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 2 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, Thakker et al. 2004). It is characterised 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, arched eyebrows). Less freqently 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, Thakker et al. 2004, Horn, Chyrek et al. 2005, Oberoi, Winder et al. 2005, Hilton, Johnston et al. 2009, Davoody, Chen et al. 2012, Lozic, Ljubkovic et al. 2012, Kantaputra 2014, Surapornsawasd, Ogawa et al. 2015, Ma, Grigg 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, Johnston et al. 2009). Furthermore, individuals with *BCOR* pathogenic variants with mainly ocular features are also reported (Ng, Thakker et al. 2004; Hilton, Johnston et al. 2009; Ma, Grigg 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, Thakker et al. 2004) and since then further cases

described (Hilton, Johnston et al. 2009, Suzumori, Kaname 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, Dai 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, Johnston 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, Thakker et al. 2004, Hilton, Johnston et al. 2009, Suzumori, Kaname et al. 2013). Although the features of so-called 'Lenz' microphthalmia are broader (Lenz 1955, Traboulsi, Lenz et al. 1988), some of these may be explained by the newly described genes *HMGB3* (Scott, Mohr et al. 2014) and *NAA10* which have been identified as other causes of X-linked 'Lenz' microphthalmia syndrome (Esmailpour, Riazifar 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 eleven 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 Cambridgeshire 1 Ethics Committee 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, Schmidt, et al, 2010; Ng, Hennekoff et al, 2003; Schwarz, Cooper, 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, Fitzgerald 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. 600ng 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 75bp 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, Cottle 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, Johnston, 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 (www.mutalyzer.nl)(Wildeman, van Ophuizen et al. 2008).

Case Descriptions (Table 1)

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 2nd 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 (Figure 1a-e). She had reduced bladder control and decreased reflexes. WES revealed a *de novo* heterozygous variant in *BCOR* c.2428C>T 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, Johnston et al. 2009) (see Supplementary Table 1).

Case 2

This 21-year-old Caucasian male first presented to the ophthalmic genetics clinic at the age of 9 years with bilateral microphthalmia (Figure 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 vesico-ureteric 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 (Figure 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 Computerised 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 3 half-brothers on his mother's side, including case 5 (Figure 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 33.5cm (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, Karczewski, et al, 2016) and is predicted to be deleterious by in *silico* software Polyphen-2, SIFT and Mutation Taster.

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 1 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 (Figure 1o).

She had normal growth and development. She had distinctive facial features with a short bulbous nose, microtia 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 y 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 (Figure 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 in order 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 (Figure 1p-r).

Her mother had surgery in infancy for bilateral congenital cataract, had frequent dental issues and suffered 8 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 one 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 (Figure 1s-w). At age 6 ½ 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 (Figure 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 (Figure 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 +20DS both eyes)

and her intellectual achievement was equivalent to her sighted peers. In addition to her right 2-3 toe syndactyly, she demonstrated left 2nd toe clinodactyly and 4th toe camptodactyly. She had hypodontia, a broad bifid nasal tip, mild heterochromia of the left iris, with bialteral 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: 262217), confirmed with Sanger sequencing (Wright, Fitzgerald 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 (Figure1aj-am). She also had hypermobility of the elbows. Her first teeth erupted at one 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) (Figure 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 one 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 (Figure 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, Hamroun 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 (Figure 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 anaemic at birth. A cleft palate was identified and she was also found to have a cardiac defect, which closed spontaneously. At nine 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 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 (Figure 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 to 15, confirmed by array CGH Xp11.4 (39910845_39922793)x1 (Agilent 60k 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 harbouring 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 2 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, harbouring 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, Feenstra 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, Thakker et al. 2004, Hilton, Johnston et al. 2009, Davoody, Chen et al. 2012), with features not universally described in OFCD cases (see Figure 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 Figure 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 (Figure 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 tumours is more common in OFCD cases compared to the general population, especially in view of the tumour 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, Mazan 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 harboured 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 analysed (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, Lenz et al. 1988, Hilton, Johnston et al. 2009). Hilton and colleagues analysed 21 male patients with presumed 'Lenz' microphthalmia and identified 1 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, Chyrek 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 7 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, vesico-ureteric 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, Ragge et al. 2003, Ragge, Lorenz et al. 2005, Bakrania, Robinson 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 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, Dai 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,

687 haemangiomas, cleft palate, posterior arachnoid cyst and severe growth and
688 intellectual delay (in the older boy). The younger, but not the older brother,
689 received WES and this revealed the c.4807A>C; p.(Ser1603Arg) *BCOR* variant
690 present in his affected brother and his unaffected mother, but absent in his
691 unaffected half-brothers. There are enough features of *BCOR* X-linked syndrome
692 to suggest this as the underlying diagnosis. However, as this is the first
693 description of an intellectual disability syndrome associated with *BCOR*, without
694 the characteristic findings of microphthalmia, this gene should be considered in
695 other males with intellectual disability with or without overlapping features to
696 explore this potential new phenotype more fully.
697
698 Case 12 showed a boy with high myopia and large globes and who also
699 demonstrates a splice site variant, and therefore distinct from the classical
700 missense variant c.254C>T; p.(Pro85Leu), seen in males with severe
701 microphthalmia. The organs involved in the phenotype in this boy overlap with
702 OFCD syndrome and/or Lenz microphthalmia. However, his eye phenotype is
703 distinct from the phenotype of those two disorders in causing increased ocular
704 growth and myopia, and he additionally showed posterior embryotoxon, also
705 seen in cases 4 and 5. Interestingly, his unaffected mother and sister who carry
706 the same variant show highly skewed X-inactivation.
707
708 The mechanism by which *BCOR* acts to promote eye growth is not precisely
709 known. Loss of bcor function leads to coloboma formation in the zebrafish.
710 Through evidence from oncogenic pathways, it is known that the
711 BCOR/BCL6/SIRT1 complex interacts with the SHH signaling pathway, also
712 important in human eye development (and medulloblastoma) (Tiberi, Bonnefont
713 et al. 2014). In zebrafish, the bcor/bcl6a complex appears to interact with hdacs,
714 and there is some evidence that part of the mechanism may occur by bcor/bcl6a
715 and Hdac1 co-repressing p53 expression, although there is no evidence that
716 humans with germline p53 mutations have developmental eye anomalies (Lee,
717 Lee et al. 2013).
718

BCOR is a co-repressor 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 tumours (Dobashi, Tsuyama et al. 2016). Furthermore, Tanaka and colleagues (Tanaka, Nakajima-Takagi 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, Tirode et al. 2012, Ueno-Yokohata, Okita 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

752 megalophthalmos and myopia, thus extending the phenotype. We would
753 recommend that males with severe microphthalmia or anophthalmia and
754 relevant extraocular features described be tested for *SOX2* and *BCOR* as part of a
755 panel. Furthermore, females with early onset cataract should be examined for
756 extraocular features of the OFCD syndrome, and if any present tested for *BCOR*
757 variants, with the caveat that occasionally an ocular-only phenotype can exist. In
758 view of our cases with posterior embryotoxon or megalophthalmos, we suggest
759 that individuals with similar phenotypes that include suggestive extraocular
760 features are tested for *BCOR* variants. Furthermore, we would recommend long
761 term multicentre follow-up studies of individuals with *BCOR* pathogenic variants
762 to determine the incidence of tumour formation. We would also propose
763 abandoning the use of the generic term 'Lenz' microphthalmia since this refers to
764 Lenz' clinical description of a particular pedigree with a severe microphthalmia
765 phenotype affecting males and is not representative of a genetically defined
766 syndrome. Instead, we suggest a new term referring to *BCOR* conditions as X-
767 linked *BCOR*-related syndrome, specifying male or female as appropriate.

Legends:

Figure 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.

Figure 2. A. Pedigree of cases 4 and 5; B. Pedigree of case 7; C. Pedigree of case 12

Figure 3: Summary of the described and new (in bold) variants in *BCOR*

Tables:

Table 1: Summary of Phenotypic Findings

Supplementary Table 1: Summary of Clinical Features and Variants of Published cases identified with BCOR variants (including current series)

Supplementary Table 2: Summary of OFCD cases

Supplementary Table 3: Summary of X-linked BCOR male cases

Conflict of Interest Statement

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

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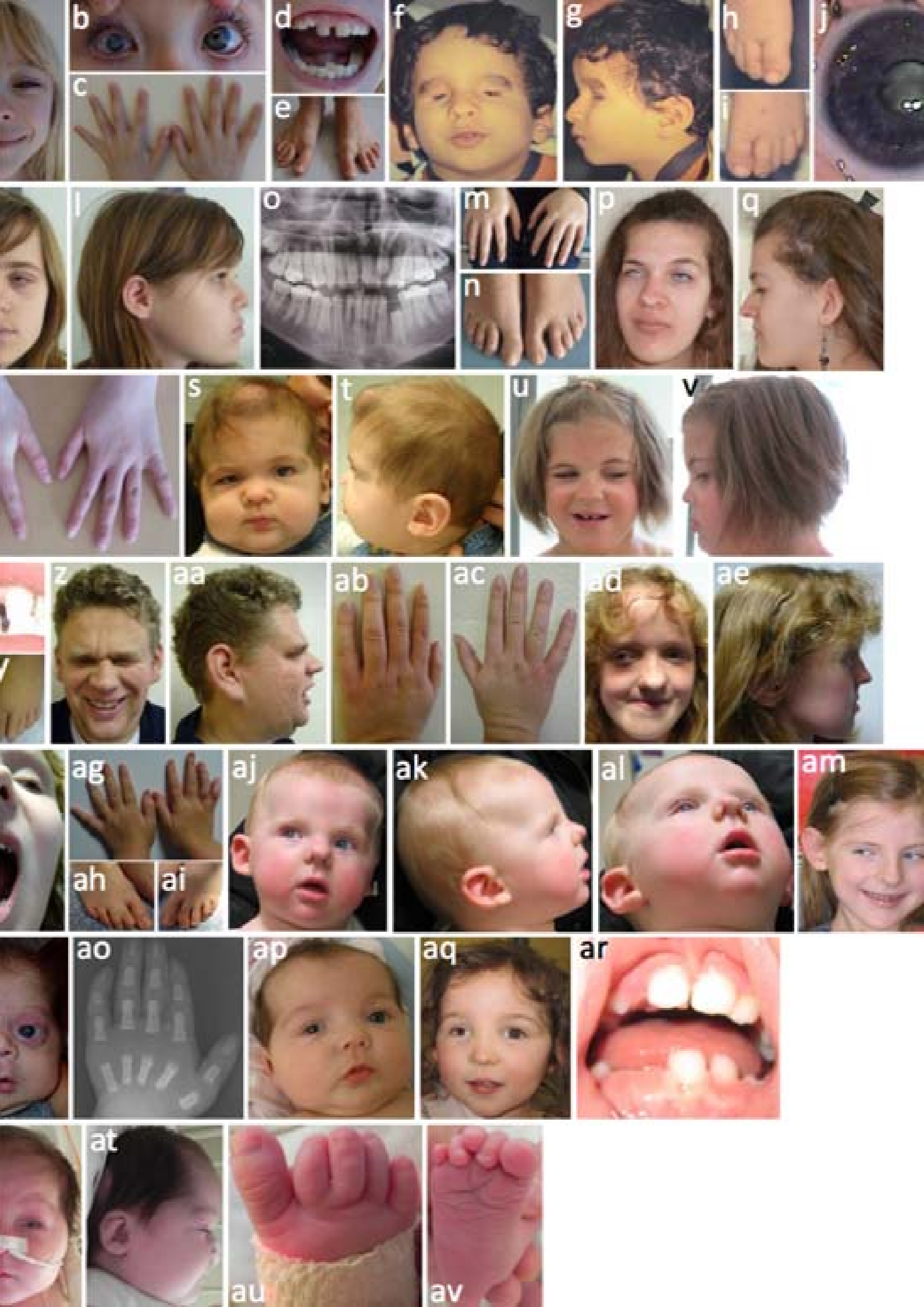
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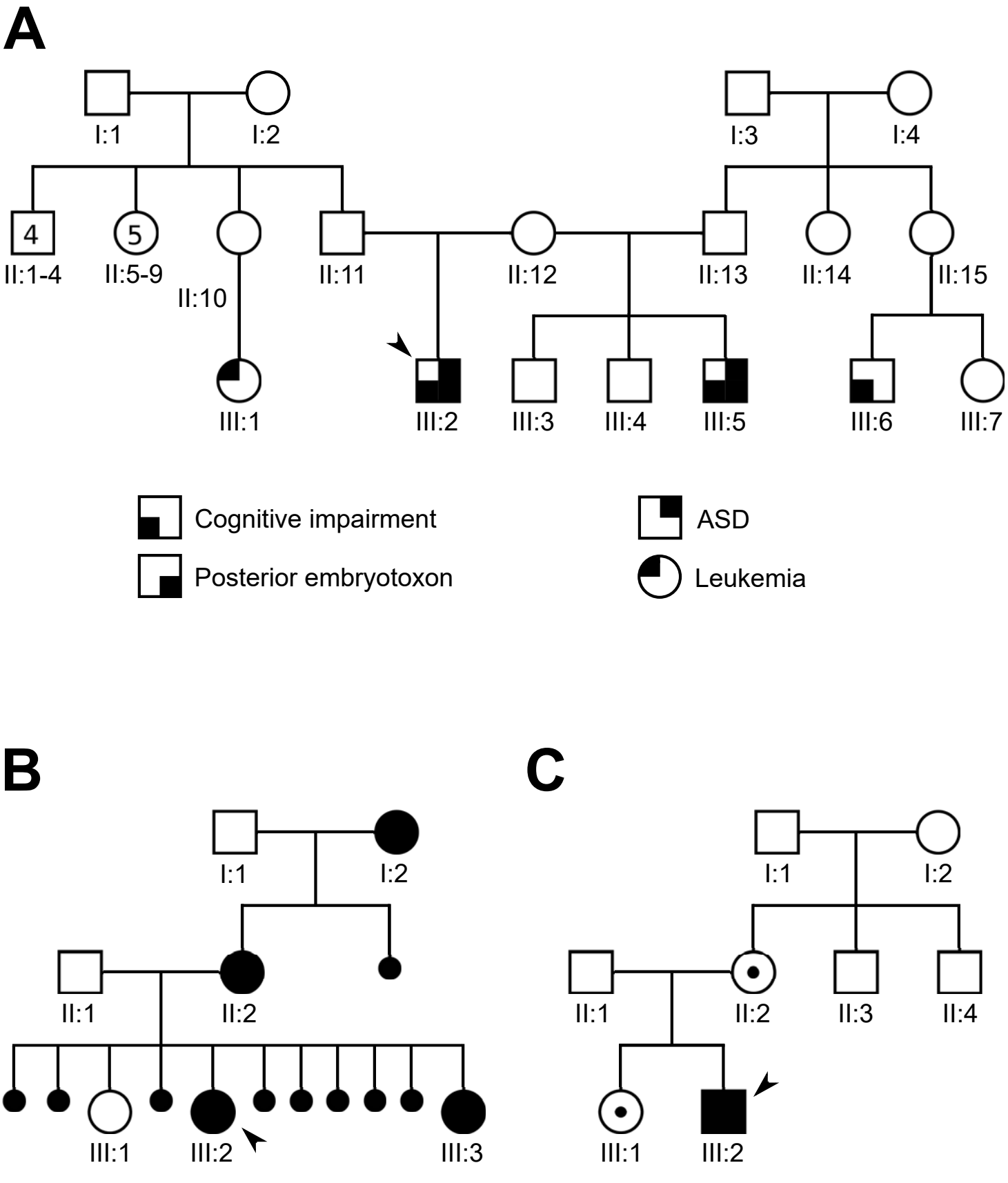
A
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II:14
II:15
III:1
III:2
III:3
III:4
III:5
III:6
III:7
Cognitive impairment
Posterior embryotoxon
ASD
Leukemia
B
I:1
I:2
II:1
II:2
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III:2
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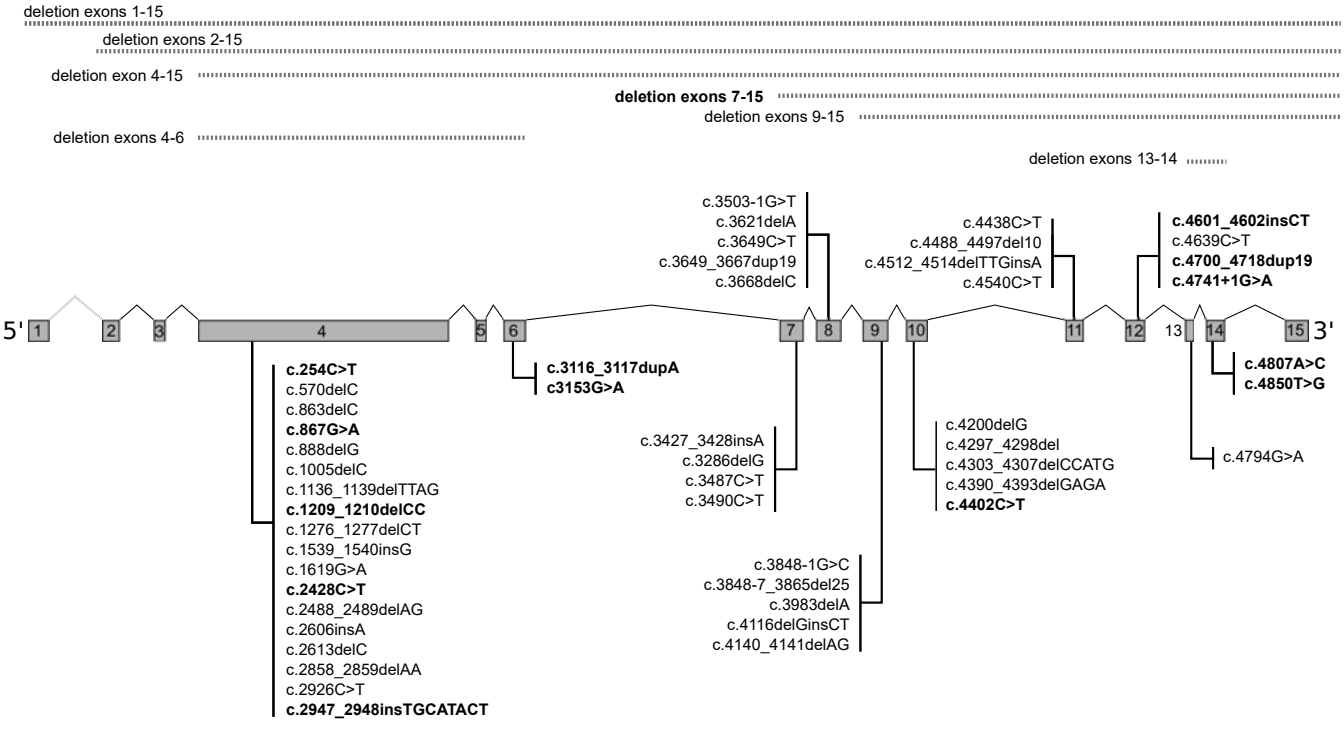
deletion exons 1-15
deletion exons 2-15
deletion exon 4-15
deletion exons 7-15
deletion exons 9-15
deletion exons 4-6
deletion exons 13-14
c.3503-1G>T
c.3621delA
c.3649C>T
c.3649_3667dup19
c.3668delC
c.4438C>T
c.4488_4497del10
c.4512_4514delTTGinsA
c.4540C>T
c.4601_4602insCT
c.4639C>T
c.4700_4718dup19
c.4741+1G>A
5'
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
3'
c.254C>T
c.570delC
c.863delC
c.867G>A
c.888delG
c.1005delC
c.1136_1139delTTAG
c.1209_1210delCC
c.1276_1277delCT
c.1539_1540insG
c.1619G>A
c.2428C>T
c.2488_2489delAG
c.2606insA
c.2613delC
c.2858_2859delAA
c.2926C>T
c.2947_2948insTGCATACT
c.3116_3117dupA
c.3153G>A
c.3427_3428insA
c.3286delG
c.3487C>T
c.3490C>T
c.3848-1G>C
c.3848-7_3865del25
c.3983delA
c.4116delGinsCT
c.4140_4141delAG
c.4200delG
c.4297_4298del
c.4303_4307delCCATG
c.4390_4393delGAGA
c.4402C>T
c.4794G>A
c.4807A>C
c.4850T>G

Table 1: Summary of Phenotypic Findings

General information	case 1	case 2	case 3	case 4	case 5	case 6	case 7	case 8	case 9	case 10	case 11	case 12	case 13	case 14	case 15	case 16
Age	13y	21y	3y	18m	5y	17y	15y	6y 6m	27y	9y	11y	3y	2y	3y	14y	2m
Gender	F	M	F	M	M	F	F	F	M	F	F	M	F	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	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.(Asp1040Lysfs*16)	arr[GRCh37] Xp11.4(39910845_39922793)x1, and 2p15 deletion
inheritance	*de novo*	mat	*de novo*	mat	mat	*de novo*	mat	mat	mat	*de novo*	NK	mat	*de novo*	mat	NK	*de novo*
affected family members				brother (case 5)	brother (case 4)		mother; gmother; aunt	mother						mother		
growth																
birth weight (kg)	3.99	NK	3.59	2.88	2.86	2.64	3.6	3.54	3.09	3.35	3.62	4.04	1.89	2.21	2.72	3.25
height centile (age)	2nd (11y)	9th (9y); 0.4-2nd (21y)	50th (3y)	80th (birth)	-1 SD (4y 6m)	50th (17y)	+0.5 SD (15y)	+2 SD (6y 6m)	50th (27y)	91st (8y)	NK	+1.5 SD (birth)	NK	13th (3m), 2nd (3y)	NK	NK
weight centile (age)	< 0.4th (11y)	0.4-2nd (9y); <3rd (21y)	60th (3y)	25th (birth)	0 SD (4y 6m)	90th (17y)	10th (15y)	+3 SD (6y 6m)	91st (27y)	98-99.6th (8y)	NK	60 th (birth)	NK	6 th (3m), 23rd (3y)	NK	NK
HC centile (age)	50th (11y)	25th (9y); 9th (21y)	NK	28th (birth)	-2.5 SD (4y 6m)	95th (17y)	+0.5 SD (15y)	+1 SD (6y 6m)	75th -91st (27y)	> 99th (8y)	NK	+1 SD (birth)	NK	96th (3m)	NK	NK
ocular																
microphthalmia	B	B (severe)	B				B	B (mild)		B	U (RE)		B	U (RE)		B
anophthalmia									B							
congenital cataract	B		B			B	B	B		B	B		B	B	B	B
glaucoma	U					B	B								B	
posterior embryotoxon				B	B							B				
other						RD				PFV, iris hetero-chromia	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		Down-slanting PF long face, tall forehead, thick eyebrows, LP				Prominent chin			small PF	prominent forehead, small mouth, narrow palate, widening of cerebral falx	upslanting PF	full cheeks, ptosis, ex-ophthalmos, glabellar naevus flammeus,			ptosis, macro-cephaly, alveolar cleft	square shaped face, upslanting PF
cardiac																
ASD				+	+		+			+	+	+		+		+
VSD												+		+		+

other		triple heart sounds								dysplastic pulmonary valve	PDA	PDA, persistent L vena cava			cardiac defect	
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		oligodontia				oligodontia		
skeletal																
hands	long Fi	5th Fi clin, long Fi	long Fi	long Fi, 4-5 Cam	cam all Fi	5th Fi Clin	long Fi		long Fi	4th fi Poly-syn, 5/6 fi poly-syn		long Fi short metacarpals, 5th Fi Bra				
feet	SG, 2nd toe Clin			short, deep set toe nails	fetal toe pads	2-3 toe Syn	long toes	2-3 toe Syn	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	scoliosis									Joint HM				Joint HM	
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									cerebellar hypoplasia, BA, ventricular enlargement
other findings																
GU anomalies	reduced bladder control	CR, VUR, primary enuresis							urethral hypoplasia, renal dysplasia, renal failure, VUR,			CR, grade 4-5 VUR, kidney stone				
other		hypotonia, thin body habitus	Stage III T-cell lymphoma	left temporal haemangioma	hypotonia, capillary malformation, feeding difficulty				hypotonia			seizure disorder		thyroglossal cyst		hearing loss, hypotonia, abnormal movements

Abbreviations:

* (NM_001123385.1)
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

Supplementary Table 1 - Summary of published cases identified with BCOR variants (including current series)

year	paper	family	variant (NM_001123385.1 unless otherwise stated)	M/F	Ocular	Craniofacial	Cardiovascular	Dental	Skeletal	Brain	Developmental Delay	Genitourinary	Other
heterozygous (female OFCD) cases													
2004	Ng *et al.*	OFCD1	c.3503-1G>T	F	Congenital nuclear cataract	High nasal bridge, Broad nasal tip, Prominent mandible	Atrial Septal Defect (ASD)	Persistent primary teeth with radiculomegaly	2-3 Toe syndactyly, Hammer toes				
2004	Ng *et al.*	OFCD2	c.3848-1G>A	F	Microphthalmia, Congenital cataract, Optic disc dysplasia	High nasal bridge with broad nasal tip	ASD	Persistent primary teeth with radiculomegaly, Fused secondary dentitition	Hammer toes, Recurrent anterior elbow dyslocation				
2004	Ng *et al.*	OFCD3	c.4140_4141del p.(Glu1382Ilefs*26)	F	Microphthalmia, Congenital cataract	Submucous cleft palate, High nasal bridge with broad nasal tip	Floppy mitral valve	Persistent primary teeth with canine radiculomegaly	2-3 Toe syndactyly, Hammer toes				
2004	Ng *et al.*	OFCD4	c.2606dup p.(Tyr869*)	F	Microphthalmia and microcornea, Congenital cataract	High nasal bridge with broad nasal tip	ASD	Persistent primary teeth with radiculomegaly					
2004	Ng *et al.*	OFCD5 case 1	c.2926C>T p.(Arg976*)	F	Microphthalmia, Congenital cataract, Lens dislocation	Cleft palate, Prominent mandible, High nasal bridge with broad nasal tip	ASD, Ventricular septal defect (VSD)	Persistent primary teeth with canine radiculomegaly, Fused secondary dentitition	2-3 Toe syndactyly, Hammer toes				
2004	Ng *et al.*	OFCD5 case 2	c.2926C>T p.(Arg976*)	F	Congenital cataract				Hammer toes				
2004	Ng *et al.*	OFCD5 case 3	c.2926C>T p.(Arg976*)	F	Microphthalmia, Congenital cataract	Cleft palate	Double outlet Right Ventricle with large ASD and subpulmonary VSD, Hypoplasia of aortic arch	NR as fetal death *in utero*	2-5 Toe syndactyly	Dandy Walker malformation			
2004	Ng *et al.*	OFCD6 case 1	c.3983del p.(Gln1328Argfs*41)	F	Unilateral Microphthalmia, Congenital cataract	High nasal bridge with broad nasal tip	ASD	Persistent primary teeth with radiculomegaly	Toes 2-4 hammer-type flexion deformity				
2004	Ng *et al.*	OFCD6 case 2	c.3983del p.(Gln1328Argfs*41)	F	Bilateral microphthalmia, Congenital cataract, Persistent hyperplastic primary vitreous	High nasal bridge with broad nasal tip, High-arched palate	Secundum ASD with perimembranous VSD	Persistent primary teeth with radiculomegaly	2-3 Toe syndactyly				
2004	Ng *et al.*	OFCD7	deletion encompassing at least exons 9-15	F	Bilateral microphthalmia, Congenital cataracts	Submucous cleft palate, High nasal bridge with broad nasal tip, Small cupped shaped ears		Persistent primary teeth, Single mandibular central incisor, Canine root dilacerations	2-3 Toe syndactyly, Hammer type flexion deformity				
2005	Horn *et al*	1	c.3286del p.(Glu1096Argfs*17) *de novo*	F	Microphthalmia, Congenital cataract, Ptosis	Cleft palate, Broad nasal tip, Long philtrum	VSD	Delayed dentition, Oligodontia, Radiculomegaly	Sandal gaps, Broad halluces, Camptodactyly 2-3 toes				

2005	Horn *et al*	2	c.2488_2489del p.(Ser830Cysfs*6)	F	Microphthalmia, Congenital Cataract	Long Philtrum, High palate	VSD	Delayed dentition	Sandal gaps, Broad halluces, Camptodactyly 2-3 toes			
2005	Horn *et al*	3	deletion encompassing at least exons 4-6 *de novo*	F	Microphthalmia, Congenital Cataract, Iris Coloboma	Cleft palate, Broad nasal tip, Long philtrum		Delayed dentition, Oligodontia	Syndactyly and Camptodactyly 2-3 toes	Developmental delay		
2005	Oberoi *et al.*	2	c.2613del p.(Phe871Leufs*8)	F	Microphthalmia, Congenital cataract, Ptosis	Bifid nasal tip, Long philtrum, Cup-shaped ears, Micrognathia	Cardiac murmur	Delayed eruption permanent teeth, fused incisors, retained primary teeth	Radioulnar synostosis			
2008	Fujimaki *et al.*	1	c.4639C>T p.(Arg1547*)	F	Microphthalmia, Congenital Cataract, Secondary glaucoma		ASD	Radiculomegaly	Digit anomaly			
2009	Hilton *et al.*	I (case 1)	c.2926C>T p.(Arg976*)	F	Congenital cataract, Ptosis	Septate nasal cartilage	Heart murmur	Unerupted secondary teeth, Root radiculomegaly, Hypodontia	Hammer toes, Radioulnar synostosis			
2009	Hilton *et al.*	I (case 2)	c.2926C>T p.(Arg976*)	F	Microphthalmia, Congenital cataract, Lens dislocation, Optic disc dysplasia	Septate nasal cartilage, High nasal bridge	ASD, VSD, Pulmonary valve stenosis	Not recorded				Poor feeding
2009	Hilton *et al.*	II	c.1539dup p.(Pro514Alafs*4)	F	Microphthalmia, Congenital cataract	Septate nasal cartilage	VSD, Patent ductus arteriosus, Mitral valve insufficiency, Dextrocardia	Persistent primary teeth, Unerupted secondary teeth, Root radiculomegaly, Hypodontia	Hammer toes			Hearing impairment
2009	Hilton *et al.*	III (case 1)	c.4116delGinsCT p.(Glu1372Aspfs*37)	F	Microphthalmia, Congenital cataract, Phthisis bulbi	Septate nasal cartilage	Not recorded	Persistent primary teeth, Unerupted secondary teeth, Root radiculomegaly, Hypodontia	Hammer toes			
2009	Hilton *et al.*	III (case 2)	c.4116delGinsCT p.(Glu1372Aspfs*37)	F	Microphthalmia, Congenital cataract, Glaucoma	Not affected	Not recorded	Unerupted secondary teeth, Root radiculomegaly	Hammer toes			
2009	Hilton *et al.*	III (case 3)	c.4116delGinsCT p.(Glu1372Aspfs*37)	F	Microphthalmia, Congenital cataract	Septate nasal cartilage	Not recorded	Persistent primary teeth, Unerupted secondary teeth, Root radiculomegaly,	2-3 Toe syndactyly			
2009	Hilton *et al.*	III (case 4)	NM_001123385.1: c.4116delGinsCT p.(Glu1372Aspfs*37)	F	Microphthalmia, Congenital cataract, Glaucoma	Septate nasal cartilage	Not recorded	Unerupted secondary teeth	Hammer toes, Radioulnar synostosis			

2009	Hilton *et al.*	III (case 5)	c.4116delGinsCT p.(Glu1372Aspfs*37)	F	Microphthalmia, Congenital cataract	Septate nasal cartilage	Not recorded	Persistent primary teeth, Unerupted secondary teeth, Root radiculomegaly, Hypodontia	Hammer toes		
2009	Hilton *et al.*	III (case 6)	c.4116delGinsCT p.(Glu1372Aspfs*37)	F	Microphthalmia, Congenital cataract	Cleft palate	ASD, VSD, Double outlet right ventricle		2-3 toe syndactyly, Radioulnar synostosis	Mental retardation	Asplenia
2009	Hilton *et al.*	IV (case 1)	c.4488_4497del p.(Gly1497Profs*68)	F	Microphthalmia, Microcornea, Congenital Cataract, Iris synechia	Septate nasal cartilage, High nasal bridge, Long narrow face	Aortic valve stenosis	Persistent Primary teeth, Unerupted secondary teeth, Root radiculomegaly, Hypodontia, Fusion of teeth	Hammer toes, 2-3 Toe syndactyly, Lordosis		Hearing impairment, Vomiting/reflux
2009	Hilton *et al.*	IV (case 2)	c.4488_4497del10 p.(Gly1497Profs*68)	F	Microphthalmia, Microcornea, Congenital Cataract	Septate nasal cartilage, High nasal bridge, High arched palate	Not affected	Persistent Primary teeth, Unerupted secondary teeth, Root radiculomegaly, Hypodontia, Duplicated teeth	2-3 Toe syndactyly, Lordosis	Mild mental retardation	Hearing impairment, Vomiting/reflux
2009	Hilton *et al.*	IX	c.3848-7_3865del25 alters conserved splice acceptor site and predicts: p.(delexon9fs*18)	F	Microphthalmia, Microcornea, Congenital Cataract	Septate nasal cartilage, Cleft palate	ASD	Persistent primary teeth, Unerupted secondary teeth, Root radiculomegaly, Hypodontia	Hammer toes, Bilateral radioulnar synostosis		
2009	Hilton *et al.*	V	c.4512_4514delGinsA p.(Ala1506*)	F	Microphthalmia, Congenital cataract	Septate nasal cartilage, High nasal bridge	ASD	Persistent primary teeth, Unerupted secondary teeth, Root radiculomegaly	Hammer toes, Radioulnar synostosis, Lumbar scoliosis		
2009	Hilton *et al.*	VI (case 1)	c.3621del p.(Lys1207Asnfs*31)	F	Congenital Cataract	Not recorded	Not recorded	Not recorded	Not recorded		Hearing impairment
2009	Hilton *et al.*	VI (case 2)	c.3621del p.(Lys1207Asnfs*31)	F	Microphthalmia, Congenital Cataract , Iris synechia	Septate nasal cartilage	not affected	Persistent primary teeth, Unerupted secondary teeth, Hypodontia, Duplicated teeth	Hammer toes, 2-3 toe syndactyly		
2009	Hilton *et al.*	VI (case 3)	c.3621del p.(Lys1207Asnfs*31)	F	Congenital Cataract	Not recorded	Not affected	Not recorded	Not recorded		
2009	Hilton *et al.*	VI (case 4)	c.3621del p.(Lys1207Asnfs*31)	F	Microphthalmia, Congenital Cataract	Septate nasal cartilage, Submucosal cleft palate, Bifid Uvula	ASD	Persistent primary teeth, Unerupted secondary teeth, Root radiculomegaly, Fusion of teeth, Duplicated teeth	Scoliosis		
2009	Hilton *et al.*	VII	c.4303_4308del p.(Pro1435Leufs*24)	F	Microphthalmia, Congenital Cataract	Not affected	Not recorded	Persistent primary teeth	2-3 Toe syndactyly		

2009	Hilton *et al.*	VIII	c.4200delG p.(Pro1401Argfs*83)	F	Microcornea, Congenital cataract	Septate nasal cartilage, High nasal bridge, Submucosal cleft palate	Pentalogy of Fallot	Delayed dentition, Root radiculomegaly, Hypodontia	2-3 Toe syndactyly, Radioulnar synostosis		Mild mental retardation	Vesicoureteral reflux	
2009	Hilton *et al.*	X	NM_001123385.1: c.2428C>T p.(Arg810*)	F	Microphthalmia, Microcornea, Congenital cataract	Septate nasal cartilage, High nasal bridge, Submucosal cleft palate	ASD	Delayed primary dentition	Hammer toes		Mild mental retardation		
2009	Hilton *et al.*	XI (case 1)	NM_001123385.1: c.1276_1277delCT p.(Leu426Valfs*13)	F	Microphthalmia, Congenital Cataract, Glaucoma, Retinal Detachment	Septate nasal cartilage, Long narrow face	ASD, VSD, Persistent ductus arteriosus	Root radiculomegaly, Hypodontia	Short fingers				
2009	Hilton *et al.*	XI (case 2)	NM_001123385.1: c.1276_1277delCT p.(Leu426Valfs*13)	F	Microphthalmia, Congenital Cataract	Septate nasal cartilage, Simple ears	ASD, VSD, Persistent ductus arteriosus, Tricuspid valve insufficiency	Root radiculomegaly, Hypodontia	Hammer toes	Cerebral atrophy	ADHD		
2009	Hilton *et al.*	XII	Large deletion encompassing at least exons 2-15	F	Congenital cataract, Glaucoma	Sptate nasal cartilage, High arched palate	ASD	Root radiculomegaly	Hammer toes, 2-3 Toe syndactyly		Mild mental retardation		
2009	Hilton *et al.*	XIII	c.3649_3667dup19 p.(Ala1224Metfs*27)	F	Congenital cataract	Not affected	ASD	Delayed primary dentition	Hammer toes, 2-3 Toe syndactyly				Hearing impairment
2009	Hilton *et al.*	XIV	c.3427_3428insA p.(Ser1143Leufs*4)	F	Microphthalmia, Congenital cataract, Coloboma	Septate nasal cartilage, Simple ears	ASD, VSD	Primary dentition unaffected	2-3 Toe syndactyly, Limited supination at wrist, Partial fusion of C2-C3 vertebrae				
2009	Hilton *et al.*	XIX	c.570delC p.(Trp191Glyfs*25)	F	Microphthalmia, Congenital cataract, Ptosis	Septate nasal cartilage, High nasal bridge, Long narrow face, Simple ears	Not affected	Delayed dentition, Root radiculomegaly, Hypodontia, Fusion of teeth	Not recorded		Mild mental retardation		
2009	Hilton *et al.*	XV	c.3848-1G>C p.(delexon9fs*18)	F	Microphthalmia, Congenital cataract	Not affected	ASD	Primary dentition unaffected	Not recorded				
2009	Hilton *et al.*	XVI (case 1)	large deletion encompassing at least exons 4-15 mosaic	F	Microphthalmia, Congenital cataract	Septate nasal cartilage, High nasal bridge, Long narrow face	VSD	Delayed dentition, Persistent primary teeth, Root radiculomegaly	2-3 Toe syndactyly				
2009	Hilton *et al.*	XVI (case 2)	large deletion encompassing at least exons 4-15 mosaic	F	Microphthalmia, Congenital cataract	Septate nasal cartilage, High nasal bridge, Long narrow face	Not affected	Delayed dentition, Persistent primary teeth, Root radiculomegaly	2-3 Toe syndactyly, Radioulnar synostosis, Scoliosis				
2009	Hilton *et al.*	XVI (case 3)	large deletion encompassing at least exons 4-15 maternal	F	Microphthalmia, Congenital cataract	Not affected	ASD	Delayed primary dentition	2-3 Toe syndactyly				
2009	Hilton *et al.*	XVII (case 1)	c.4844-141_5078+821del1410 p.(Asp1615Glyfs*15) mosaic	F	Not affected	Not affected	Not affected	Not affected	Not affected				
2009	Hilton *et al.*	XVII (case 2)	c.4844-141_5078+821del1410 p.(Asp1615Glyfs*15) mat	F	Microcornea, Congenital cataract	Septate nasal cartilage, Long narrow face	Not affected	Delayed primary dentition	2-3 Toe syndactyly				

2009	Hilton *et al.*	XVIII	c.4540C>T p.(Arg1514*)	F	Microphthalmia, Congenital cataract, Ptosis	Septate nasal cartilage, High nasal bridge, Long narrow face, Cleft palate	ASD	Root radiculomegaly, Hypodontia	2-3 Toe syndactyly, Limited supination		
2009	Hilton *et al.*	XX	c.863delC p.(Pro288Argfs*90)	F	Congenital cataract	Septate nasal cartilage, High nasal bridge, Long narrow face	Not affected	Delayed dentition, Persistent primary teeth, Root radiculomegaly, Hypodontia	Hammer toes, 2-3 Toe syndactyly, Scoliosis		
2009	Hilton *et al.*	XXI	c.2926C>T p.(Arg976*)	F	Microphthalmia, Congenital cataract	Not recorded	ASD	Not recorded	Not recorded		
2009	Jiang *et al.*	1	c.1005delC p.(Ser336Argfs*42) *de novo*	F	Bilateral posterior cataracts	Wide anterior columella, Mildly protuberant cup shaped ears	ASD	Delayed eruption of primary dentition	2-3 Toe syndactyly		Duchenne Muscular Dystrophy (*DMD* deletion)
2012	Davoody *et al.*	1	c.2858_2859delAA p.(Lys593Serfs*8)	F	Microphthalmia, Microcornea, Congenital cataracts	Broad nasal tip, Long philtrum, Submucosal cleft palate	Not affected	Missing teeth, Malocclusion, Radiculomegaly	Hammer toes, 4-5 Clinodactyly		Mild velopharyngeal insufficiency
2012	Kondo *et al.*	1 (case MC17)	c.888delG p.(Asn297Ilefs*81) maternal	F	Bilateral congenital cataract		ASD, VSD, Patent ductus arteriosus	Delayed dentition	Broad halluces, 2-3 Toe syndactyly, Hammer toes, Brachyphalangia of forth toe		
2012	Kondo *et al.*	1 (case MC17b)	c.888delG p.(Asn297Ilefs*81)	F	Bilateral congenital cataracts			Dental anomalies, Hypodontia, All teeth removed	2-3 Toe syndactyly, Hammer toes		
2012	Kondo *et al.*	1 (case MC18)	c.888delG p.(Asn297Ilefs*81) maternal	F	Bilateral congenital cataracts			Delayed Dentition	Broad halluces, Hammer toes, 2-3 Toe syndactyly	Learning difficulties	Right inguinal hernia
2012	Lozić *et al.*	1 (grandmother)	c.4438C>T p.(Arg1480*)	F	Bilateral congenital cataracts, Glaucoma	Long face, Long philtrum, Mildly broad nasal tip	Not affected	Radiculomegaly, Root dilacerations canines, Missing teeth, Mild overbite, Delayed dental eruption, Hypodontia	Syndactyly 2-3 toes		
2012	Lozić *et al.*	1 (mother)	c.4438C>T p.(Arg1480*) maternal	F	Bilateral congenital cataracts, Ptosis, Iris coloboma, Nystagmus	Long face, Long philtrum, High arched palate	Heart murmur	Delayed eruption of primary and secondary dentition, Missing teeth, Deep overbite, Radiculomegaly, Root dilaceration canines, Hypodontia	Thoracic kyphoscoliosis, Syndactyly of 2-3 toes, Camptodactyly, Broad halluces		
2012	Lozić *et al.*	1 (twin 1)	c.4438C>T p.(Arg1480*) maternal	F	Congenital cataract, Asymmetric size of eyes	Long philtrum, Mildly broad nasal tip, Downward eyebrows	ASD	Delayed eruption of primary dentition	Camptodactyly of 2-3 toes	Mild to moderate developmental delay	Umbilical hernia

2012	Lozić *et al.*	1 (twin 2)	c.4438C>T p.(Arg1480*) maternal	F	Bilateral microphthalmia, Congenital cataracts, Ptosis	Dolichocephaly, Long face, Downward eyebrows, Long philtrum, Mildly broad nasal tip, Cleft dental ridge in midline, High palate	ASD, VSD	Delayed eruption of primary dentition	2-3 Toe syndactyly, Broad halluces	Mild to moderate developmental delay	
2014	Danda *et al.*	1 (proband)	c.3490C>T p.(Arg1164*) *de novo*	F	Bilateral cataracts, Microcornea, Nystagmus	High forehead, Frontal bossing, Broad nasal tip with bifid cartilage, Low set posteriorly roated ears, High arched palate, Bifid uvula	Double outlet right ventricle, VSD, Pulmonary stenosis	Delayed eruption of permanent teeth, Malocclusion with deep overbite, Radiculomegaly	Radioulnar synostosis	Rectovaginal fistula	
2014	Danda *et al.*	1 (sister)	c.3490C>T p.(Arg1164*) *de novo*	F	Congenital cataract, Microcornea	High nasal bridge, V-shaped maxilla with high palate		Delayed eruption of permanent molars	Sandal gap		
2014	Feberwee *et al.*	1	c.4297_4298del p.(Gln1433Alafs*27) *de novo*	F	Microphthalmia, Bilateral congenital cataracts, Ptosis	Broad nasal tip, Long philtrum, Facial asymmetry, Laterally curved eyebrows	Open ductus botalli	Delayed eruption of teeth, Radiculomegaly			
2014	Feberwee *et al.*	2	c.3649C>T p.(Arg1217*) *de novo*	F	Bilateral Microphthalmia, Congenital cataract	Prominent forehead, Hypertelorism, Broad nasal tip	ASD		Camptodactyly		
2014	Surapornsawasd *et al.*	1	c.4794G>A p.(Trp1598*) *de novo*	F	Eye phenotype characteristic of OFCD	Cleft palate		Missing teeth, Persistent primary teeth, Delayed secondary dentition, Radiculomegaly, Malformed teeth			
2014	Surapornsawasd *et al.*	2	c.3668delC p.(Ser1223Trpfs*15) *de novo*	F	Eye phenotype characteristic of OFCD	Submucous cleft palate		Missing teeth			
2015	Di Stefano *et al.*	1	arr[hg19]Xp11.4(38,060,296-40,338,791)x1	F	Microphthalmia, Secondary cataract, Strabismus and Epicanthus	Broad forehead, Round face with pointed chin, Laterally extended eyebrows, Broad nasal tip, Depressed nasal bridge with deep philtrum, Protruding ears, Bifid uvula	ASD, VSD, Mild patent ductus arteriosus, Persistent left superior vena cava	Delayed dentition, Radiculomegaly, Hypodontia	2-3 Cutaneous syndactyly, Second toe camptodactyly, 5th Finger clinodactyly		
2016	Ma *et al.*	7	c.4390_4393del p.(Glu1464Profs*1)	F	Microphthalmia, Cataracts, Glaucoma						
2016	Ma *et al.*	44	c.1136_1139del p.(Val379Alafs*62)	F	Cataracts, Glaucoma	Cleft palate, Facial features consistent with OFCD	ASD	Dental features consistent with OFCD			
2016	O'Byrne *et al.*	1	c.4540C>T p.(Arg1514*) *de novo*	F	Microphthalmia, Bilateral cataracts	Temporal hypertrichosis, Supraorbital grooving, Gum hypertrophy, Craniosynostosis, Cleft palate, Deviation of nasal septum, Opafication of right middle ear cleft	ASD, Persistent ductus arteriosus, Pulmonary hypertention	Not recorded	Not affected		Unilateral severe conductive hearing loss

2017	Zhou *et al.*	1	c.3487C>T p.(Arg1163*) *de novo*	F	Posterior cortical cataracts, Posterior lenticonus, Scattered vacuoles in posterior cortex, Blepharoptosis	Mild hypertelorism, Epicanthal folds, Low set ears, Narrow palpebral fissures, Almond shaped eyes, Flat nasal bridge, Broad nasal tip, Small mouth, Laryngeal cleft	ASD, Patent ductus arteriosus	Not affected	Right talipes, 2-3 Toe syndactyly			Left hearing impairment
2018	Ragge *et al.*	1	c.2428C>T p.(Arg810*) *de novo*	F	Microphthalmia, Early onset cataracts, Glaucoma			Late eruption of primary dentition, Delayed loss of primary dentition, Small adult teeth, Second row of teeth	Long slender fingers, Increased sandal gap feet, 2nd Toe clinodactyly, Hyperextensible joints	Lipoma of corpus callosum	Recurrent urinary tract infections, Growth hormone deficiency, Reduced bladder control	
2018	Ragge *et al.*	3	c.1209_1210delCC p.(Gln404Alafs*35) *de novo*	F	Microphthalmia, Congenital cataract	Downslanting dysplastic ears, High arched narrow palate	ASD	Late eruption of primary dentition, Abnormal crown volume	Long slender fingers and hands			T-cell lymphoma
2018	Ragge *et al.*	6	c.4700_4718dup p.(Glu1573Aspfs*7) *de novo*	F	Congenital cataract, Right retinal detachment	Short bulbous nose, Microtia, Prognathism		Late eruption of secondary dentition, Radiculomegaly	5th Finger clinocactyly, 2-3 Toe partial syndactyly	Not affected		
2018	Ragge *et al.*	10	c.3153G>A p.(Trp1051*) *de novo*	F	Microphthalmia, Congenital cataract, Persistent fetal vasculature, Small optic nerves, Mild left iris heterochromia	Prominent flat nasal bridge, Upturned nose, Short nose, Small mouth, Narrow palate	ASD, Mildly dysplastic pulmonary valve	Delayed eruption of secondary dentition, Hypodontia	Mesaxial poly syndactyly 4th digit, 5/6 Syndactyly R hand, Partial 2-3 syndactyly of right toes.			
2018	Ragge *et al.*	11	c.4850T>G p.(Leu1617*) *de novo*	F	Microphthalmia, Bilateral cataracts, Nystagmus	Cleft palate, Upslanting palpebral fissures, Slit-like nostrils, Simple ears	ASD, Patent ductus arteriosus	Delayed loss of primary dentition, Fused teeth	Hypermobility of elbows		Not affected	
2018	Ragge *et al.*	13	c.4402C>T p.(Gln1468*) *de novo*	F	Bilateral microphthalmia, Cataracts, Nystagmus			Late eruption of primary dentition			Not affected	
2018	Ragge *et al.*	15	c.3116_3117dup p.(Asp1040Lysfs*16)	F	Bilateral cataracts, Glaucoma	Cleft palate, Macrocephaly, Bilateral ptosis, Hypoplastic alae nasi, Broad nasal tip, Mild alveolar cleft	Unspecified cardiac defect		Hypermobility of hips, Knees and ankles, Long great toes, Wide sandal gap		Not affected	
2018	Ragge *et al.*	16	arr[hg19] Xp11.4(39910845_39922793)x1 *de novo*	F	Bilateral Microphthalmia, Bilateral congenital cataract, Iris rubeosis, Flat anterior chamber	Cleft palate, Square-shaped face, Upslanting palpebral fissures, Large nasal tip with septate nasal cartilage, Simple ears	ASD, VSD		Camptodactyly of 2-4 toes, Syndactyly of 2-3 toes, Long, Large halluces	Asymmetrical pontocerebellar hypoplasia, Cerebral atrophy, Enlargement of the ventricles without obstruction		Hearing loss, Hypotonia
2018	Ragge *et al.*	14 (mother)	c.4601_4602insCT p.(His1535Cysfs*34)	F	Bilateral cataracts			Radiculomegaly, Thin enamel				
2018	Ragge *et al.*	14 (proband)	c.4601_4602insCT p.(His1535Cysfs*34) maternal	F	Microphthalmia, Bilateral congenital cataracts		ASD, VSD	Late eruption of primary dentition, oligodontia			Not affected	Thyroglossal cyst

2018	Ragge *et al.*	7 (mother)	c.867G>A p.(Trp289*) maternal	F	Congenital cataract			Frequent dental issues					8 miscarriages
2018	Ragge *et al.*	7 (proband)	c.867G>A p.(Trp289*) maternal	F	Bilateral Microphthalmia, Bilateral Cataracts, Glaucoma	Broad nose	ASD	Delayed loss of primary dentition with radiculomegaly	Long slender fingers and toes				
2018	Ragge *et al.*	7 (sister)	c.867G>A p.(Trp289*) maternal	F	Congenital cataract								
2018	Ragge *et al.*	8 (mother)	c.2947_2948insTGCATACT p.Glu983Val*41 mosaic	F	Microphthalmia, Congenital cataract	Haemangiomas on forehead and neck		Absent upper lateral incisors					
2018	Ragge *et al.*	8 (proband)	c.2947_2948insTGCATACT p.Glu983Val*41 maternal	F	Microphthalmia, Congenital cataract			Missing teeth	2-3 toe syndactyly				Lipomatous lesion in thyroid lobe
hemizygous (male) cases													
2004	Ng *et al.*	MAA2/1	c.254C>T p.(Pro85Leu)	M	Bilateral micropthalmia	Microcephaly	Not affected	Not affected	Not affected	Microcephaly, Hypoplastic corpus callosum, Cingulate gyrus			
2009	Hilton *et al.*	Lenz I	c.254C>T p.(Pro85Leu)	M	Microphthalmia	Narrow forehead, Simple ears	ASD	Not affected	Multiple partial Finger syndactyly, Fifth finger clinodactyly, Radioulnar synostosis		Mental retardation	Hypospadias	
2013	Suzumori *et al.*	1 (male infant)	c.254C>T p.(Pro85Leu) maternal	M	Anophthalmia		Cardiac defects resulting in death at 6m						
2013	Suzumori *et al.*	1 (foetus)	c.254C>T p.(Pro85Leu) maternal	M	Bilateral anophthalmia								
2015	Zhu *et al.*	1	c.1619G>A p.(Arg540Gln) *de novo*	M	Glaucoma		VSD, dextrocardia, Anomalous origin of left pulmonary artery from ascending aorta, Absent pulmonary valve			Cerebral white matter hypoplasia			
2018	Ragge *et al.*	2	c.254C>T p.(Pro85Leu) maternal	M	Bilateral severe microphthalmia	Midface hypoplasia, Downslanting palpebral fissures, Long face, Thick eyebrows, Broad nasal root and tip, Long philtrium, Large low set rotated ears	Triple heart sounds	Recurrent dental infections requiring extraction	Severe scoliosis, Long slender fingers, Fifth finger clinodactyly, Broad halluces		No speech at 9 years, Autistic spectrum disorder	Cryptorchidism, Vesico-ureteric reflux, Primary enuresis	
2018	Ragge *et al.*	9	c.254C>T p.(Pro85Leu) maternal	M	Bilateral anophthalmia, Small palpebral apertures	Large ears withsquared off earlobes			Long fingers and toes		Not affected	Bilateral renal dysplasia with associated bilateral vesicoureteric reflux, Urethral dysplasia	

2018	Ragge *et al.*	12	NM_001123385.1: c.4741+1G>A maternal	M	Megalophthalmos, Posterior embryotoxon, Nystagmus, High myopia	Full cheeks, Mild ptosis, exophthalmos, Uplifted earlobes, Glabellar naevus flammeus, Long philtrum and full nasal tip	VSD, ASD, Persistent ductus arteriosus, Persistent left vena cava, Non-compaction of left ventricle		Long thumbs, Left talipes, Short metacarpals, Brachymesophal angy of 5th fingers	Seizure disorder	Cognitive and motor milestones severely delayed	Bilateral cryptorchidism, Vesico-ureteric reflux	
2018	Ragge *et al.*	4 (proband)	c.4807A>C p.(Ser1603Arg) maternal	M	Bilateral posterior embryotoxon	Large earlobes, Left temporal haemangioma	ASD		Long fingers with 4-5 finger camptodactyly, Short and deep-set toe nails		Developmental delay		
2018	Ragge *et al.*	5 (brother case 4)	c.4807A>C p.(Ser1603Arg) maternal	M	Bilateral posterior embryotoxon	Posterior cleft palate, Asymmetrical dysplastic ears	ASD		Camptodactyly of all fingers, Fetal toe pads	Posterior arachnoid cyst	Severe developmental delay		Axial hypotonia with hypertonic limbs

heterozygous cases (female, OFCD)	**no of families for which information was available**	number of cases or families	%	comment
total number of cases		85		
total number of families		58		
type of mutation				
frameshift		28 out of 58	48	
nonsense		19 out of 58	33	
splice site		4 out of 58	7	
partial gene deletion		5 out of 58	9	
whole gene deletion		2 out of 58	3	
inheritance				
familial		15/58	26	
sporadic		43/58	74	
sporadic cases with parental BCOR analysis		15/43	35	
de novo inheritance in sporadic cases		15/15	100	
cases with BCOR variants				
anomalies in all 4 OFCD categories		35	41	
anomalies in 3 OFCD categories		30	35	
anomalies in 2 OFCD categories		14	16	
anomales in 1 OFCD categories		5	6	
no OFCD anomalies		1	1	mosaic
ocular anomalies	*83*			
eye anomalies		82	96	
no eye anomalies		1	1	mosaic
information not available		2	2	
microphthalmia		56		
congenital cataract		82		
craniofacial anomalies	*69*			
craniofacial anomalies		63	74	
no craniofacial anomalies		6	7	1 mosaic
information not available		16	19	
Cleft palate		20		
Other palatal anomalies		9		
Nasal anomalies		57		
Ear anomalies		11		
cardiac anomalies	*61*			
cardiac anomalies		51	60	
No cardiac anomalies		10	12	2 mosaic
information not available		24	28	
ASD		38		
VSD		15		
Patent ductus arteriosus		9		
dental anomalies	*72*			
dental anomalies		68	80	
no dental anomalies		4	5	1 mosaic
information not available		13	15	
radiculomegaly		39		
missing teeth / oligodontia		27		
fused incisors		4		
delayed eruption of primary and/or secondary dentition		55		
skeletal anomalies	*67*			
skeletal anomalies		65	76	
no skeletal anomalies		2	2	1 mosaic
information not available		18	21	
digit anomalies		55		
syndactyly		36		
camptodactyly		34		
radioulnar synostosis		9		
scoliosis/lordosis		7		
joint hypermobility		3		
other anomalies				
hearing loss		8		
brain malformation		4		
developmental delay		9		

Supplementary Table 3: Summary of X-linked BCOR male cases

hemizygous cases (male)	**no of families for which information was available**	number of cases or families	%
total number of cases		10	
total number of families		8	
type of mutation			
missense		7	
splice site		1	
inheritance			
maternal		5	63
de novo		1	13
not known		2	25
ocular anomalies	10		
number of cases with ocular anomalies		10	100
anophthalmia		3	
microphthalmia		3	
posterior embryotoxon		3	
glaucoma		1	
craniofacial anomalies	7		
number of cases with craniofacial anomalies		7	70
information not available		3	30
ear malformation		6	
cardiac anomalies	9		
number of cases with cardiac anomalies		8	80
number of cases with no cardiac anomalies		1	10
information not available		1	10
ASD		4	
VSD		2	
persistent ductus arteriosus		2	
skeletal anomalies	7		
number of cases with skeletal anomalies		6	60
number of cases with no skeletal anomalies		1	10
information not available		3	30
digit anomalies		6	
radioulnar synostosis		1	
scoliosis		1	
development	6		
number of cases with developmental delay		5	50
number of cases with no developmental delay		1	10
information not available		4	40
genitourinary anomalies	4		
number of cases with genitourinary anomalies		4	40
number of cases with no genitourinary anomalies		1	10
information not available		5	50