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ORIGINAL INVESTIGATION

Expanding the phenotype of the X-linked *BCOR* microphthalmia syndromes

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Abstract

Two distinct syndromes arise from pathogenic variants in the X-linked gene *BCOR* (BCL-6 corepressor): oculofaciocardiodental (OFCD) syndrome, which affects females, and a severe microphthalmia ('Lenz'-type) syndrome affecting males. OFCD is an X-linked dominant syndrome caused by a variety of *BCOR* null mutations. As it manifests only in females, it is presumed to be lethal in males. The severe male X-linked recessive microphthalmia syndrome ('Lenz') usually includes developmental delay in addition to the eye findings and is caused by hypomorphic *BCOR* variants, mainly by a specific missense variant c.254C > T, p.(Pro85Leu). Here, we detail 16 new cases (11 females with 4 additional, genetically confirmed, affected female relatives; 5 male cases each with unaffected carrier mothers). We describe new variants and broaden the phenotypic description for OFCD to include neuropathy, muscle hypotonia, pituitary underdevelopment, brain atrophy, lipoma and the first description of childhood lymphoma in an OFCD case. Our male X-linked recessive cases show significant new phenotypes: developmental delay (without eye anomalies) in two affected half-brothers with a novel *BCOR* variant, and one male with high myopia, megalophthalmos, posterior embryotoxon, developmental delay, and heart and bony anomalies with a previously undescribed *BCOR* splice site variant. Our female OFCD cases and their affected female relatives showed variable features, but consistently had early onset cataracts. We show that a mosaic carrier mother manifested early cataract and dental anomalies. All female carriers of the male X-linked recessive cases for whom genetic confirmation was available showed skewed X-inactivation and were unaffected. In view of the extended phenotype, we suggest a new term of X-linked *BCOR*-related syndrome.

Introduction

Oculofaciocardiodental (OFCD) and severe X-linked microphthalmia syndromes are related conditions caused by allelic pathogenic alterations in *BCOR* (BCL-6 corepressor). OFCD is an X-linked dominant condition, affecting females (presumed male lethal), with examples of mother-to-daughter transmission. Skewed X-inactivation (90–100%) has been demonstrated in informative cases (Ng et al. 2004). It is characterized by the pathognomonic association of congenital or early onset cataract with dental anomalies (including radiculomegaly, delayed primary/secondary dentition, hypodontia, fusion of teeth), with a variety of other features. These other features are principally ocular (microphthalmia, cataract, glaucoma, retinal detachment), cardiac (septal defects), skeletal (hammer toes or camptodactyly, 2–3 toe syndactyly, broad halluces, radioulnar synostosis, scoliosis), and facial anomalies (cleft palate, septate nasal cartilage, long narrow face, and arched eyebrows). Less frequently, they include mild developmental delay (11%), posterior fossa anomalies (in a fetal loss), hearing impairment (9%) and defects of laterality (situs inversus, asplenia) in a single case (Ng et al. 2004; Horn et al. 2005; Oberoi et al.

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2005; Hilton et al. 2009; Davoody et al. 2012; Lozic et al. 2012; Kantaputra 2014; Surapornsawasd et al. 2015; Ma et al. 2016). In typical OFCD cases, *BCOR* is affected by a variety of null variants: nonsense, splicing, frameshift, deletions of part or all of the coding sequence, predicted to lead to nonsense-mediated decay. Asymptomatic mosaic female carriers have been described: Hilton and colleagues refer to the asymptomatic mother of case XVII; mosaicism was estimated by a reduction of the Sanger sequencing peak to 75% as opposed to 50% for her fully manifesting daughter (Hilton et al. 2009). Furthermore, individuals with *BCOR* pathogenic variants with mainly ocular features are also reported (Ng et al. 2004; Hilton et al. 2009; Ma et al. 2016).

BCOR pathogenic variants have also been identified in affected males with X-linked recessive severe ('Lenz') microphthalmia. In 2004, the missense variant c.254C>T, p.(Pro85Leu) was identified in an affected male, and segregated with disease phenotype (Ng et al. 2004) and since then further cases described (Hilton et al. 2009; Suzumori et al. 2013). Recently, a de novo novel *BCOR* missense variant (c.1619G>A; pArg540Gln) was identified in a boy with congenital glaucoma, complex cardiac anomalies, dextrocardia and cerebral white matter hypoplasia, following sequencing analysis of *PITX2, FOXC1* and *BCOR* (Zhu et al. 2015). Although the causative nature of this missense variant could not be established with certainty, supporting evidence from in silico analysis and absence of variant from control cohorts was highly suggestive.

Only a small percentage of males with severe microphthalmia (< 1% in our series, unpublished data), even with an X-linked inheritance pattern, carry *BCOR* variants (Hilton et al. 2009). The features described in males harboring the p.(Pro85Leu) variant in *BCOR* include: bilateral microphthalmia or anophthalmia, microcephaly, hypoplastic corpus callosum, mild–severe developmental delay, radioulnar synostosis, simple ears, no dental anomalies, cardiac anomalies, multiple partial finger syndactyly, fifth finger clinodactyly, and hypospadias (Ng et al. 2004; Hilton et al. 2009; Suzumori et al. 2013). Although the features of so-called 'Lenz' microphthalmia are broader (Lenz 1955; Traboulsi et al. 1988), some of these may be explained by the newly described genes *HMGB3* (Scott et al. 2014) and *NAA10* which have been identified as other causes of X-linked 'Lenz' microphthalmia syndrome (Esmailpour et al. 2014).

Here, using whole exome and targeted gene sequencing, we identified 16 further index cases (15 families) with pathogenic variants in *BCOR*. The female cases comprised of 11 females with OFCD, and additionally 3 affected mothers and 1 affected sister manifesting variable phenotypes. The five male index cases comprised of two unrelated cases with the recurrent c.254C>T (p.Pro85Leu) variant and manifesting a severe microphthalmia syndrome, two half-brothers with a previously undescribed c.4807A>C (p.Ser1603Arg) variant with developmental delay and posterior embryotoxon, and one boy with high myopia, posterior embryotoxon, severe developmental delay, wrist and finger anomalies with a previously undescribed splice-site variant c.4741 + 1G>A (p.[?]). We review the literature and show that male cases have demonstrably high prevalence of cardiac, skeletal, craniofacial, and genitourinary anomalies in addition to their well-described severe eye anomalies and developmental delay. We also show a surprising proportion of female OFCD cases with skeletal anomalies, hearing loss and developmental delay, and one with childhood lymphoma.

Materials and methods

Patient cohort

Cases 1–9 were recruited as part of a UK national study of developmental eye anomalies and a French cohort of microphthalmic or anophthalmic patients. Informed consent was obtained from all individuals in the study in accordance with Ethics Approval obtained for the study from Cambridge East REC (04/Q0104/129) (UK patients) and local Ethics Committee (CPP Sud-Ouest et Outre-Mer II) (French patients). Case 13 was recruited as part of a Spanish study of congenital ocular anomalies approved by the Ethics Committee of the Fundación Jiménez Díaz University Hospital. Cases 10 and 14 were recruited to the DDD (Deciphering Developmental Disorders) Study, which has UK Research Ethics Committee approval (10/H0305/83, granted by the Cambridge South REC, and GEN/284/12 granted by the Republic of Ireland REC). Cases 11, 12, 15 and 16 were consented for diagnostic genetic testing: single gene, or whole exome sequencing (WES). Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Methods

Whole exome sequencing (cases 1, 4, 5, 9, 10, 12, 13, 14)

WES was undertaken in 24 previously undiagnosed UK/French eye anomaly patients (12 males and 12 females). Case 4 had exome sequencing because of the association of developmental delay, dysmorphic features and posterior embryotoxon. Exome capture was performed using the Nimblegen V3 Enrichment kit following the manufacturer's protocol. The captured libraries were sequenced with an Illumina HiSeq2000 with 100-bp paired-end reads. We used PolyPhen-2, SIFT and Mutation Taster software tools to predict the functional effects of variants (Adzhubei et al. 2010; Ng et al. 2003; Schwarz et al. 2014). This strategy allowed the identification of *BCOR* variants in cases 1, 5 and 9. Case

12 had similar WES, but not captured and instead using an Illumina HiSeq2500 and 125-bp paired-end sequencing. For cases 10 and 14 identified via the DDD study, trio-based exome sequencing was performed on the affected individual and their parents, as previously described (Wright et al. 2015). Case 13 had targeted clinical exome sequencing. Libraries were prepared using TruSightOne (Illumina) following the manufacturer's protocol. The captured libraries were sequenced with an Illumina NextSeq500 with 150-bp paired-end reads.

Targeted resequencing of 187 genes (case 2)

Targeted resequencing of 187 genes, including *BCOR*, was performed for 96 UK/French individuals (44 males and 52 females) with undiagnosed microphthalmia or anophthalmia. 600 ng of subject genomic DNA was used to capture the 2310 coding exons using a custom Agilent SureSelect Target Enrichment System kit. Sequence capture, enrichment and elution were performed according to manufacturer's instruction and protocols (SureSelect, Agilent) without modification except for library preparation performed with the NEBNext® Ultra kit (New England Biolabs®). Libraries were pooled and sequenced on an Illumina HiSeq2000 as paired-end 75 bp reads. We used PolyPhen-2, and SIFT software tools to predict the functional effects of variants. This strategy allowed the identification of the *BCOR* variant in case 2.

Sanger sequencing

All pathogenic *BCOR* variants retained after filtering from the whole exome or targeted resequencing data were confirmed by Sanger sequencing. Parental studies were performed to determine whether these variants were inherited or appeared de novo. Direct *BCOR* (NM_001123385.1, 1755 aa) sequencing was performed in the other female cases (3, 6, 7, 8, 11, 13, 14, 15) and one male case (2) because of suggestive features and to confirm WES findings.

Case 16 had a copy number variant detected by array comparative genomic hybridisation (CGH) (Agilent 60k ISCA) and confirmed by qPCR.

Non-random X-inactivation analysis

This was performed using a fluorescent PCR assay encompassing the X chromosome androgen receptor CAG repeat polymorphism. The methylation-sensitive restriction enzyme, HpaI was used for prior digestion of genomic DNA. X-inactivation classification ratios: complete skewing = 100:1; highly skewed = 90:10–99:1; moderate skewing = 80:20–89:11; random X-inactivation = 50:50–79:21 (Amos-Landgraf et al. 2006).

Assessment of mosaicism

This was performed using semi-quantitative multiplex fluorescent PCR (QMF-PCR) analysis of the *BCOR* gene to determine the level of mosaicism. This method was previously published as described in the paper by Hilton and colleagues (Hilton et al. 2009).

Literature review

Published cases with pathogenic *BCOR* variants were identified through previous literature reviews and PubMed searches. Variants were annotated using a common reference sequence, NM_001123385.1, and all variants were checked using mutalyzer (http://www.mutalyzer.nl) (Wildeman et al. 2008).

Case descriptions

Cases are described individually and summarised in Table 1; clinical photographs are included in Fig. 1, pedigrees in Fig. 2 and mutations summarised in Fig. 3.

Case 1

Case 1 is a 13-year-old Caucasian girl with right microphthalmia with dense cataract and left microphthalmia with secondary aphakia, secondary glaucoma and a left visual acuity of 20/300. She was born at full term following ultrasound scans during pregnancy that detected choroid plexus cysts. Early cranial magnetic resonance imaging (MRI) revealed a corpus callosal lipoma. She had early onset cataracts and left cataract surgery at 6 weeks of age. Her development was slightly delayed: she smiled at 3–4 months, sat at 10 months and walked at 23 months of age. Her speech was normal. She had recurrent urinary tract infections (normal renal ultrasound), and growth hormone deficiency diagnosed at 3 years of age and treated with growth hormone. She had late eruption of her first teeth and delayed loss of first teeth at 9 years of age. She had unusual positioning of her adult teeth, which were small, with a second row of teeth.

At 11 years of age, her growth had reached: height second centile, weight < 0.4th centile and head circumference 50th centile. She had long slender fingers and hyperextensible joints. Her feet showed an increased sandal gap and she had right second-toe clinodactyly (Fig. 1a–e). She had reduced bladder control and decreased reflexes. WES revealed a de novo heterozygous variant in *BCOR* c.2428C>T

Table 1 Summary of phenotypic findings

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
General information								
Age	13 y	21 y	3 y	18 m	5 y	17 y	15 y	6 y 6 m
Gender	F	M	F	M	M	F	F	F
BCOR variant*	c.2428C>T p.(Arg810*)	c.254C>T p.(Pro85Leu)	c.1209_1210delCC p.(Gln404Alafs*35)	c.4807A>C p.(Ser1603Arg)	c.4807A>C p.(Ser1603Arg)	c.4700_4718dup p.(Glu1573Aspfs*7)	c.867G>A p.(Trp289*)	c.2947_2948insTGCATACT p.Glu983Val*41
Inheritance	De novo	Mat	De novo	Mat	Mat	De novo	Mat	Mat
Affected family members				Brother (case 5)	Brother (case 4)		Mother; gmother; aunt	Mother
Growth								
Birth weight (kg)	3.99	NK	3.59	2.88	2.86	2.64	3.6	3.54
Height centile (age)	2nd (11 y)	9th (9 y); 0.4–2 nd (21 y)	50th (3 y)	80th (birth)	−1 SD (4 y 6 m)	50th (17 y)	+0.5 SD (15 y)	+2 SD (6 y 6 m)
Weight centile (age)	<0.4th (11 y)	0.4–2nd (9 y); <3rd (21 y)	60th (3 y)	25th (birth)	0 SD (4 y 6 m)	90th (17 y)	10th (15 y)	+3 SD (6 y 6 m)
HC centile (age)	50th (11 y)	25th (9 y) 9th (21 y)	NK	28th (birth)	−2.5 SD (4 y 6 m)	95th (17 y)	+0.5 SD (15 y)	+1 SD (6 y 6 m)
Ocular								
Microphthalmia	B	B (severe)	B				B	B (mild)
Anophthalmia								
Congenital cataract	B		B			B	B	B
Glaucoma	U					B	B	
Posterior embryotoxon				B	B			
Other						RD		
Craniofacial								
Midface hypoplasia		+						
Nasal anomalies		+				+	+	
Ear anomalies		+	+	+	+	+		
Cleft palate					+			
High arched palate			+					
Other		Downslanting PF long face, tall forehead, thick eyebrows, LP				Prominent chin		
Cardiac								
ASD				+	+		+	
VSD								
Other		Triple heart sounds						

Table 1 (continued)

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Dental								
Late eruption of first teeth	+		+					
Delayed loss of primary dentition	+					+	+	
Radiculomegaly						+	+	
Fused incisors								
Other	Double row of teeth	Recurrent dental infections	Abnormal crown canines + incisors				Teeth misaligned	Agenesis two lateral incisors
Skeletal								
Hands	Long Fi	5th Fi clin, long Fi	Long Fi	Long Fi, 4–5 Cam	Cam all Fi	5th Fi Clin	Long Fi	
Feet	SG, 2nd toe Clin			Short, deep-set toe nails	Fetal toe pads	2–3 toe Syn	Long toes	2–3 toe Syn
Other	Joint HM	scoliosis						
Developmental								
ID				+	+			
Motor delay	+	+		+	+			
Speech delay		+		+	+			
AuSD		+						
MRI findings								
Lipomatous lesion	Lipoma corpus callosum	N		NK		NK	NK	
Other			Moderate BA, broad lateral ventricles	NK	Posterior arachnoid cyst	NK	NK	
Other findings								
GU anomalies	Reduced bladder control	CR, VUR, primary enuresis						
Other		Hypotonia, thin body habitus	Stage III T-cell lymphoma	Left temporal haemangioma	Hypotonia, capillary malformation, feeding difficulty			

Table 1 (continued)

Characteristic	Case 9	Case 10	Case 11	Case 1	Case 13	Case 14	Case 15	Case 16
General information								
Age	27 y	9 y	11 y	3 y	2 y	3 y	14 y	2 m
Gender	M	F	F	M	F	F	F	F
BCOR variant*	c.254C>T p.(Pro85Leu)	c.3153G>A p.(Trp1051*)	c.4850T>G p.(Leu1617*)	c.4741 + 1G>A	c.4402C>T p.(Gln1468*)	c.4601_4602insCT p.(His1535Cysfs*34)	c.3116_3117dup p.(Asp1040 Lysfs*16)	arr[GRCh37] Xp11.4(39910845_39922793) x1, and 2p15 deletion
Inheritance	Mat	De novo	NK	Mat	De novo	Mat	NK	De novo
Affected family members						Mother		
Growth								
Birth weight (kg)	3.09	3.35	3.62	4.04	1.89	2.21	2.72	3.25
Height centile (age)	50th (27 y)	91st (8 y)	NK	+ 1.5 SD (birth)	NK	13th (3 m) 2nd (3 y)	NK	NK
Weight centile (age)	91st (27 y)	98–99.6th (8 y)	NK	60th (birth)	NK	6th (3 m), 23rd (3 y)	NK	NK
HC centile (age)	75th–91st (27 y)	> 99th (8 y)	NK	+ 1 SD (birth)	NK	96th (3 m)	NK	NK
Ocular								
Microphthalmia		B	U (RE)		B	U (RE)		B
Anophthalmia	B							
Congenital cataract		B	B		B	B	B	B
Glaucoma							B	
Posterior embryotoxon				B				
Other		PFV, iris heterochromia	Nystagmus	B Mo, nystagmus, high myopia	Nystagmus			Iris rubeosis, flat anterior chambers
Craniofacial								
Midface hypoplasia								
Nasal anomalies		+	+	+			+	+
Ear anomalies	+		+	+				+
Cleft palate			+				+	+
High-arched palate								
Other	Small PF	Prominent forehead, small mouth, narrow palate, widening of cerebral falx	Upslanting PF	Full cheeks, ptosis, ex-ophthalmos, glabellar naevus flammeus			Ptosis, macrocephaly, alveolar cleft	Square shaped-face, upslanting PF
Cardiac								
ASD		+	+	+		+		+
VSD				+		+		+
Other		Dysplastic pulmonary valve	PDA	PDA, persistent L vena cava			Cardiac defect	

Table 1 (continued)

Characteristic	Case 9	Case 10	Case 11	Case 1	Case 13	Case 14	Case 15	Case 16
Dental								
Late eruption of first teeth		+	+		+	+		
Delayed loss of primary dentition		+	+					
Radiculomegaly								
Fused incisors			+					
Other		Oligodontia				Oligodontia		
Skeletal								
Hands	Long Fi	4th fi Poly-syn, 5/6 fi poly-syn		Long Fi short metacarpals, 5th Fi Bra				
Feet	Long toes	2/3 Syn, 2nd toe Clin, 4th toe Camp		Left talipes			long g toes, SG	2,4 toe Camp, 2–3 toe Syn, long,halluces
Other			Joint HM				Joint HM	
Developmental								
ID				+				
Motor delay		+		+				
Speech delay				+				
AuSD								
MRI findings								
Lipomatous lesion								
Other								Cerebellar hypoplasia, BA, ventricular enlargement
Other findings								
GU anomalies	Urethral hypoplasia, renal dysplasia, renal failure, VUR			CR, grade 4–5 VUR, kidney stone				
Other	Hypotonia			Seizure disorder		Thyroglossal cyst		Hearing loss, hypotonia, abnormal movements

ASD atrial septal defect; *AuSD* autistic spectrum disorder; *B* bilateral; *BA* brain atrophy; *Bra* brachymesophalangy ; *Cam* camptodactyly; *Clin* clinodactyly; *CR* cryptorchidism; *F* female; *Fi* fingers; *gmother* grandmother; *GU* genitourinary; *ID* Intellectual delay, *Joint HM* joint hypermobility; *kg* kilogram; *LE* left eye; *LP* long philtrum; *M* male; *m* months; *mat* maternal; *Mo* megalophthalmos; *MRI* magnetic resonance imaging; *N* normal; *NK* not known; *pat* paternal; *PDA* patent ductus arteriosus; *PF* palpebral fissures; *PFV* persistent fetal vasculature; *RD* retinal detachment; *RE* right eye; *SD* standard deviation; *SG* increased sandal gap; *Syn* syndactyly; *U* unilateral; *VSD* ventriculoseptal defect; *VUR* vesicoureteric reflux; *y* year

*(NM_001123385.1)

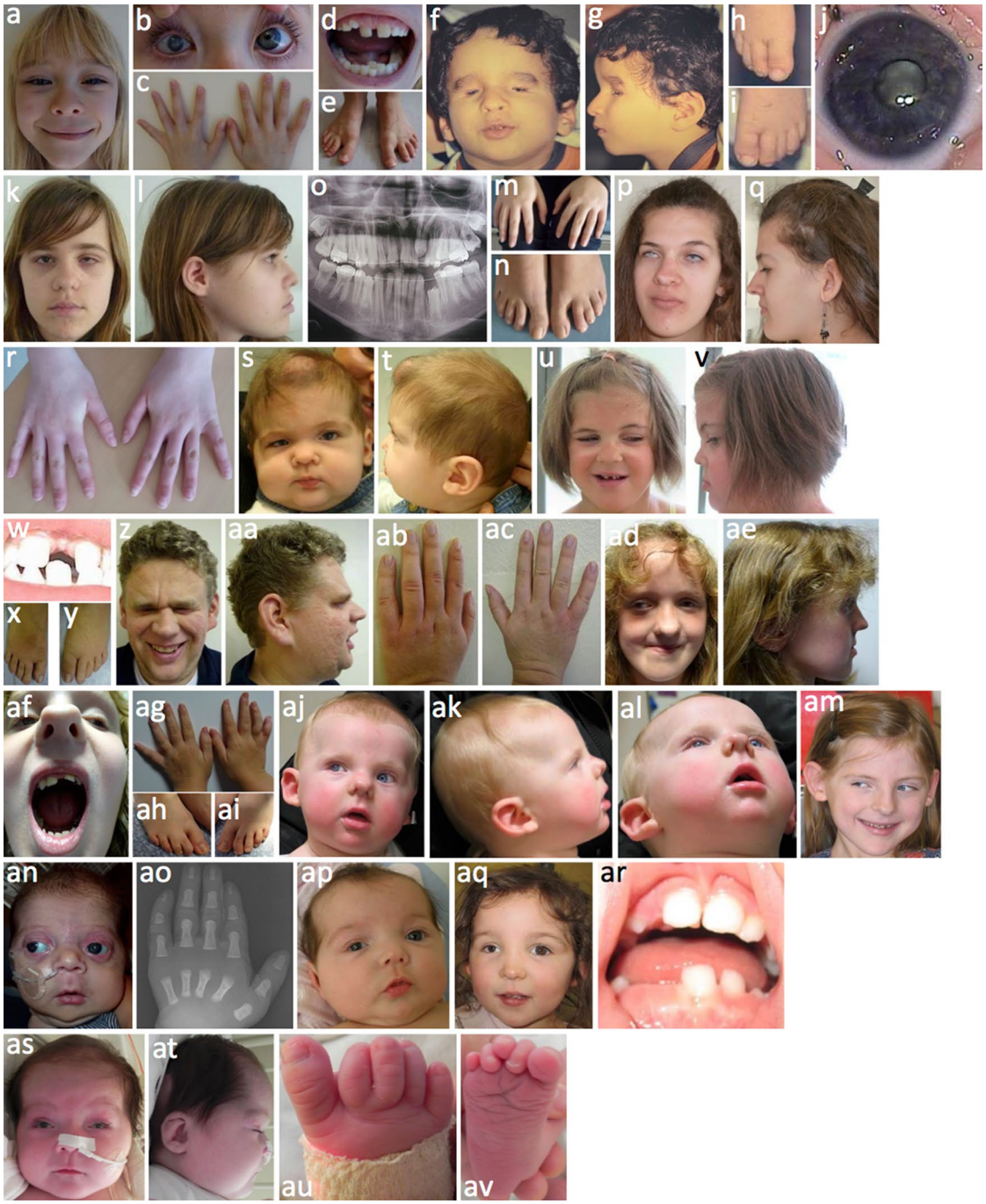

Fig. 1 Clinical photographs. **a–e** Case 1 showing broad nasal base, right microphthalmia, tooth abnormalities, long slender fingers, increased sandal gap, and right second toe clinodactyly. **f–i** Case 2 showing bilateral severe microphthalmia, downslanting palpebral fissures, thick eyebrows, a broad nasal root and tip, a long philtrum, large low set posteriorly rotated ears, and broad halluces. **j** Case 3 – eye photograph demonstrating congenital cataract. **k–o** Case 6 showing short bulbous nose, small ears and prognathism, 5th finger clinodactyly and 2–3 partial syndactyly of the left toes and orthopantomogram showing radiculopathy. **p–r** Case 7 showing bilateral microphthalmia, broad nose, and long, slender fingers. **s–w** Case 8 showing large hemangioma on the forehead, and tooth anomalies with agenesis of both superior lateral incisors. **x–ac** Case 9 showing bilateral anophthalmia, relatively large ears, partial 2–3 toe syndactyly. **ad–ai** Case 10 showing bilateral microphthalmia, prominent forehead, flat nasal bridge, upturned nose with a broad bifid tip, hypodontia, mesaxial polysyndactyly of the 4th digit with 5/6 syndactyly of the right hand partial 2/3 syndactyly of the right toes. **aj–am** Case 11 showing right microphthalmia, upslanting palpebral fissures, broad nasal tip with slit-like nostrils and simple ears. **an–ao** Case 12 showing bilateral megalophthalmos and exophthalmos, full cheeks, uplifted earlobes, long philtrum and full nasal tip, long thumbs and left talipes; (ao) short metacarpals and brachymesophalangy 5th fingers. **ap–ar** Case 14 showing right microphthalmia and oligodontia. **as–av** Case 16 showing asymmetric microphthalmia, upslanting palpebral fissures, large nasal tip (obscured by tape), simple ears; **au**–**av** showing camptodactyly of second and fourth toes, mild cutaneous syndactyly of second and third toes and long, large halluces

p.(Arg810*). This variant has been previously described as causing OFCD with a strikingly similar phenotype in a paper by Hilton and colleagues (case X) (Hilton et al. 2009) (see Supplementary Table 1).

Case 2

This 21-year-old Caucasian male first presented to the ophthalmic genetic clinic at the age of 9 years with bilateral microphthalmia (Fig. 1f–i). He was born at term, birth weight unknown. He had delayed motor milestones and walked with assistance by 4 years of age. He had bilateral cryptorchidism and vesicoureteric reflux, requiring surgical correction at 7 years of age after repeated pyelonephritis. His social development was delayed; he was diagnosed with autistic spectrum disorder. There was a family history of paternal bilateral cataracts requiring surgery at the age of 30 years, and low vision. His mother had stellate irides and he had a healthy younger sister.

At 9 years-of-age, he had no speech and difficulty swallowing, tolerating only liquid food. He suffered from primary enuresis and had undergone surgical correction for severe scoliosis. He suffered from recurrent dental infections requiring dental extraction. His height was 1.25 m (9th centile), weight 20.5 kg (0.4–2nd centile) and head circumference 53 cm (25th centile). He had bilateral severe microphthalmia with no light perception, short (10 mm) downslanting palpebral fissures and secondary midface hypoplasia. He had a long face with abundant hair, tall forehead, thick eyebrows, a broad nasal root and tip, a long philtrum, thin upper lip and thick lower lip. He had large low set posteriorly rotated ears with prominent antihelices. He had a thin body habitus with a barrel-shaped chest, long slender fingers with fifth finger clinodactyly, and broad halluces. He showed hypotonia with reduced muscle mass and marked ligamentous laxity. His cranial MRI was normal.

At the age of 21 years, his height was 1.6 m (0.4–2nd centile), weight 40.5 kg (< 3rd centile) and head circumference 55 cm (90th centile). He had limited speech of a few words. He walked with a spastic gait, had poor muscle mass and suffered from scoliosis. He attended a daytime-assisted care facility, functioning reasonably independently, and played the piano.

Genetic testing of *SOX2, OTX2, VSX2, RAX*, and *FOXE3* were normal. Targeted sequencing identified a *BCOR* c.254C>T; p.(Pro85Leu) variant inherited from his healthy mother. His maternal aunt had previously had a termination of pregnancy for a severely malformed male fetus suspected of trisomy 13, without genetic analysis or fetal pathology examination. She may be a carrier of the same *BCOR* variant, although genetic analysis was declined.

Case 3

This 3-year-old Caucasian girl was born with bilateral microphthalmia and cataract (Fig. 1j) having had bilateral congenital cataract detected at 22 weeks of pregnancy. She also had an atrial septal defect (ASD) that was managed conservatively. The cataracts were removed without intraocular lens implantation at 2 months of age, with a subsequent right vitrectomy for capsular opacity at 2 years of age. However, she developed a T-cell lymphoma (stage III on St Jude's classification) at the age of 12 months and was treated with chemotherapy, achieving remission after 2 years of treatment. She had late eruption of her first teeth and abnormal crown volume on the upper maxillary canines and central incisors on the palatal side, without any misalignment of the teeth. All primary and permanent teeth were present on the head computerized tomography (CT) scan. At the age of 3 years, her microphthalmic eyes measured right eye (RE) corneal diameter of 9.5 mm, axial length of 17.59 mm and left eye (LE) corneal diameter of 8.5 mm, axial length of 16.06 mm, with an increase of corneal thickness RE 635 µm and LE 680 µm. At 4 years, following patching, she achieved visual acuities of RE 0.7 logMar and LE 0.2 logMar.

She had normal growth and no developmental delay. She had long slender fingers and hands, downslanting, dysplastic ears and a high arched narrow palate. Targeted analysis of *BCOR* revealed the de novo variant c.1209_1210delCC; p.(Gln404Ala*fs**35), predicted as pathogenic.

Case 4

Case 4 is an 18-month-old Caucasian boy, only child of unrelated healthy parents. He has three half-brothers on his mother's side, including case 5 (Fig. 2a). He was born at 38 weeks' gestation with a birth weight 2.875 kg (25th centile), length 50.7 cm (80th centile) and head circumference 33.5 cm (28th centile). He had a large ASD. Ophthalmological examination showed bilateral posterior embryotoxon. He had distinctive features, including large earlobes, long fingers with 4th and 5th camptodactyly, and short and deep-set toenails and a left temporal haemangioma. His growth was normal, however, he had some developmental delay: he sat at 12 months, at 18 months of age he could not stand unsupported; he could say one word. While his array CGH was normal, WES revealed the variant c.4807A>C; p.(Ser1603Arg) in *BCOR*, inherited from his asymptomatic mother. This variant involves a highly conserved amino acid, is absent from the general population (gnomAD database) (Lek et al. 2016) and is predicted to be deleterious by in silico software Polyphen-2, SIFT and Mutation Taster (Adzhubei et al. 2010; Ng et al. 2003; Schwarz et al. 2014).

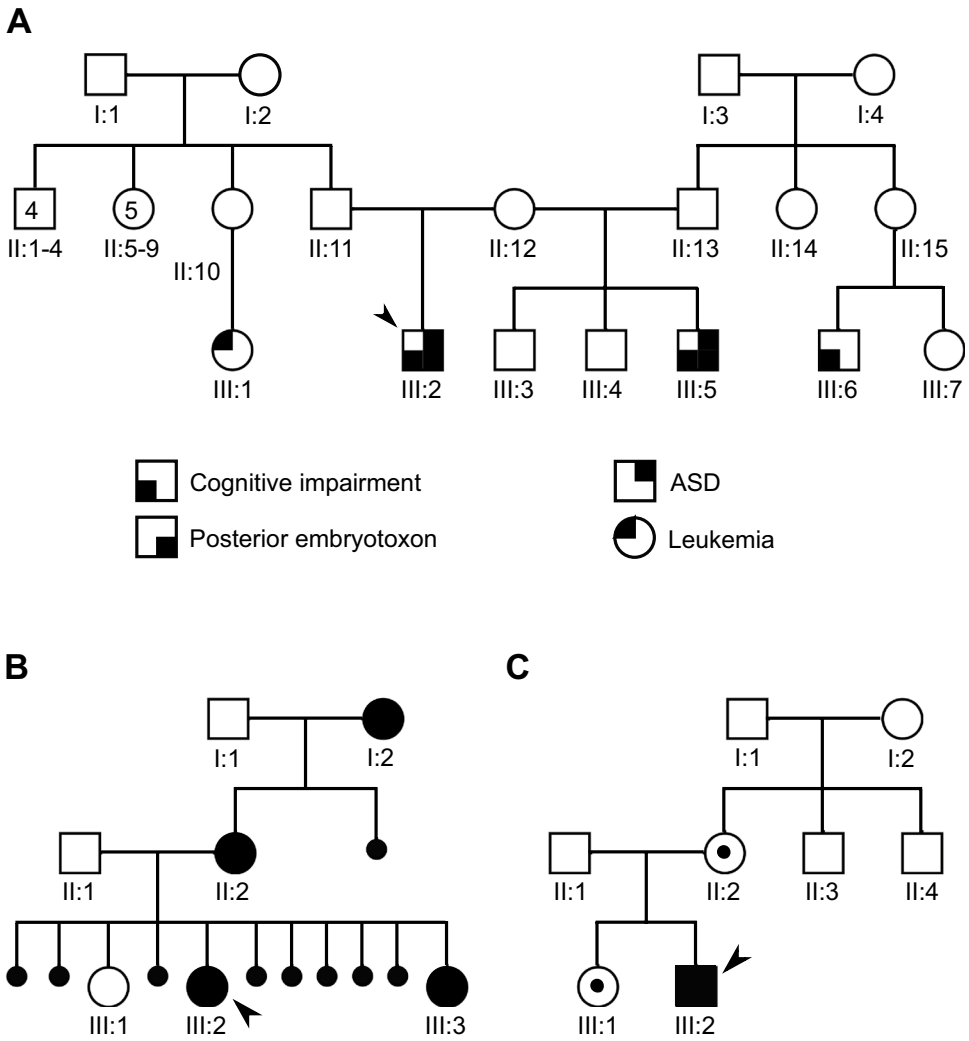

Fig. 2 **a** Pedigree of cases 4 and 5; **b** pedigree of case 7; **c** pedigree of case 12

Case 5

Case 5 is a 5-year-old Caucasian boy, half-brother of case 4. He was born at full term with asymmetrical intrauterine growth retardation. His birth weight was 2.860 kg (5th centile), length 50 cm (37th centile) and OFC 33.5 cm (12th centile). He had initial feeding difficulties and presented with posterior cleft palate, major axial hypotonia with highly hypertonic limbs, and a large ASD. Ophthalmological examination at birth showed bilateral posterior embryotoxon. He also had asymmetrical dysplastic ears, camptodactyly of all fingers, fetal toe pads, and multiple capillary malformations. He had severe developmental delay; he spoke fewer than 10 words at 5 years and walked at 4 years and 10 months. He had severe feeding difficulties causing initial growth retardation, but at age 4½ years, his weight was 17.5 kg (0 SD), height 100.5 cm (− 1 SD) and OFC 48.5 cm (− 2.5 SD). His brain MRI showed a posterior arachnoid cyst. Sanger sequencing revealed the same variant c.4807A>C; p.(Ser1603Arg) in *BCOR* as his brother (case 4). This variant was absent in the two healthy brothers of cases 4 and 5.

Case 6

Case 6 is a 17-year-old Caucasian girl, first child of unrelated healthy parents, with two unaffected siblings. She was born at 37 weeks' gestation and bilateral congenital cataract was diagnosed at 1st month, with surgery performed at 3 months of age. Later, she developed secondary bilateral glaucoma with significant reduction in visual acuity, and received further surgery on the left eye at 7 years of age. She developed a right retinal detachment at the age of 12 years and now her visual acuity is RE 30/100 and LE no perception of light. She had delayed replacement of her primary teeth with a secondary dentition. Radiographs showed radiculomegaly; all teeth were present (Fig. 1o).

She had normal growth and development. She had distinctive facial features with a short bulbous nose, microtia

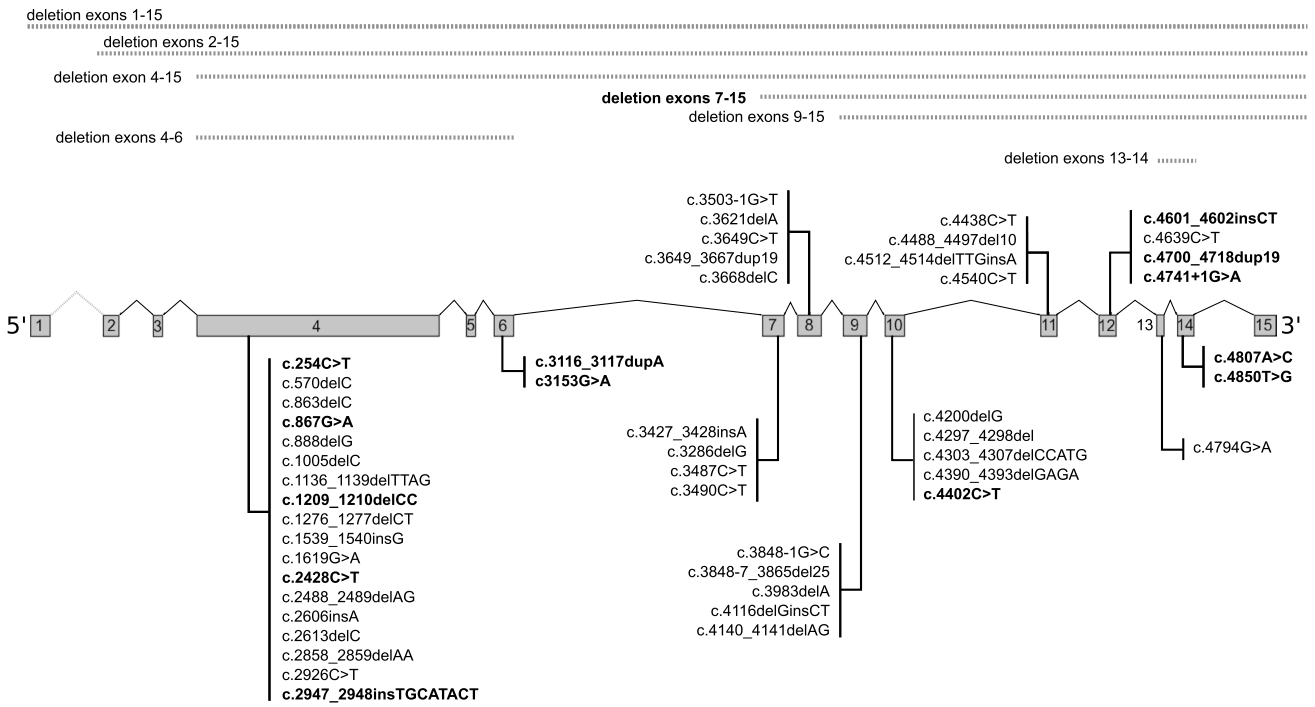

Fig. 3 Summary of the described and new (in bold) variants in *BCOR*

and prognathism. She also showed 5th finger clinodactyly and left 2–3 toe partial syndactyly.

Targeted *BCOR* analysis initiated by the geneticist at age 13 years 9 months revealed the de novo variant c.4598_4616dup; p.(Glu1539Asp*fs**7), predicted as pathogenic.

Case 7

Case 7 is a 15-year-old Caucasian girl, the second of three girls, born at full term with bilateral microphthalmia and cataract (Fig. 2b). She had bilateral cataract surgery in the first months of life, but subsequently developed chronic bilateral glaucoma with acute episodes, requiring surgery. Her visual acuity is reduced to RE: light perception and LE: count fingers at 1 m wearing aphakia-correcting glasses. She also had an ASD, corrected by cardiac surgery at the age of 4 years. She had delayed loss of her primary teeth, with radiculomegaly, causing a misalignment of the teeth. All the primary teeth had to be removed to enable permanent teeth to erupt. She had normal growth and development. She exhibited distinctive facial features including broad nose, and long, slender fingers and toes (Fig. 1p–r).

Her mother had surgery in infancy for bilateral congenital cataract, had frequent dental issues and suffered eight miscarriages. Her maternal grandmother had at least one miscarriage and bilateral early onset cataract. Her younger sister also had surgery for bilateral congenital cataract and also had dental anomalies.

Targeted *BCOR* analysis initiated by the geneticist at 12 years of age revealed the variant c.867G>A; p.(Trp289*), predicted as pathogenic. This variant was inherited from the affected mother and was also present in the younger affected sister.

Case 8

This 6½-year-old girl was born at full term. At 1 month of age, after initial feeding difficulties, she was diagnosed with bilateral congenital cataract and mild microphthalmia. She had two large haemangiomas (one on the forehead, one in the neck), a lipomatous lesion in the thyroid lobe diagnosed clinically and on ultrasound and a thyroglossal cyst (Fig. 1s–w). At age 6½ years, she had normal growth and development. She had agenesis of both superior lateral incisors and cutaneous syndactyly of second and third toes. Subsequent follow-up revealed left ventricular noncompaction, without rhythm disturbance and with good ventricular function, and a small persistent ductus arteriosus. Sanger sequencing of *BCOR* revealed a frameshift variant c.2947_2948insTGCATACT; p.(Glu983Valfs*41). The same variant was identified in her mother, who had bilateral congenital cataract, microphthalmia and agenesis of the two lateral incisors with large spacing of the two upper median incisors, but in a mosaic state (about 20% of mutated p.(Glu983Valfs*) alleles in blood).

Case 9

This 27-year-old male was born at 38 weeks following a normal pregnancy during which an ultrasound scan at 18/40 demonstrated urinary reflux and one kidney larger than the other. At birth, he was diagnosed with bilateral anophthalmia, small palpebral apertures, hypotonia, moderate degree of chronic renal failure secondary to bilateral renal dysplasia with associated bilateral vesicoureteric reflux (corrected age 2 years) and urethral hypoplasia. He had normal growth and developmental milestones, and excellent musical and verbal skills. His mother had a history of neurofibromatosis type 1 and multiple strawberry nevi, but was otherwise healthy. His MRI scan was reported as normal. At age 27 years, he had normal growth parameters, with long fingers and toes, and large ears with squared-off earlobes (Fig. 1x–ac). WES revealed a maternally inherited *BCOR* c.254C>T; p.(Pro85Leu) variant.

Case 10

Case 10 is a 9-year-old girl born at 38 weeks' gestation by Caesarian section due to delayed rupture of membranes. She had bilateral congenital cataract and microphthalmia with corneal diameters of 9 mm, persistent fetal vasculature and small optic nerves. She was noted to have a prominent forehead, flat nasal bridge, upturned nose, mesaxial polysyndactyly (of 4th digit) with 5/6 syndactyly of the right hand and partial 2/3 syndactyly of the right toes (Fig. 1ad–ai). She also had a moderate secundum ASD with a mildly dysplastic pulmonary valve on echocardiography. She had slight widening of her cerebral falx on cranial ultrasound. Her maternal grandmother had postaxial polydactyly on one hand and a maternal first cousin once removed had bilateral postaxial hand polydactyly. At 10 months of age, she had delayed motor milestones and was not yet sitting unsupported. She did not have any teeth yet and her anterior fontanelle was still open. She had fine hair, a short nose with slightly broad nasal tip, small mouth and narrow palate. She had surgery for her ASD at the age of 3 years. Interestingly, her growth parameters progressed from length 0.4th centile, weight 25th centile and head circumference 75th centile at 1 month, to height and weight 9th centile, and head circumference 75th–91st centile at 10 months, and by 8 years of age she reached a height on the 91st centile, weight 98–99.6th centile and a head circumference of 58.9 cm (> 99th centile). She had had delayed eruption of her secondary dentition. She received 1:1 help for her visual impairment (with visual acuity RE 0.70 LE 0.45 corrected with + 20 DS both eyes) and her intellectual achievement was equivalent to her sighted peers. In addition to her right 2–3 toe syndactyly, she demonstrated left second toe clinodactyly and fourth toe camptodactyly. She had hypodontia, a broad bifid nasal tip, mild heterochromia of the left iris, with bilateral aphakia and normal fundal appearances.

She had normal array CGH and was diagnosed with a de novo *BCOR* variant c.3153G>A; p.(Trp1051*) by the Deciphering Developmental Disorders (DDD) study (DECIPHER ID: 262,217), confirmed with Sanger sequencing (Wright et al. 2015).

Case 11

Case 11 is an 11-year-old girl born by emergency Caesarian section for face presentation at 42 weeks' gestation following a pregnancy complicated by polyhydramnios. She has one full sister and a maternal half sister and brother, all healthy. She was noted to have cleft palate, right microphthalmia, roving eye movements, bilateral cataracts, ASD and patent ductus arteriosus (PDA) in the neonatal period. Cataract surgery was performed at 12 and 13 weeks. She now has no vision in the right eye and is partially sighted on the left. Surgery to close the cleft palate was performed in infancy. The ASD and PDA closed spontaneously. She had nystagmus and upslanting palpebral fissures, slit-like nostrils and simple ears (Fig. 1aj–am). She also had hypermobility of the elbows. Her first teeth erupted at 1 year of age and all deciduous teeth were still present at the age of 7 years.

At the age of 11 years, she had no learning difficulties, but was assisted by a teacher for the visually impaired at school. Her dentist noted fused upper right central and lateral incisors and lower left lateral and central incisors. An orthopantomogram performed at the age of 4 years showed at least 2 years' delay of dental development and probable similar fusions in the permanent dentition. No comment was made regarding root size.

Sequencing of *BCOR* revealed a heterozygous nonsense variant: c.4850T>G; p.(Leu1617*) with complete skewing of X-inactivation. Neither parent was available for genetic testing.

Case 12

This 3-year-old boy is the second child of non-consanguineous parents born at 40 weeks' gestation with a birth weight of 4.040 kg (60th centile), length 56 cm (+ 1.5 SD), and head circumference 37 cm (+ 1 SD) (Fig. 2c). The pregnancy was uneventful, apart from unilateral talipes detected on scan. Echocardiography shortly after birth revealed a ventricular septal defect (VSD), ASD, persistent ductus arteriosus, persistent left vena cava, and non-compaction of the left ventricle. Furthermore, bilateral cryptorchidism was observed. At the age of 1 month, he was admitted because of respiratory insufficiency. He also had bilateral grade 4–5 vesicoureteral reflux and a single kidney stone was observed. On ophthalmic assessment he

had nystagmus, high myopia (− 17.00 D) with megalophthalmos, and posterior embryotoxon. He was noted to have full cheeks, mild ptosis, exophthalmos, uplifted earlobes, a glabellar naevus flammeus, a long philtrum and full nasal tip, long thumbs and left talipes (Fig. 1an–ao). Brain MRI showed no abnormalities. X-rays of the hand showed short metacarpals and bilateral brachymesophalangy of the 5th fingers. He developed a seizure disorder from 1 year of age. His cognitive and motor milestones were severely delayed and at the age of 35 months he was nonverbal, could sit, but was unable to stand. His SNP array, array CGH, FISH-analysis for Pallister Killian syndrome and analysis of *CHD7, ASXL1* and *SETBP1* were normal. WES analysis revealed a hemizygous variant in *BCOR* (c.4741 + 1G>A; p.(?)). This variant is located within the donor splice site of intron 12, predicted to result in aberrant splicing Human Splicing Finder tool (http://www.umd.be/HSF3/index.html) (Desmet et al. 2009). His healthy mother is a carrier and showed 100% skewed X-inactivation. His healthy 4-year-old sister is also a carrier and also showed skewed X-inactivation (ratio 96:4). The variant was not present in both maternal grandparents and a healthy maternal uncle.

Case 13

Case 13 is a 2-year-old Caucasian girl, only child of unrelated and healthy parents. There is no familiar history of congenital or developmental anomalies. Pregnancy was complicated by intrauterine growth restriction in the third trimester. She was born by induced delivery at 37 weeks' gestation with birth weight of 1.890 kg (< 3rd centile). At birth she showed bilateral microphthalmia and cataracts, but no other anomalies. At 2 months of age, cataract surgery was performed and at 3 months of age she showed low vision and nystagmus. She had normal psychomotor and cognitive development. She had late eruption of her first teeth at 14 months of age and primary dentition was complete except for the right lateral lower incisor. At 20 months of age she was referred for genetic testing and targeted sequencing revealed a heterozygous de novo nonsense variant in *BCOR* c.4402C>T; p.(Gln1468*), predicted as pathogenic.

Case 14

This 3-year-old girl is the second of two daughters born to non-consanguineous parents. Her mother was diagnosed with bilateral cataracts at 7 months of age, which had been attributed to maternal rubella infection in pregnancy. She also had dental abnormalities with radiculomegaly and thin enamel. Case 14 was delivered at 35 weeks due to placental failure and had breathing difficulties at birth necessitating 4 days of ventilator support. She was diagnosed with bilateral congenital cataracts and underwent surgery to the right eye at 7 weeks of age. She also had right microphthalmia, a small restricted perimembranous VSD and secundum ASD. The VSD spontaneously closed and the ASD did not require any intervention. She had a thyroglossal cyst that required intravenous antibiotics and drainage. Primary dentition was delayed with eruption of first teeth at 18 months and oligodontia (Fig. 1ap–ar). Her development was normal. The DDD study (Decipher ID: 303226) identified a maternally inherited heterozygous frameshift variant, c.4601_4602insCT; p.(His1535CysfsTer34) in *BCOR*.

Case 15

Case 15 is a 14-year-old Caucasian girl, the third child of non-consanguineous parents. There was no relevant family history. She was born following a normal pregnancy and was mildly oedematous and anemic at birth. A cleft palate was identified and she was also found to have a cardiac defect, which closed spontaneously. At 9 weeks of age, bilateral cataracts were diagnosed, which were surgically removed by 12 weeks of age. She then developed pupil block glaucoma in her left eye, which required surgery. She has ongoing problems with bilateral glaucoma. She also has hypermobility of hips, knees and ankles, but this is improving.

Developmentally, there have been no concerns about achieving milestones. She attended a school for the visually impaired previously, but is now at a mainstream school with some vision support. Her facial features are in keeping with a diagnosis of OFCD with macrocephaly (OFC-97th centile), bilateral ptosis, hypoplastic alae nasi and broad nasal tip. Her great toes are very long and she has a wide sandal gap on both her feet. There is a mild alveolar cleft (forme fruste) in the midline. Sanger sequencing revealed a pathogenic frameshift variant, c.3116_3117dup; p.(Asp1040Lysfs*16) in *BCOR*; parents declined testing.

Case 16

Case 16 is a 2-month-old Caucasian female born following a normal pregnancy at 38 weeks' gestation with a birth weight of 3.245 kg (50th centile) with normal ultrasound scans. She presented with cleft palate and facial dysmorphism consisting of square-shaped face with asymmetric microphthalmia, upslanting palpebral fissures, large nasal tip with septate nasal cartilage and simple ears (Fig. 1as–av). She also had camptodactyly of the second and fourth toes, mild cutaneous syndactyly of the second and third toes and long, large halluces and congenital heart anomalies, consisting of a large ASD and two VSDs. In addition to bilateral microphthalmia, her eye examination revealed bilateral congenital cataract, iris rubeosis and flat anterior chambers. She is being

investigated for hearing loss, since the auditory-evoked potentials were negative. As she also exhibited hypotonia and abnormal movements, brain MRI was performed and showed asymmetrical pontocerebellar hypoplasia, cerebral atrophy and enlargement of the ventricles without obstruction. Electroencephalogram was normal.

Molecular analysis of *BCOR* revealed a de novo deletion of the exons 7–15, confirmed by array CGH Xp11.4 (39910845_39922793)x1 (Agilent 60 k ISCA) and qPCR. In addition, there was a 162 kb deletion in 2p15 (arr[GRCh37] 2p15[63190016_63352116]x1) that includes *OTX1* and the 3′ region of *WDPCP*. This second CNV is of unknown significance, and could explain the neurologic phenotype since *OTX1* has a putative role in brain development.

Summary of our cases and previously published BCOR cases (Supplementary Tables 1, 2, and 3).

Including the cases presented in this paper, a total of 95 cases from 66 families harboring pathogenic *BCOR* variants have been described in the literature. We have summarized the findings of our cases in Table 1, and of all published cases including ours in supplementary Table 1. This includes 85 heterozygous (female) OFCD cases from 58 families (also detailed in Supplementary table 2) and 10 hemizygous (male) cases from 8 families (also detailed in Supplementary Table 3).

Discussion

Pathogenic variants in *BCOR* have been associated with two distinct phenotypes. The first is the oculofaciocardiodental (OFCD) X-linked dominant syndrome, affecting exclusively females, presumed male lethal, and caused by a variety of null *BCOR* variants. The second is a severe X-linked recessive microphthalmia syndrome ('Lenz') affecting males only and caused in the majority of cases to date by a specific missense variant, c.254C>T, predicting a p.(Pro85Leu) substitution at the protein level. However, in this report, we present additional male phenotypes associated with novel *BCOR* variants that include developmental delay in the absence of eye anomalies in two brothers, and one male with high myopia, megalophthalmos, posterior embryotoxon, severe developmental delay, and heart and bone anomalies. We also describe one male with severe ocular involvement, but without psychomotor delay, harboring the previously described p.(Pro85Leu) variant.

We reviewed 85 OFCD cases from 58 families with pathogenic *BCOR* variants in the literature, including the new cases described here (Supplementary Table 1). Many have been recently summarized in the article by Feberwee and colleagues (Feberwee et al. 2014). Although the classic phenotypic characteristics of OFCD (eye anomalies, craniofacial anomalies, cardiac anomalies and dental anomalies) occurred in a majority of the described cases, only 41% of cases had anomalies in all four categories. In addition to these classical characteristics, skeletal anomalies were frequently observed: 82% of cases had digit anomalies; 13% had radioulnar synostosis and 10% had vertebral anomalies. Strikingly, hearing loss, which has not previously been highlighted as a feature of OFCD, was present in 9% of published cases. This cannot solely be attributed to secretory otitis media relating to cleft palate, as only two out of the nine cases with hearing loss had cleft palate. One of our cases (16) had presumed hearing loss as indicated by negative auditory-evoked potentials, but this case also had other brain anomalies.

Apart from one mosaic case, all cases presented with features characteristic of OFCD, which suggests complete penetrance for the protein-truncating *BCOR* variants underlying OFCD. All non-mosaic individuals, as well as three mosaic cases, manifested congenital or early onset cataract, with or without additional ocular features, such as microphthalmia, coloboma, lens dislocation, optic disc dysplasia, secondary glaucoma and retinal detachment (the latter two possible sequelae of early cataract surgery). The facial features include separated nasal cartilage, high nasal bridge, long narrow face, palate/uvula anomalies, and simple ears (Ng et al. 2004; Hilton et al. 2009; Davoody et al. 2012), with features not universally described in OFCD cases (see Fig. 1). Cardiac anomalies, including septal defects, patent ductus arteriosus, double outlet right ventricle, Fallot's tetralogy, and dextrocardia were reported in 63% of individuals. The dental anomalies can affect primary and secondary dentition and can show a virtually pathognomonic radiculomegaly, or delayed, persistent or unerupted primary and/or secondary dentition, hypodontia, duplication or fusion of teeth (Kantaputra 2014) and are illustrated in Fig. 1. Only four cases were reported to be without dental anomalies. The skeletal anomalies included 2–3 toe syndactyly, broad halluces, hammer toes, camptodactyly, short fingers, radioulnar synostosis, scoliosis, and vertebral fusion (Fig. 1).

We would like to highlight some additional features of OFCD. Mild developmental delay was present in around 10% of cases. Strikingly, hearing deficits, which are not usually described as part of the OFCD spectrum, occurred in 9% of cases, and should be considered as a new feature of this syndrome. Two individuals in our series had joint hypermobility, also described once before. Although this a relatively common finding in children in the general population, further studies would help to determine if it is a manifestation of OFCD. Other findings include: intrauterine growth retardation, poor feeding/reflux, vesicoureteral reflux and asplenia, growth hormone deficiency, delayed bladder control, decreased reflexes, thyroglossal cysts, lipoma in the

thyroid lobe, lipoma of the corpus callosum and other brain anomalies. We suggest that neuropathy or muscle hypotonia, pituitary underdevelopment and lipoma may be additional features of the OFCD syndrome. This paper is the first to describe a childhood lymphoma in an OFCD case. This case highlights the importance of follow-up of OFCD cases, and indicates that further research is needed to investigate whether the occurrence of childhood or adult tumors is more common in OFCD cases compared to the general population, especially in view of the tumor suppressor role of BCOR described below. Interestingly, haemangiomas seem to be a frequent feature, and were also seen in one of our carrier females, although are relatively common in the general population. Case 16 had a distinct neurological phenotype that included pontocerebellar hypoplasia, cerebral atrophy and enlargement of the ventricles. She had a deletion of exons 7–15 of *BCOR* and an additional 162 kb deletion in 2p15 that included *OTX1* and the 3′ region of *WDPCP*. The *OTX1* deletion may be contributing to the neurological phenotype, since mice with deletions in *Otx1* have brain anomalies (Acampora et al. 1996).

The majority of heterozygous variants in OFCD cases were predicted to cause protein truncation, with 48% of them causing a frameshift, 33% nonsense, and 7% affecting splicing. The remaining 12% of cases harbored a whole or partial gene deletion. In 26% of OFCD cases, the condition was familial and in 74% it was sporadic or unknown. For all apparently sporadic cases where parental samples were analyzed (35%), the variant appeared de novo, suggesting that protein-truncating variants, including nonsense and frameshift mutations, are fully penetrant. However, the possibility of gonosomal mosaicism could not be excluded.

Lenz first described his microphthalmia syndrome in 1955 in an X-linked pedigree manifesting male cases with severe microphthalmia syndrome with delayed development, palatal and dental anomalies, skeletal anomalies, congenital heart defects, unilateral renal aplasia and cryptorchidism (Lenz 1955). Since this paper, it is clear that many descriptions have loosely referred to male patients with severe microphthalmia as having ‘Lenz microphthalmia’, both sporadic male cases and those with an X-linked pedigree. Although due credit should be attributed to Lenz for drawing attention to this severe microphthalmia affecting males, the generic use of the term ‘Lenz’ microphthalmia to describe affected males with severe syndromic microphthalmia is perhaps best avoided, since it is a genetically heterogeneous group (Traboulsi et al. 1988; Hilton et al. 2009). Hilton and colleagues analysed 21 male patients with presumed ‘Lenz’ microphthalmia and identified one with the typical c.254C>T; p.(Pro85Leu) missense variant in *BCOR*, demonstrating that *BCOR* is not the major cause of severe male microphthalmia, a finding supported by other groups (Ng et al. 2004; Horn et al. 2005; Hilton et al. 2009; Suzumori et al. 2013).

The phenotypes of the hemizygous male cases with *BCOR* variants partially overlaps with the female cases, with eye, craniofacial, cardiac and skeletal anomalies present in the majority of male cases. Dental anomalies were not reported in this group, whereas half of these cases presented with developmental delay, and 40% with genitourinary anomalies. No protein-truncating variants have been described in male cases, with missense variants in seven families and a splice site variant in another one.

Our case 2 with the typical c.254C>T; p.(Pro85Leu) shows an interesting phenotype, displaying additional features to previous descriptions. He shows a severe microphthalmia phenotype, with developmental delay associated with autistic features, short stature, cardiac anomalies, broad halluces, long thin fingers, vesicoureteric reflux, cryptorchidism, hypotonia, reduced muscle mass, scoliosis, and large low set ears in the absence of microcephaly. However, case 9, who displays high intelligence and no autistic features and also carrying c.254C>T; p.(Pro85Leu), clearly demonstrates that males with the typical *BCOR* variant do not universally display these features. The phenotype of severe eye anomalies plus cryptorchidism, hypotonia, and autistic features in the male *BCOR*-related syndrome shows some overlap with SOX2 anophthalmia syndrome (Fantes et al. 2003; Ragge et al. 2005; Bakrania et al. 2007), such that male cases with severe microphthalmia or anophthalmia, developmental delay, reduced growth and cryptorchidism, might benefit from panel testing that includes both *SOX2* and *BCOR*, Specific features, such as lack of developmental delay with the presence of other extraocular features including long thin fingers or toes, large ears, cardiac anomalies, vesicoureteric reflux in association with severe bilateral eye anomalies might suggest *BCOR* is more likely to be the responsible gene.

Recently, Zhu and colleagues described a boy with multiple birth anomalies, congenital glaucoma, AV canal type ventricular septal defect and cerebral white matter hypoplasia (Zhu et al. 2015). Molecular testing revealed a de novo novel missense variant in *BCOR* (c.1619G>A; p.[Arg540Glu]) predicted to be ‘probably damaging’. As the authors indicated, it was unclear if the variant in *BCOR*, although suggestive, was the underlying diagnosis. However, in view of posterior embryotoxon seen in our cases, which can be part of anterior segment dysgenesis, and can be associated with primary glaucoma, this might imply that posterior embryotoxon is part of the spectrum of eye anomalies associated with *BCOR* variants. Furthermore, our case 12 (see below) with posterior embryotoxon with megalophthalmos and myopia had a novel splice site variant in *BCOR* (c.4741+1G>A; p.[?]).

Cases 4 and 5 are two half-brothers who have an interesting constellation of features that include early neonatal diabetes, hypotonia, ASD, bilateral posterior embryotoxon (without cataract), long slender fingers, camptodactyly, haemangiomas, cleft palate, posterior arachnoid cyst and severe growth and intellectual delay (in the older boy). The younger, but not the older brother, received WES and this revealed the c.4807A>C; p.(Ser1603Arg) *BCOR* variant present in his affected brother and his unaffected mother, but absent in his unaffected half-brothers. There are enough features of *BCOR* X-linked syndrome to suggest this as the underlying diagnosis. However, as this is the first description of an intellectual disability syndrome associated with *BCOR*, without the characteristic findings of microphthalmia, this gene should be considered in other males with intellectual disability with or without overlapping features to explore this potential new phenotype more fully.

Case 12 showed a boy with high myopia and large globes and who also demonstrates a splice site variant, and therefore, distinct from the classical missense variant c.254C>T; p.(Pro85Leu), seen in males with severe microphthalmia. The organs involved in the phenotype in this boy overlap with OFCD syndrome and/or Lenz microphthalmia. However, his eye phenotype is distinct from the phenotype of those two disorders in causing increased ocular growth and myopia, and he additionally showed posterior embryotoxon, also seen in cases 4 and 5. Interestingly, his unaffected mother and sister who carry the same variant show highly skewed X-inactivation.

The mechanism by which *BCOR* acts to promote eye growth is not precisely known. Loss of bcor function leads to coloboma formation in the zebrafish. Through evidence from oncogenic pathways, it is known that the BCOR/BCL6/SIRT1 complex interacts with the SHH signaling pathway, also important in human eye development (and medulloblastoma) (Tiberi et al. 2014). In zebrafish, the bcor/bcl6a complex appears to interact with hdacs, and there is some evidence that part of the mechanism may occur by bcor/bcl6a and Hdac1 co-repressing p53 expression, although there is no evidence that humans with germline *p53* mutations have developmental eye anomalies (Lee, Lee et al. 2013).

BCOR is a corepressor that interacts with BCL6 at the POZ domain. BCL6 is an oncogene important in B cell development and oncogenesis. It encodes a zinc-finger transcriptional repressor, which is a regulator of germinal centre formation. *BCOR* aberrations have been identified in extranodal NK/T cell lymphomas and in secondary acute myeloid leukemias, and other tumors (Dobashi et al. 2016). Furthermore, Tanaka et al. (2017) have demonstrated a likely tumour suppressor role for BCOR in T lymphocytes in mice. This provides supporting evidence that T cell lymphoma described in case 3 may be linked to the germline *BCOR* variant in this patient. The role of *BCOR* in tumorigenesis does not appear to be limited to tumour suppression. Various *BCOR* rearrangements, including in-frame internal tandem duplications of *BCOR* exon 15 and gene fusions involving *BCOR*, illustrate an emerging role in tumour enhancement in various sarcoma subtypes (Pierron et al. 2012; Ueno-Yokohata et al. 2015).

There appears to be interesting genotype–phenotype correlation in *BCOR*-related conditions. Affected males tend to have hypomorphic missense variants, although some interesting new phenotypes are emerging with missense and splice variants, and their carrier mothers are unaffected (although they have skewed X-inactivation). In contrast, affected females with OFCD have protein-truncating variants or partial/whole gene deletions, and exhibit skewed X-inactivation. If the OFCD is inherited from their mothers, the mothers will also express the disorder, show skewed X-inactivation, and the variant is presumed lethal in affected male offspring as evidenced by miscarriages.

This paper has aimed to summarize the X-linked *BCOR* syndrome, and to extend the phenotypic spectrum associated with *BCOR*-pathogenic variants. Females tend to have features of OFCD, but in addition can manifest further features, including neuropathy, muscle hypotonia, pituitary underdevelopment, lipoma and lymphoma. We have shown that males with the typical *BCOR* variant c.254C>T; p.(Pro85Leu), contrary to existing information, can have normal intellectual development. We have also demonstrated that new variants in *BCOR* can be associated with X-linked syndromic intellectual disability in males, and megalophthalmos and myopia, thus extending the phenotype. We would recommend that males with severe microphthalmia or anophthalmia and relevant extraocular features described be tested for *SOX2* and *BCOR* as part of a panel. Furthermore, females with early onset cataract should be examined for extraocular features of the OFCD syndrome, and if any present tested for *BCOR* variants, with the caveat that occasionally an ocular-only phenotype can exist. In view of our cases with posterior embryotoxon or megalophthalmos, we suggest that individuals with similar phenotypes that include suggestive extraocular features are tested for *BCOR* variants. Furthermore, we would recommend long-term multicentre follow-up studies of individuals with *BCOR*-pathogenic variants to determine the incidence of tumour formation. We also propose abandoning the use of the generic term ‘Lenz’ microphthalmia since this refers to Lenz’ clinical description of a particular pedigree with a severe microphthalmia phenotype affecting males and is not representative of a genetically defined syndrome. Instead, we suggest a new term referring to *BCOR* conditions as X-linked *BCOR*-related syndrome, specifying male or female as appropriate.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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