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CLINICAL REPORT

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Oculo–facio–cardio–dental syndrome with craniosynostosis, temporal hypertrichosis, and deafness

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We report the case of a 7-month-old girl with atypical oculo–facio–cardio–dental syndrome (OFCD). A novel de novo pathogenic mutation in the BCL6 interacting co-repressor gene (*BCOR*) (c.4540C>T; p.Arg1514*), was identified on the X chromosome. This case expands the phenotype of OFCD as it is the first report of a case presenting with craniosynostois, temporal hypertrichosis, supraorbital grooving, and underdevelopment of the midface.

KEYWORDS
BCL 6 interacting co-repressor gene, Gorlin–Chaudhry–Moss syndrome, oculo–facio–cardio–dental syndrome

1 | INTRODUCTION

Oculo–facio–cardio–dental syndrome (OFCD) (OMIM 300166) is an X-linked dominant disorder with characteristic ocular, craniofacial, cardiac, and dental findings in females with apparent lethality in males, first coined in 1996 (Gorlin et al., 1996). OFCD results from mutations in the BCL6 co-repressor (*BCOR*) gene on chromosome Xp11.4 and by 2009 over 60 cases had been reported in the literature (Hilton et al., 2009; Ng et al., 2004).

Since the first report of a likely case of OFCD the phenotype has expanded to include ocular findings such as congenital cataracts and microphthalmia, craniofacial features such as bifid nasal tip and high arched narrow/cleft palate, cardiac anomalies such as atrial and ventricular septal defects and dental anomalies such as radiculomegaly, delayed eruption, oligodontia, and retained primary teeth (Davoody, Chen, Nanda, Uribe & Reichenberger, 2012; Gorlin, 1998; Hayward, 1980; Hilton et al., 2009; Oberoi, Winder, Johnston, Vargervik & Slavotinek, 2005; Obwegeser and Gorlin, 1997; Opitz, Horn, Lehmann, Dimitrova, & Fasmers-Henke, 1998; Wilkie and Chambers, 1990). Intelligence is usually normal (Tsukawaki, Tsuji, Kawamoto & Ohyama, 2005).

This report describes an infant girl with atypical OFCD due to a mutation in *BCOR* and is the first case presenting with craniosynostosis, temporal hypertrichosis, supraorbital grooving, and midface hypoplasia.

2 | CLINICAL REPORT

A female child was born to non-consanguineous polish parents at 39 weeks, weighing 3.44 kg (50th centile). Paternal and maternal ages were 34 and 32 years, respectively, and the child was conceived naturally. Polyhydramnios was noted at 32 weeks gestation. The family history was unremarkable and the child has a healthy 5-year-old brother.

At birth a number of dysmorphic features were observed including temporal hypertrichosis, underdevelopment of the midface, supraorbital grooving, microphthalmia and gum hypertrophy (see Figure 1a–c). Several other congenital anomalies were present including craniosynostosis (right coronal, right lambdoid, and squamous temporal craniosynostosis with gross deformity of the calvarium, see Figure 2a–d), cleft palate, significant deviation of nasal septum, ventricular, and atrial septal defects with persistent ductus arteriosus and pulmonary hypertension, and bilateral cataracts. Unilateral severe conductive hearing loss was identified. Later, opacification of the right middle ear cleft with normal inner ear structures were noted on magnetic resonance imaging (MRI). Brain MRI, renal/abdominal ultrasound along with examination of the digits and genitalia were normal. At 2 weeks of age, the patient developed one short episode of supraventricular tachycardia. At 6 months of age, the patient was developmentally appropriate with a length and weight plotting between the 25–50th and 2nd–9th centiles, respectively.

3 | MATERIALS AND METHODS WITH RESULTS

High resolution array comparative genomic hybridization (Agilent SurePrint G3 CGH Microarray 4 × 180 K, Agilent design 022060) (aCGH) was performed postnatally and detected a maternally inherited

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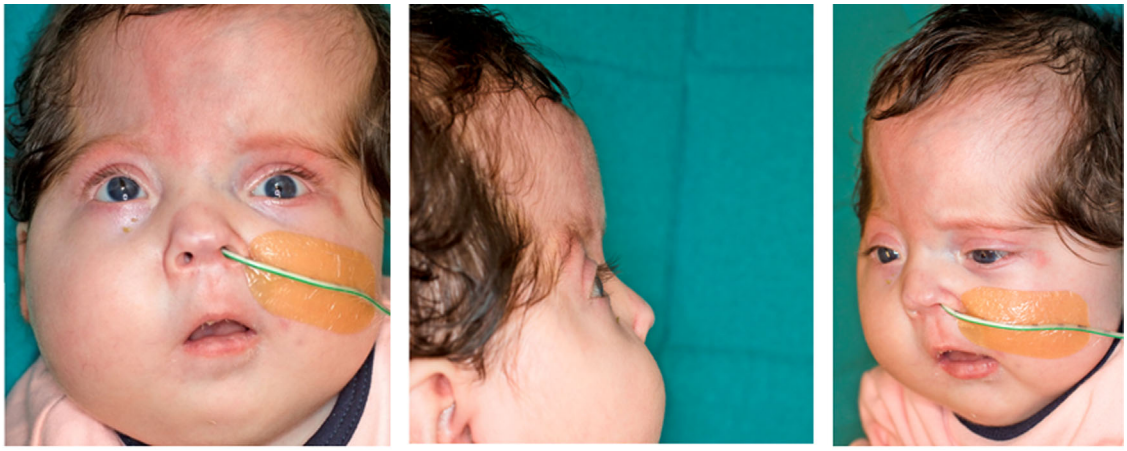

FIGURE 1 (a–c) Clinical photographs of the patient aged 3 months. Note the severe downward displacement of the frontal hair line [Color figure can be viewed at wileyonlinelibrary.com].

loss of approximately 554 Kb at chromosome 8p23.2-p23.1 which is considered a benign finding. Analysis of an extensive craniosynostosis gene panel (Sanger sequence analysis of *FGFR1* exon 7, *FGFR2* exons IIIa and IIIc, *FGFR3* exons 7 and 10, *TWIST1* exon 1, and *TCF12* and MLPA analysis of *TWIST1*, *RUNX2*, *ALX1*, *ALX3*, *ALX4*, *MSX2*, *EFNB1*) detected no pathogenic change. Whole exome sequencing (WES) (CentroXome PLATINUM) on the patient and both parents identified a single de novo pathogenic (class 1) variant (c.4540C>T; p.Arg1514*) in *BCOR*, consistent with a diagnosis of OFCD. Maternity and paternity was also confirmed. No other variants of unknown significance were identified and Sanger sequencing confirmed the presence of this mutation.

4 | DISCUSSION

This work further expands the phenotype of OFCD with the identification of a patient with features that have not been previously described, including temporal hypertrichosis, craniosynostosis with brachycephaly, supraorbital grooving and underdevelopment of the midface. Many of the previously described features of OFCD including microphthalmia, bilateral congenital cataracts, a broad nasal tip, cleft palate, ventricular and atrial septal defects and unilateral severe conductive hearing loss were also present (see Table 1). At 7 months of age, the infant was too young to assess for radiculomegaly or other classical OFCD dental abnormalities but the authors would wish to do

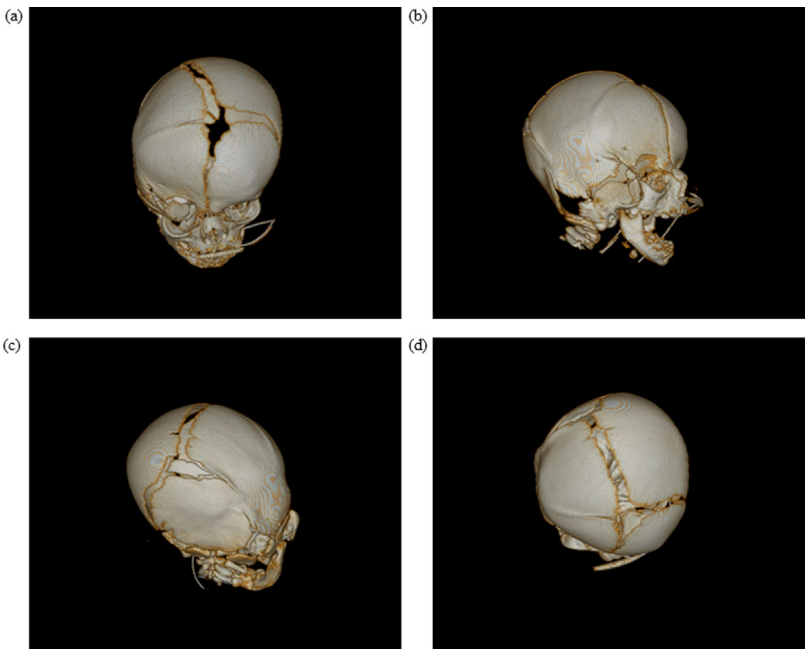

FIGURE 2 (a–d)Computed tomography of the skull. The four images are 3D reconstructions of the skull viewed from various positions and demonstrate right coronal, right lambdoid, and squamous temporal craniosynostosis with gross deformity of the calvarium and right orbital cavity [Color figure can be viewed at wileyonlinelibrary.com].

TABLE 1 Summary of the clinical features of oculo–facio–cardio–dental syndrome and the presented case

Clinical feature	Classical OFCD (%)	Presented case
Teeth		
Abnormalities	22/22 (100)	Too early (may be detected in the future)
Radiculomegaly	20/22 (91)	Too early
Delayed/persistant/unerupted dentition	18/22 (82)	Too early
Hypodontia/duplication/fusion	14/22 (63)	Too early
Skeletal		
Abnormalities	28/29 (97)	+
Craniosynostosis	ND	+ (multiple sutures)
Hands and feet—Abnormal distal phalanges	1/28 (4)	–
Orofacial		
Brachycephaly	ND	+
Underdevelopment of the midface	ND	+
Hypertrichosis of scalp,face, trunk	ND	+
Depressed supraorbital ridges	ND	+
Broad nasal tip +/– septated nasal cartilages	25/26 (96)	+
High arched narrow palate/cleft	8/26 (31)	+
Ocular		
Microopthalmia/microcornea	28/34 (82)	+
Congenital cataract	34/34 (100)	+
Coloboma	1/34 (3)	–
Secondary glaucoma	4/32 (12)	–
Ears		
Hearing loss	5/34 (15)	+
Congenital heart		
VSD/ASD	20/27 (74)	+
Genitalia		
Underdevelopment of the genitalia	ND	–
Intellect/psychomotor delay		
Intellectual disability	6/34 (18)	–

This table is constructed from modifications made to a published table [Hilton et al., 2009].
ND, Not described.

so when the patient is an appropriate age (Barthelemy, Samuels, Kahn, & Schendel, 2001).

The mutation identified in *BCOR* (c.4540C>T; p.Arg1514*) introduces a stop codon. Such premature stop codons may trigger nonsense-mediated decay of the mRNA although the generation of C-terminally truncated protein species is also possible. Hilton et al. (2009) observed in females with OFCD that X-inactivation is grossly skewed in favor of the wild-type allele which suggests loss of wild-type BCOR protein confers significant selective disadvantage. Females with OFCD syndrome are therefore functional mosaics, with cell populations and tissues expressing either wild-type BCOR (where lack of BCOR function is presumed lethal) or no BCOR/truncated BCOR (where lack of BCOR function can be supported). In hemizygous males, truncating mutations are hypothesized to lead to a complete loss of *BCOR* function and are presumed to be lethal. To date, no genotype–phenotype correlation has been identified.

Human Gene Mutation Database (HGMD) and literature reviews did not identify a previous case of OFCD with craniosynostosis as a clinical feature. This raises the possibility that the current case might represent a clinical fusion of two unrelated genetic events, mutation in the *BCOR* locus, and an unidentified other pathology. The alternative explanation is that *BCOR* mutation can cause craniosynostosis in this and a minority of other patients. As analysis of an extensive craniosynostosis gene panel and exome sequencing did not identify any putative pathogenic mutation in a gene known to result in craniosynostosis, and WES is otherwise unremarkable, we lean toward the possibility that the craniosynostosis in the presented case may be attributable to the mutation in *BCOR*.

In some clinical aspects, the presented case resembles the very rare Gorlin–Chaudhry–Moss syndrome (GCMS) (OMIM 233500) (Gorlin, Chaudhry, & Moss, 1960). Craniosynostois, hypertrichosis, and underdevelopment of the midface are fundamental features of

GCMS but, until this case report, have not been associated with OFCD (Adolphs et al., 2011; Aravena, Passalacqua, Pizarro, & Aracena, 2011; Ippel, Gorlin, Lenz, van Doorne, & Bijlsma, 1992; Rosti et al., 2013). Common features to both OFCD and GCMS, present in this case, include microphthalmia and/or microcornea, palatal, cardiac, and dental abnormalities (Adolphs et al., 2011; Aravena et al., 2011; Hilton et al., 2009; Rosti et al., 2013). Rosti et al. (2013) also noted that all patients with reported GCMS have been female with no history of parental consanguinity and subsequently suggested that GCMS may follow an X-linked dominant inheritance pattern, resulting in male lethality. The authors however recognize in the presented case the facial features and pattern of craniosynostosis, involving multiple sutures (right coronal, right lambdoid, and squamous temporal) are not in keeping with the usual pattern noted in GCMS (isolated coronal). There is also absence of labial hypoplasia which is considered a cardinal feature of GCMS. We await further reports to that which may establish an association between OFCD and GCMS.

In summary, we present an atypical case of OFCD, due to a novel mutation in *BCOR*. The case expands the phenotype of OFCD to include temporal hypertrichosis, craniosynostosis with consequent brachycephaly, supraorbital grooving, and underdevelopment of the midface.

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CONFLICTS OF INTEREST

The authors have no disclosures or other conflicts of interest to report.

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