagnose OFCD syndrome patients. However, the reported number of patients with OFCD syndrome diagnosed upon ophthalmological examination is very small, which indicates that ophthalmologists generally do not have a thorough understanding of the disease. Including OFCD syndrome in the regular professional education of ophthalmologists will help raise awareness of this disease and, it is hoped, lead to earlier diagnosis of OFCD syndrome in clinical settings. Early diagnosis and treatment of patients are crucial to improving their prognosis. Simultaneously, *BCOR* gene testing and genetic counseling and physical examination should be carried out for patients and other family members, especially patient's mothers or daughters or sisters, so that early intervention and treatment can be carried out. At present, there is no gene therapy for OFCD syndrome, which may be resolved with the rapid development of gene technology in the near future[4].

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