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## **Expanding the Phenotype of the X-linked *BCOR* Microphthalmia syndromes**

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### 3 Abstract

4 Two distinct syndromes arise from pathogenic variants in the X-linked gene  
5 *BCOR* (BCL-6 corepressor): OculoFacioCardioDental (OFCD) syndrome, which  
6 affects females, and a severe microphthalmia ('Lenz'-type) syndrome affecting  
7 males. OFCD is an X-linked dominant syndrome caused by a variety of *BCOR* null  
8 mutations. As it manifests only in females, it is presumed to be lethal in males.  
9 The severe male X-linked recessive microphthalmia syndrome ('Lenz') usually  
10 includes developmental delay in addition to the eye findings and is caused by  
11 hypomorphic *BCOR* variants, mainly by a specific missense variant c.254C>T,  
12 p.(Pro85Leu). Here we detail 16 new cases (11 females with 4 additional,  
13 genetically confirmed, affected female relatives; 5 male cases each with  
14 unaffected carrier mothers). We describe new variants and broaden the  
15 phenotypic description for OFCD to include neuropathy, muscle hypotonia,  
16 pituitary underdevelopment, brain atrophy, lipoma and the first description of  
17 childhood lymphoma in an OFCD case. Our male X-linked recessive cases show  
18 significant new phenotypes: developmental delay (without eye anomalies) in 2  
19 affected half-brothers with a novel *BCOR* variant, and one male with high myopia,  
20 megalophthalmos, posterior embryotoxon, developmental delay, and heart and  
21 bony anomalies with a previously undescribed *BCOR* splice-site variant. Our  
22 female OFCD cases and their affected female relatives showed variable features,  
23 but consistently had early onset cataracts. We show that a mosaic carrier  
24 mother manifested early cataract and dental anomalies. All female carriers of  
25 the male X-linked recessive cases for whom genetic confirmation was available  
26 showed skewed X-inactivation and were unaffected. In view of the extended  
27 phenotype, we suggest a new term of X-linked *BCOR*-related syndrome.  
28

29 Introduction

30 Oculofaciocardiodental (OFCD) and severe X-linked microphthalmia syndromes  
31 are related conditions caused by allelic pathogenic alterations in *BCOR* (BCL-6  
32 corepressor). OFCD is an X-linked dominant condition, affecting females  
33 (presumed male lethal), with examples of mother-to-daughter transmission.  
34 Skewed X-inactivation (90-100%) has been demonstrated in informative cases  
35 (Ng, Thakker et al. 2004). It is characterised by the pathognomonic association of  
36 congenital or early onset cataract with dental anomalies (including  
37 radiculomegaly, delayed primary/secondary dentition, hypodontia, fusion of  
38 teeth), with a variety of other features. These other features are principally  
39 ocular (microphthalmia, cataract, glaucoma, retinal detachment), cardiac (septal  
40 defects), skeletal (hammer toes or camptodactyly, 2-3 toe syndactyly, broad  
41 halluces, radioulnar synostosis, scoliosis), and facial anomalies (cleft palate,  
42 septate nasal cartilage, long narrow face, arched eyebrows). Less frequently they  
43 include mild developmental delay (11%), posterior fossa anomalies (in a fetal  
44 loss), hearing impairment (9%) and defects of laterality (situs inversus, asplenia)  
45 in a single case (Ng, Thakker et al. 2004, Horn, Chyrek et al. 2005, Oberoi, Winder  
46 et al. 2005, Hilton, Johnston et al. 2009, Davoody, Chen et al. 2012, Lozic,  
47 Ljubkovic et al. 2012, Kantaputra 2014, Surapornsawasd, Ogawa et al. 2015, Ma,  
48 Grigg et al. 2016). In typical OFCD cases, *BCOR* is affected by a variety of null  
49 variants: nonsense, splicing, frameshift, deletions of part or all of the coding  
50 sequence, predicted to lead to nonsense mediated decay. Asymptomatic mosaic  
51 female carriers have been described: Hilton and colleagues refer to the  
52 asymptomatic mother of case XVII; mosaicism was estimated by a reduction of  
53 the Sanger sequencing peak to 75% as opposed to 50% for her fully manifesting  
54 daughter (Hilton, Johnston et al. 2009). Furthermore, individuals with *BCOR*  
55 pathogenic variants with mainly ocular features are also reported (Ng, Thakker  
56 et al. 2004; Hilton, Johnston et al. 2009; Ma, Grigg et al. 2016).

57

58 *BCOR* pathogenic variants have also been identified in affected males with X-  
59 linked recessive severe ('Lenz') microphthalmia. In 2004, the missense variant  
60 c.254C>T, p.(Pro85Leu)\_was identified in an affected male, and segregated with  
61 disease phenotype (Ng, Thakker et al. 2004) and since then further cases

62 described (Hilton, Johnston et al. 2009, Suzumori, Kaname et al. 2013).  
63 Recently, a *de novo* novel *BCOR* missense variant (c.1619G>A; pArg540Gln) was  
64 identified in a boy with congenital glaucoma, complex cardiac anomalies,  
65 dextrocardia and cerebral white matter hypoplasia, following sequencing  
66 analysis of *PITX2*, *FOXC1* and *BCOR* (Zhu, Dai et al. 2015). Although the causative  
67 nature of this missense variant could not be established with certainty,  
68 supporting evidence from *in silico* analysis and absence of variant from control  
69 cohorts was highly suggestive.

70

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

84

85 Here, using whole exome and targeted gene sequencing, we identified 16 further  
86 index cases (15 families) with pathogenic variants in *BCOR*. The female cases  
87 comprised of eleven females with OFCD, and additionally 3 affected mothers and  
88 1 affected sister manifesting variable phenotypes. The five male index cases  
89 comprised of two unrelated cases with the recurrent c.254C>T (p.Pro85Leu)  
90 variant and manifesting a severe microphthalmia syndrome, two half-brothers  
91 with a previously undescribed c.4807A>C (p.Ser1603Arg) variant with  
92 developmental delay and posterior embryotoxon, and one boy with high myopia,  
93 posterior embryotoxon, severe developmental delay, wrist and finger anomalies  
94 with a previously undescribed splice site variant c.4741+1G>A (p.[?]). We

95 review the literature and show that male cases have demonstrably high  
96 prevalence of cardiac, skeletal, craniofacial, and genitourinary anomalies in  
97 addition to their well described severe eye anomalies and developmental delay.  
98 We also show a surprising proportion of female OFCD cases with skeletal  
99 anomalies, hearing loss and developmental delay, and one with childhood  
100 lymphoma.

101

## 102 Materials and Methods

### 103 Patient cohort

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

119

### 120 Methods

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

122 WES was undertaken in 24 previously undiagnosed UK/French eye anomaly  
123 patients (12 males and 12 females). Case 4 had exome sequencing because of the  
124 association of developmental delay, dysmorphic features and posterior  
125 embryotoxon. Exome capture was performed using the Nimblegen V3  
126 Enrichment kit following the manufacturer's protocol. The captured libraries  
127 were sequenced with an Illumina HiSeq2000 with 100-bp paired-end reads. We



128 used PolyPhen-2, SIFT and Mutation Taster software tools to predict the  
129 functional effects of variants (Adzhubei, Schmidt, et al, 2010; Ng, Hennekoff et al,  
130 2003; Schwarz, Cooper, et al, 2014). This strategy allowed the identification of  
131 *BCOR* variants in cases 1, 5 and 9. Case 12 had similar WES, but not captured and  
132 instead using an Illumina HiSeq2500 and 125-bp paired end sequencing. For  
133 cases 10 and 14, identified via the DDD study, trio-based exome sequencing was  
134 performed on the affected individual and their parents, as previously described  
135 (Wright, Fitzgerald et al. 2015). Case 13 had targeted clinical exome sequencing.  
136 Libraries were prepared using TruSightOne (Illumina) following the  
137 manufacturer's protocol. The captured libraries were sequenced with an  
138 Illumina NextSeq500 with 150-bp paired-end reads.

139

140 Targeted resequencing of 187 genes (case 2)

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

152

153 Sanger sequencing

154 All pathogenic *BCOR* variants retained after filtering from the whole exome or  
155 targeted resequencing data were confirmed by Sanger sequencing. Parental  
156 studies were performed to determine whether these variants were inherited or  
157 appeared *de novo*. Direct *BCOR* (NM\_001123385.1, 1755 aa) sequencing was  
158 performed in the other female cases (3, 6, 7, 8, 11, 13, 14, 15) and one male case  
159 (2) because of suggestive features and to confirm WES findings.

160 Case 16 had a copy number variant detected by array Comparative Genomic

161 Hybridisation (CGH) (Agilent 60k ISCA) and confirmed by qPCR.

162

163 Non-random X-inactivation analysis

164 This was performed using a fluorescent PCR assay encompassing the X  
165 chromosome androgen receptor CAG repeat polymorphism. The methylation  
166 sensitive restriction enzyme, HpaI was used for prior digestion of genomic DNA.

167 X-inactivation classification ratios: Complete skewing=100:1; Highly

168 skewed=90:10-99:1; Moderate skewing=80:20-89:11; Random X-

169 inactivation=50:50-79:21 (Amos-Landgraf, Cottle et al, 2006).

170

171 Assessment of Mosaicism

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

176

177 Literature review

178 Published cases with pathogenic *BCOR* variants were identified through previous  
179 literature reviews and Pubmed searches. Variants were annotated using a  
180 common reference sequence, NM\_001123385.1, and all variants were checked  
181 using mutalyzer ([www.mutalyzer.nl](http://www.mutalyzer.nl))(Wildeman, van Ophuizen et al. 2008).

182

183 Case Descriptions (Table 1)

184 Case 1

185 Case 1 is a 13-year-old Caucasian girl with right microphthalmia with dense  
186 cataract and left microphthalmia with secondary aphakia, secondary glaucoma  
187 and a left visual acuity of 20/300. She was born at full term following ultrasound  
188 scans during pregnancy that detected choroid plexus cysts. Early cranial  
189 Magnetic Resonance Imaging (MRI) revealed a corpus callosal lipoma. She had  
190 early onset cataracts and left cataract surgery at 6 weeks of age. Her  
191 development was slightly delayed: she smiled at 3-4 months, sat at 10 months  
192 and walked at 23 months of age. Her speech was normal. She had recurrent  
193 urinary tract infections (normal renal ultrasound), and growth hormone

194 deficiency diagnosed at 3 years of age and treated with growth hormone. She  
195 had late eruption of her first teeth and delayed loss of first teeth at 9 years of age.  
196 She had unusual positioning of her adult teeth, which were small, with a second  
197 row of teeth.

198 At 11 years of age her growth had reached: height 2<sup>nd</sup> centile, weight <0.4<sup>th</sup>  
199 centile and head circumference 50<sup>th</sup> centile. She had long slender fingers and  
200 hyperextensible joints. Her feet showed an increased sandal gap and she had  
201 right second toe clinodactyly (Figure 1a-e). She had reduced bladder control and  
202 decreased reflexes. WES revealed a *de novo* heterozygous variant in *BCOR*  
203 c.2428C>T p.(Arg810\*). This variant has been previously described as causing  
204 OFCD with a strikingly similar phenotype in a paper by Hilton and colleagues  
205 (case X) (Hilton, Johnston et al. 2009) (see Supplementary Table 1).

206

#### 207 Case 2

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

217

218 At 9 years-of-age, he had no speech and difficulty swallowing, tolerating only  
219 liquid food. He suffered from primary enuresis and had undergone surgical  
220 correction for severe scoliosis. He suffered from recurrent dental infections  
221 requiring dental extraction. His height was 1.25 m (9<sup>th</sup> centile), weight 20.5 kg  
222 (0.4-2<sup>nd</sup> centile) and head circumference 53 cm (25<sup>th</sup> centile). He had bilateral  
223 severe microphthalmia with no light perception, short (10 mm) downslanting  
224 palpebral fissures and secondary midface hypoplasia. He had a long face with  
225 abundant hair, tall forehead, thick eyebrows, a broad nasal root and tip, a long  
226 philtrum, thin upper lip and thick lower lip. He had large low set posteriorly

227 rotated ears with prominent antihelices. He had a thin body habitus with a  
228 barrel-shaped chest, long slender fingers with fifth finger clinodactyly, and broad  
229 halluces. He showed hypotonia with reduced muscle mass and marked  
230 ligamentous laxity. His cranial MRI was normal.

231

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

237

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

244

### 245 Case 3

246 This 3-year-old Caucasian girl was born with bilateral microphthalmia and  
247 cataract (Figure 1j) having had bilateral congenital cataract detected at 22 weeks  
248 of pregnancy. She also had an atrial septal defect (ASD) that was managed  
249 conservatively. The cataracts were removed without intraocular lens  
250 implantation at 2 months of age, with a subsequent right vitrectomy for capsular  
251 opacity at 2 years of age. However, she developed a T-cell lymphoma (stage III  
252 on St Jude's classification) at the age of 12 months and was treated with  
253 chemotherapy, achieving remission after 2 years of treatment. She had late  
254 eruption of her first teeth and abnormal crown volume on the upper maxillary  
255 canines and central incisors on the palatal side, without any misalignment of the  
256 teeth. All primary and permanent teeth were present on the head Computerised  
257 Tomography (CT) scan. At the age of 3 years her microphthalmic eyes measured  
258 right eye (RE) corneal diameter of 9.5 mm, axial length of 17.59 mm and left eye

259 (LE) corneal diameter of 8.5 mm, axial length of 16.06 mm, with an increase of  
260 corneal thickness RE 635  $\mu\text{m}$  and LE 680  $\mu\text{m}$ . At 4 years, following patching, she  
261 achieved visual acuities of RE 0.7 logMar and LE 0.2 logMar.

262

263 She had normal growth and no developmental delay. She had long slender  
264 fingers and hands, downslanting, dysplastic ears and a high arched narrow  
265 palate. Targeted analysis of *BCOR* revealed the *de novo* variant  
266 c.1209\_1210delCC; p.(Gln404Alafs\*35), predicted as pathogenic.

267

268 Case 4

269 Case 4 is an 18-month-old Caucasian boy, only child of unrelated healthy parents.  
270 He has 3 half-brothers on his mother's side, including case 5 (Figure 2A). He was  
271 born at 38 weeks' gestation with a birth weight 2.875 kg (25<sup>th</sup> centile), length  
272 50.7 cm (80<sup>th</sup> centile) and head circumference 33.5cm (28<sup>th</sup> centile). He had a  
273 large ASD. Ophthalmological examination showed bilateral posterior  
274 embryotoxon. He had distinctive features, including large earlobes, long fingers  
275 with 4<sup>th</sup> and 5<sup>th</sup> camptodactyly, and short and deep-set toenails and a left  
276 temporal haemangioma. His growth was normal, however, he had some  
277 developmental delay: he sat at 12 months, at 18 months of age he could not stand  
278 unsupported; he could say one word. While his array CGH was normal, WES  
279 revealed the variant c.4807A>C; p.(Ser1603Arg) in *BCOR*, inherited from his  
280 asymptomatic mother. This variant involves a highly conserved amino acid, is  
281 absent from the general population (gnomAD database) (Lek, Karczewski, et al,  
282 2016) and is predicted to be deleterious by *in silico* software Polyphen-2, SIFT  
283 and Mutation Taster.

284

285 Case 5

286 Case 5 is a 5-year-old Caucasian boy, half-brother of case 4. He was born at full  
287 term with asymmetrical intrauterine growth retardation. His birth weight was  
288 2.860 kg (5<sup>th</sup> centile), length 50 cm (37<sup>th</sup> centile) and OFC 33.5 cm (12<sup>th</sup> centile).  
289 He had initial feeding difficulties and presented with posterior cleft palate, major  
290 axial hypotonia with highly hypertonic limbs, and a large ASD. Ophthalmological  
291 examination at birth showed bilateral posterior embryotoxon. He also had

292 asymmetrical dysplastic ears, camptodactyly of all fingers, fetal toe pads, and  
293 multiple capillary malformations. He had severe developmental delay; he spoke  
294 fewer than 10 words at 5 years and walked at 4 years and 10 months. He had  
295 severe feeding difficulties causing initial growth retardation, but at age 4½ years  
296 his weight was 17.5 kg (0 SD), height 100.5 cm (-1 SD) and OFC 48.5 cm (-2.5  
297 SD). His brain MRI showed a posterior arachnoid cyst. Sanger sequencing  
298 revealed the same variant c.4807A>C; p.(Ser1603Arg) in *BCOR* as his brother  
299 (case 4). This variant was absent in the two healthy brothers of cases 4 and 5.

300

#### 301 Case 6

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

311 She had normal growth and development. She had distinctive facial features with  
312 a short bulbous nose, microtia and prognathism. She also showed 5<sup>th</sup> finger  
313 clinodactyly and left 2-3 toe partial syndactyly.

314 Targeted *BCOR* analysis initiated by the geneticist at age 13 y 9 months revealed  
315 the *de novo* variant c.4598\_4616dup; p.(Glu1539Aspfs\*7), predicted as  
316 pathogenic.

317

#### 318 Case 7

319 Case 7 is a 15-year-old Caucasian girl, the second of three girls, born at full term  
320 with bilateral microphthalmia and cataract (Figure 2B). She had bilateral  
321 cataract surgery in the first months of life, but subsequently developed chronic  
322 bilateral glaucoma with acute episodes, requiring surgery. Her visual acuity is  
323 reduced to RE: light perception and LE: count fingers at 1 m wearing aphakia-  
324 correcting glasses. She also had an ASD, corrected by cardiac surgery at the age

325 of 4 years. She had delayed loss of her primary teeth, with radiculomegaly,  
326 causing a misalignment of the teeth. All the primary teeth had to be removed in  
327 order to enable permanent teeth to erupt. She had normal growth and  
328 development. She exhibited distinctive facial features including broad nose, and  
329 long, slender fingers and toes (Figure 1p-r).

330 Her mother had surgery in infancy for bilateral congenital cataract, had frequent  
331 dental issues and suffered 8 miscarriages. Her maternal grandmother had at  
332 least one miscarriage and bilateral early onset cataract. Her younger sister also  
333 had surgery for bilateral congenital cataract and also had dental anomalies.

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

338

#### 339 Case 8

340 This 6½-year-old girl was born at full term. At one month of age, after initial  
341 feeding difficulties, she was diagnosed with bilateral congenital cataract and mild  
342 microphthalmia. She had two large haemangiomas (one on the forehead, one in  
343 the neck), a lipomatous lesion in the thyroid lobe diagnosed clinically and on  
344 ultrasound and a thyroglossal cyst (Figure 1s-w). At age 6 ½ years she had  
345 normal growth and development. She had agenesis of both superior lateral  
346 incisors and cutaneous syndactyly of second and third toes. Subsequent follow-  
347 up revealed left ventricular noncompaction, without rhythm disturbance and  
348 with good ventricular function, and a small persistent ductus arteriosus. Sanger  
349 sequencing of *BCOR* revealed a frameshift variant c.2947\_2948insTGCATACT;  
350 p.(Glu983Valfs\*41). The same variant was identified in her mother, who had  
351 bilateral congenital cataract, microphthalmia and agenesis of the two lateral  
352 incisors with large spacing of the two upper median incisors, but in a mosaic  
353 state (about 20% of mutated p.(Glu983Valfs\*) alleles in blood).

354

#### 355 Case 9

356 This 27-year-old male was born at 38 weeks following a normal pregnancy  
357 during which an ultrasound scan at 18/40 demonstrated urinary reflux and one

358 kidney larger than the other. At birth he was diagnosed with bilateral  
359 anophthalmia, small palpebral apertures, hypotonia, moderate degree of chronic  
360 renal failure secondary to bilateral renal dysplasia with associated bilateral  
361 vesicoureteric reflux (corrected age 2 years) and urethral hypoplasia. He had  
362 normal growth and developmental milestones, and excellent musical and verbal  
363 skills. His mother had a history of neurofibromatosis type 1 and multiple  
364 strawberry nevi, but was otherwise healthy. His MRI scan was reported as  
365 normal. At age 27 years, he had normal growth parameters, with long fingers  
366 and toes, and large ears with squared off earlobes (Figure 1x-ac). WES revealed a  
367 maternally inherited *BCOR* c.254C>T; p.(Pro85Leu) variant.

368

#### 369 Case 10

370 Case 10 is a 9 year-old-girl born at 38 weeks' gestation by Caesarian section due  
371 to delayed rupture of membranes. She had bilateral congenital cataract and  
372 microphthalmia with corneal diameters of 9 mm, persistent fetal vasculature and  
373 small optic nerves. She was noted to have a prominent forehead, flat nasal  
374 bridge, upturned nose, mesaxial polysyndactyly (of 4<sup>th</sup> digit) with 5/6 syndactyly  
375 of the right hand and partial 2/3 syndactyly of the right toes (Figure 1ad-ai). She  
376 also had a moderate secundum ASD with a mildly dysplastic pulmonary valve on  
377 echocardiography. She had slight widening of her cerebral falx on cranial  
378 ultrasound. Her maternal grandmother had postaxial polydactyly on one hand  
379 and a maternal first cousin once removed had bilateral postaxial hand  
380 polydactyly. At 10 months of age, she had delayed motor milestones and was not  
381 yet sitting unsupported. She did not have any teeth yet and her anterior  
382 fontanelle was still open. She had fine hair, a short nose with slightly broad nasal  
383 tip, small mouth and narrow palate. She had surgery for her ASD at the age of 3  
384 years. Interestingly, her growth parameters progressed from length 0.4<sup>th</sup> centile,  
385 weight 25<sup>th</sup> centile and head circumference 75<sup>th</sup> centile at 1 month, to height and  
386 weight 9<sup>th</sup> centile, and head circumference 75<sup>th</sup>-91<sup>st</sup> centile at 10 months, and by  
387 8 years-of-age she reached a height on the 91<sup>st</sup> centile, weight 98-99.6<sup>th</sup> centile  
388 and a head circumference of 58.9 cm (>99<sup>th</sup> centile). She had had delayed  
389 eruption of her secondary dentition. She received 1:1 help for her visual  
390 impairment (with visual acuity RE 0.70 LE 0.45 corrected with +20DS both eyes)



391 and her intellectual achievement was equivalent to her sighted peers. In addition  
392 to her right 2-3 toe syndactyly, she demonstrated left 2<sup>nd</sup> toe clinodactyly and 4<sup>th</sup>  
393 toe camptodactyly. She had hypodontia, a broad bifid nasal tip, mild  
394 heterochromia of the left iris, with bialteral aphakia and normal fundal  
395 appearances.

396 She had normal array CGH and was diagnosed with a *de novo* *BCOR* variant  
397 c.3153G>A; p.(Trp1051\*) by the Deciphering Developmental Disorders (DDD)  
398 study (DECIPHER ID: 262217), confirmed with Sanger sequencing (Wright,  
399 Fitzgerald et al. 2015).

400

#### 401 Case 11

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

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

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

423

424 Case 12

425 This 3-year-old boy is the second child of non-consanguineous parents born at  
426 40 weeks' gestation with a birth weight of 4.040 kg (60<sup>th</sup> centile), length 56 cm  
427 (+1.5 SD), and head circumference 37 cm (+1 SD) (Figure 2C). The pregnancy  
428 was uneventful, apart from unilateral talipes detected on scan. Echocardiography  
429 shortly after birth revealed a ventricular septal defect (VSD), ASD, persistent  
430 ductus arteriosus, persistent left vena cava, and non-compaction of the left  
431 ventricle. Furthermore, bilateral cryptorchidism was observed. At the age of one  
432 month he was admitted because of respiratory insufficiency. He also had  
433 bilateral grade 4-5 vesicoureteral reflux and a single kidney stone was observed.  
434 On ophthalmic assessment he had nystagmus, high myopia (-17.00 D) with  
435 megalophthalmos, and posterior embryotoxon. He was noted to have full cheeks,  
436 mild ptosis, exophthalmos, uplifted earlobes, a glabellar naevus flammeus, a long  
437 philtrum and full nasal tip, long thumbs and left talipes (Figure 1an-ao). Brain  
438 MRI showed no abnormalities. X-rays of the hand showed short metacarpals and  
439 bilateral brachymesophalangy of the 5<sup>th</sup> fingers. He developed a seizure disorder  
440 from 1 year of age. His cognitive and motor milestones were severely delayed  
441 and at the age of 35 months he was nonverbal, could sit, but was unable to stand.  
442 His SNP array, array CGH, FISH-analysis for Pallister Killian syndrome and  
443 analysis of *CHD7*, *ASXL1* and *SETBP1* were normal. WES analysis revealed a  
444 hemizygous variant in *BCOR* (c.4741+1G>A; p.(?)). This variant is located within  
445 the donor splice site of intron 12, predicted to result in aberrant splicing Human  
446 Splicing Finder tool (<http://www.umd.be/HSF3/index.html>) (Desmet, Hamroun  
447 et al, 2009). His healthy mother is a carrier and showed 100% skewed X-  
448 inactivation. His healthy 4-year-old sister is also a carrier and also showed  
449 skewed X-inactivation (ratio 96:4). The variant was not present in both maternal  
450 grandparents and a healthy maternal uncle.

451

452 Case 13

453 Case 13 is a 2-year-old Caucasian girl, only child of unrelated and healthy  
454 parents. There is no familiar history of congenital or developmental anomalies.  
455 Pregnancy was complicated by intrauterine growth restriction in the third  
456 trimester. She was born by induced delivery at 37 weeks' gestation with birth

457 weight of 1.890 kg (<3<sup>rd</sup> centile). At birth she showed bilateral microphthalmia  
458 and cataracts, but no other anomalies. At 2 months of age cataract surgery was  
459 performed and at 3 months of age she showed low vision and nystagmus. She  
460 had normal psychomotor and cognitive development. She had late eruption of  
461 her first teeth at 14 months of age and primary dentition was complete except  
462 for the right lateral lower incisor. At 20 months of age she was referred for  
463 genetic testing and targeted sequencing revealed a heterozygous *de novo*  
464 nonsense variant in *BCOR* c.4402C>T; p.(Gln1468\*), predicted as pathogenic.

465

#### 466 Case 14

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

481

#### 482 Case 15

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

490 bilateral glaucoma. She also has hypermobility of hips, knees and ankles, but this  
491 is improving.

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

501

#### 502 Case 16

503 Case 16 is a 2-month-old Caucasian female born following a normal pregnancy at  
504 38 weeks' gestation with a birth weight of 3.245 kg (50<sup>th</sup> centile) with normal  
505 ultrasound scans. She presented with cleft palate and facial dysmorphism  
506 consisting of square-shaped face with asymmetric microphthalmia, upslanting  
507 palpebral fissures, large nasal tip with septate nasal cartilage and simple ears  
508 (Figure 1as-av). She also had camptodactyly of the second and fourth toes, mild  
509 cutaneous syndactyly of the second and third toes and long, large halluces and  
510 congenital heart anomalies, consisting of a large ASD and two VSDs. In addition  
511 to bilateral microphthalmia, her eye examination revealed bilateral congenital  
512 cataract, iris rubeosis and flat anterior chambers. She is being investigated for  
513 hearing loss, since the auditory evoked potentials were negative. As she also  
514 exhibited hypotonia and abnormal movements, brain MRI was performed and  
515 showed asymmetrical pontocerebellar hypoplasia, cerebral atrophy and  
516 enlargement of the ventricles without obstruction. Electroencephalogram was  
517 normal.

518

519 Molecular analysis of *BCOR* revealed a *de novo* deletion of the exons 7 to 15,  
520 confirmed by array CGH Xp11.4 (39910845\_39922793)x1 (Agilent 60k ISCA)  
521 and qPCR. In addition, there was a 162 kb deletion in 2p15 [arr[GRCh37]  
522 2p15[63190016\_63352116]x1) that includes *OTX1* and the 3' region of *WDPCP*.

523 This second CNV is of unknown significance, and could explain the neurologic  
524 phenotype since *OTX1* has a putative role in brain development.

525

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

528

529 Including the cases presented in this paper, a total of 95 cases from 66 families  
530 harbouring pathogenic *BCOR* variants have been described in the literature. We  
531 have summarized the findings of our cases in Table 1, and of all published cases  
532 including ours in supplementary Table 1. This includes 85 heterozygous (female)  
533 OFCD cases from 58 families (also detailed in Supplementary table 2) and 10  
534 hemizygous (male) cases from 8 families (also detailed in Supplementary Table  
535 3).

536

537 Discussion

538 Pathogenic variants in *BCOR* have been associated with two distinct phenotypes.  
539 The first is the OculoFacioCardioDental (OFCD) X-linked dominant syndrome,  
540 affecting exclusively females, presumed male lethal, and caused by a variety of  
541 null *BCOR* variants. The second is a severe X-linked recessive microphthalmia  
542 syndrome ('Lenz') affecting males only and caused in the majority of cases to  
543 date by a specific missense variant, c.254C>T, predicting a p.(Pro85Leu)  
544 substitution at the protein level. However, in this report we present additional  
545 male phenotypes associated with novel *BCOR* variants that include  
546 developmental delay in the absence of eye anomalies in 2 brothers, and one male  
547 with high myopia, megalophthalmos, posterior embryotoxon, severe  
548 developmental delay, and heart and bone anomalies. We also describe one male  
549 with severe ocular involvement, but without psychomotor delay, harbouring the  
550 previously described p.(Pro85Leu) variant.

551

552 We reviewed 85 OFCD cases from 58 families with pathogenic *BCOR* variants in  
553 the literature, including the new cases described here (Supplementary Table 1).  
554 Many have been recently summarized in the article by Feberwee and colleagues  
555 (Feberwee, Feenstra et al. 2014). Although the classic phenotypic characteristics

556 of OFCD (eye anomalies, craniofacial anomalies, cardiac anomalies and dental  
557 anomalies) occurred in a majority of the described cases, only 41% of cases had  
558 anomalies in all four categories. In addition to these classical characteristics,  
559 skeletal anomalies were frequently observed: 82% of cases had digit anomalies;  
560 13% had radioulnar synostosis and 10% had vertebral anomalies. Strikingly,  
561 hearing loss, which has not previously been highlighted as a feature of OFCD, was  
562 present in 9% of published cases. This cannot solely be attributed to secretory  
563 otitis media relating to cleft palate, as only two out of the nine cases with hearing  
564 loss had cleft palate. One of our cases (16) had presumed hearing loss as  
565 indicated by negative auditory evoked potentials, but this case also had other  
566 brain anomalies.

567

568 Apart from one mosaic case, all cases presented with features characteristic of  
569 OFCD, which suggests complete penetrance for the protein truncating *BCOR*  
570 variants underlying OFCD. All non-mosaic individuals, as well as three mosaic  
571 cases, manifested congenital or early onset cataract, with or without additional  
572 ocular features, such as microphthalmia, coloboma, lens dislocation, optic disc  
573 dysplasia, secondary glaucoma and retinal detachment (the latter two possible  
574 sequelae of early cataract surgery). The facial features include separated nasal  
575 cartilage, high nasal bridge, long narrow face, palate/uvula anomalies, and  
576 simple ears (Ng, Thakker et al. 2004, Hilton, Johnston et al. 2009, Davoody, Chen  
577 et al. 2012), with features not universally described in OFCD cases (see Figure 1).  
578 Cardiac anomalies, including septal defects, patent ductus arteriosus, double  
579 outlet right ventricle, Fallot's tetralogy, and dextrocardia were reported in 63%  
580 of individuals. The dental anomalies can affect primary and secondary dentition  
581 and can show a virtually pathognomonic radiculomegaly, or delayed, persistent  
582 or unerupted primary and/or secondary dentition, hypodontia, duplication or  
583 fusion of teeth (Kantaputra 2014) and are illustrated in Figure 1. Only four cases  
584 were reported to be without dental anomalies. The skeletal anomalies included  
585 2-3 toe syndactyly, broad halluces, hammer toes, camptodactyly, short fingers,  
586 radioulnar synostosis, scoliosis, and vertebral fusion (Figure 1).

587

588 We would like to highlight some additional features of OFCD. Mild  
589 developmental delay was present in around 10% of cases. Strikingly, hearing  
590 deficits, which are not usually described as part of the OFCD spectrum, occurred  
591 in 9% of cases, and should be considered as a new feature of this syndrome. Two  
592 individuals in our series had joint hypermobility, also described once before.  
593 Although this a relatively common finding in children in the general population,  
594 further studies would help to determine if it is a manifestation of OFCD. Other  
595 findings include: intrauterine growth retardation, poor feeding/reflux,  
596 vesicoureteral reflux and asplenia, growth hormone deficiency, delayed bladder  
597 control, decreased reflexes, thyroglossal cysts, lipoma in the thyroid lobe, lipoma  
598 of the corpus callosum and other brain anomalies. We suggest that neuropathy  
599 or muscle hypotonia, pituitary underdevelopment and lipoma may be additional  
600 features of the OFCD syndrome. This paper is the first to describe a childhood  
601 lymphoma in an OFCD case. This case highlights the importance of follow-up of  
602 OFCD cases, and indicates that further research is needed to investigate whether  
603 the occurrence of childhood or adult tumours is more common in OFCD cases  
604 compared to the general population, especially in view of the tumour suppressor  
605 role of BCOR described below. Interestingly haemangiomas seem to be a  
606 frequent feature, and were also seen in one of our carrier females, although are  
607 relatively common in the general population. Case 16 had a distinct neurological  
608 phenotype that included pontocerebellar hypoplasia, cerebral atrophy and  
609 enlargement of the ventricles. She had a deletion of exons 7-15 of *BCOR* and an  
610 additional 162 kb deletion in 2p15 that included *OTX1* and the 3' region of  
611 *WDPCP*. The *OTX1* deletion may be contributing to the neurological phenotype,  
612 since mice with deletions in *Otx1* have brain anomalies (Acampora, Mazan et al.  
613 1996).

614

615 The majority of heterozygous variants in OFCD cases were predicted to cause  
616 protein truncation, with 48% of them causing a frameshift, 33% nonsense, and  
617 7% affecting splicing. The remaining 12% of cases harboured a whole or partial  
618 gene deletion. In 26% of OFCD cases, the condition was familial and in 74% it  
619 was sporadic or unknown. For all apparently sporadic cases where parental  
620 samples were analysed (35%), the variant appeared *de novo*, suggesting that

621 protein-truncating variants, including nonsense and frameshift mutations, are  
622 fully penetrant. However, the possibility of gonosomal mosaicism could not be  
623 excluded.

624

625 Lenz first described his microphthalmia syndrome in 1955 in an X-linked  
626 pedigree manifesting male cases with severe microphthalmia syndrome with  
627 delayed development, palatal and dental anomalies, skeletal anomalies,  
628 congenital heart defects, unilateral renal aplasia and cryptorchidism (Lenz  
629 1955). Since this paper, it is clear that many descriptions have loosely referred to  
630 male patients with severe microphthalmia as having 'Lenz microphthalmia', both  
631 sporadic male cases and those with an X-linked pedigree. Although due credit  
632 should be attributed to Lenz for drawing attention to this severe microphthalmia  
633 affecting males, the generic use of the term 'Lenz' microphthalmia to describe  
634 affected males with severe syndromic microphthalmia is perhaps best avoided,  
635 since it is a genetically heterogeneous group (Traboulsi, Lenz et al. 1988, Hilton,  
636 Johnston et al. 2009). Hilton and colleagues analysed 21 male patients with  
637 presumed 'Lenz' microphthalmia and identified 1 with the typical c.254C>T;  
638 p.(Pro85Leu) missense variant in *BCOR*, demonstrating that *BCOR* is not the  
639 major cause of severe male microphthalmia, a finding supported by other groups  
640 (Ng et al. 2004)(Horn, Chyrek et al. 2005)(Hilton et al. 2009, Suzumori et al.  
641 2013).

642

643 The phenotypes of the hemizygous male cases with *BCOR* variants partially  
644 overlaps with the female cases, with eye, craniofacial, cardiac and skeletal  
645 anomalies present in the majority of male cases. Dental anomalies were not  
646 reported in this group, whereas half of these cases presented with  
647 developmental delay, and 40% with genitourinary anomalies. No protein  
648 truncating variants have been described in male cases, with missense variants in  
649 7 families and a splice site variant in another one.

650

651 Our case 2 with the typical c.254C>T; p.(Pro85Leu) shows an interesting  
652 phenotype, displaying additional features to previous descriptions. He shows a  
653 severe microphthalmia phenotype, with developmental delay associated with



654 autistic features, short stature, cardiac anomalies, broad halluces, long thin  
655 fingers, vesico-ureteric reflux, cryptorchidism, hypotonia, reduced muscle mass,  
656 scoliosis, and large low set ears in the absence of microcephaly. However, case 9,  
657 who displays high intelligence and no autistic features and also carrying  
658 c.254C>T; p.(Pro85Leu), clearly demonstrates that males with the typical *BCOR*  
659 variant do not universally display these features. The phenotype of severe eye  
660 anomalies plus cryptorchidism, hypotonia, and autistic features in the male  
661 *BCOR*-related syndrome shows some overlap with *SOX2* anophthalmia syndrome  
662 (Fantès, Ragge et al. 2003, Ragge, Lorenz et al. 2005, Bakrania, Robinson et al.  
663 2007), such that male cases with severe microphthalmia or anophthalmia,  
664 developmental delay, reduced growth and cryptorchidism, might benefit from  
665 panel testing that includes both *SOX2* and *BCOR*, Specific features, such as lack of  
666 developmental delay with presence of other extraocular features including long  
667 thin fingers or toes, large ears, cardiac anomalies, vesicoureteric reflux in  
668 association with severe bilateral eye anomalies might suggest *BCOR* is more  
669 likely to be the responsible gene.

670

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

683

684 Cases 4 and 5 are two half-brothers who have an interesting constellation of  
685 features that include early neonatal diabetes, hypotonia, ASD, bilateral posterior  
686 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

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

733

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

743

744 This paper has aimed to summarize the X-linked *BCOR* syndrome, and to extend  
745 the phenotypic spectrum associated with *BCOR* pathogenic variants. Females  
746 tend to have features of OFCD, but in addition can manifest further features,  
747 including neuropathy, muscle hypotonia, pituitary underdevelopment, lipoma  
748 and lymphoma. We have shown that males with the typical *BCOR* variant  
749 c.254C>T; p.(Pro85Leu), contrary to existing information, can have normal  
750 intellectual development. We have also demonstrated that new variants in *BCOR*  
751 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:

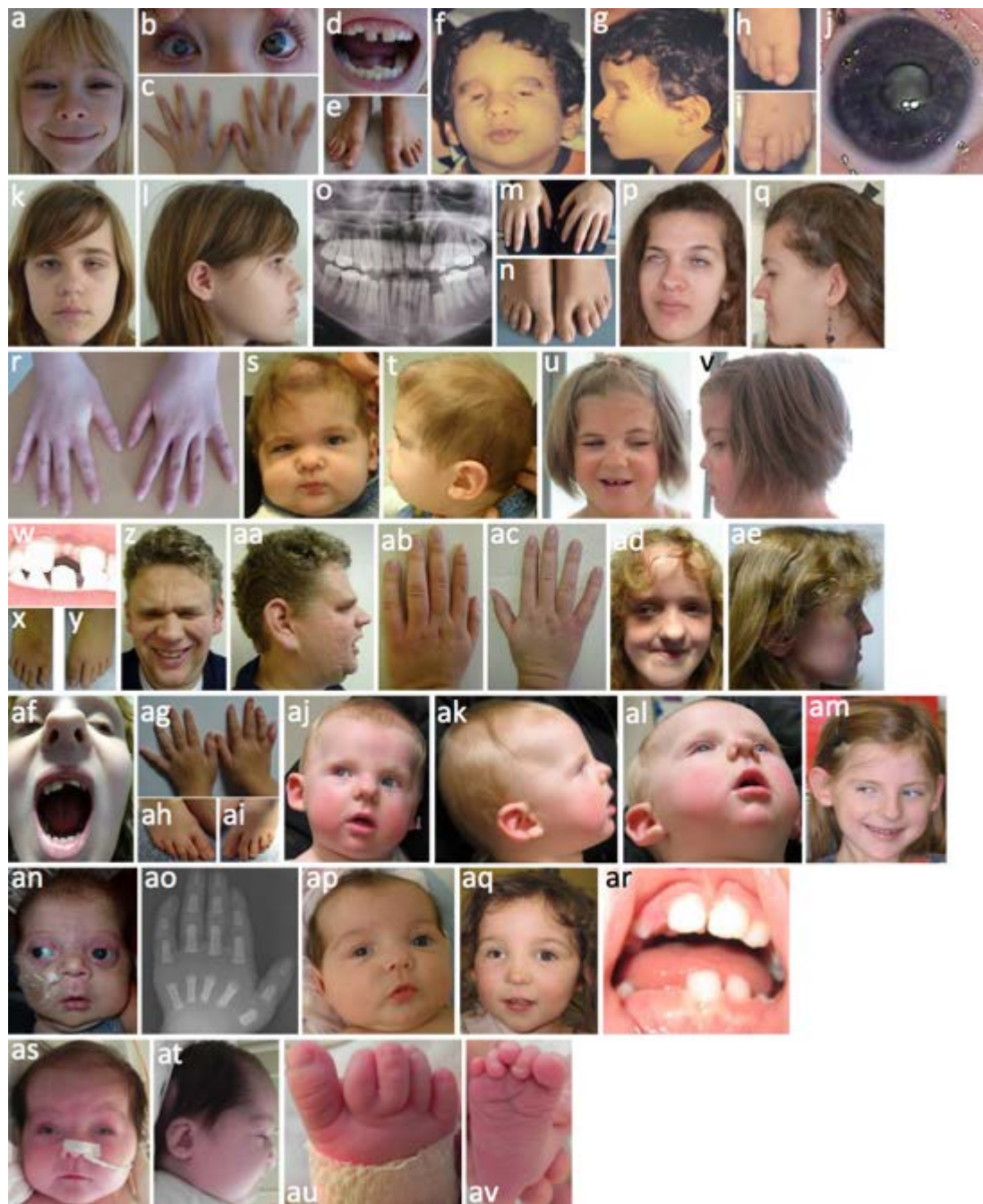


Figure 1 – Clinical Photographs

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, 5<sup>th</sup> 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 4<sup>th</sup> 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 5<sup>th</sup> 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.

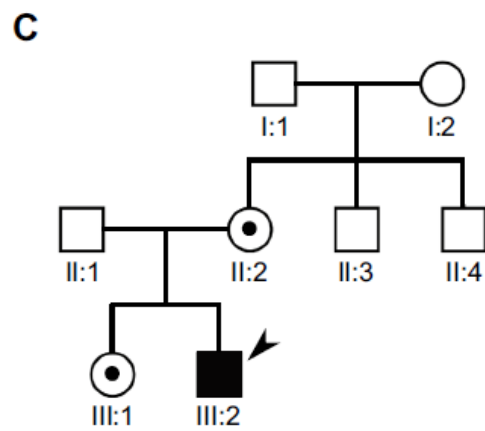
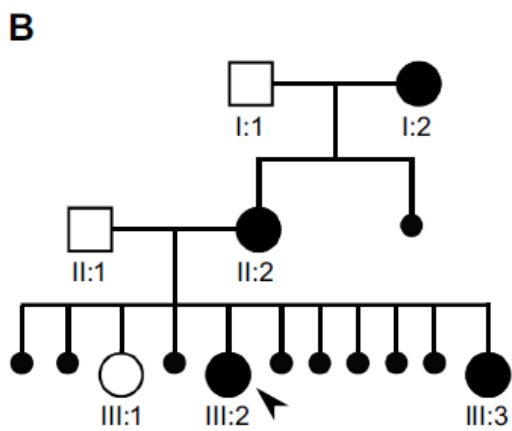
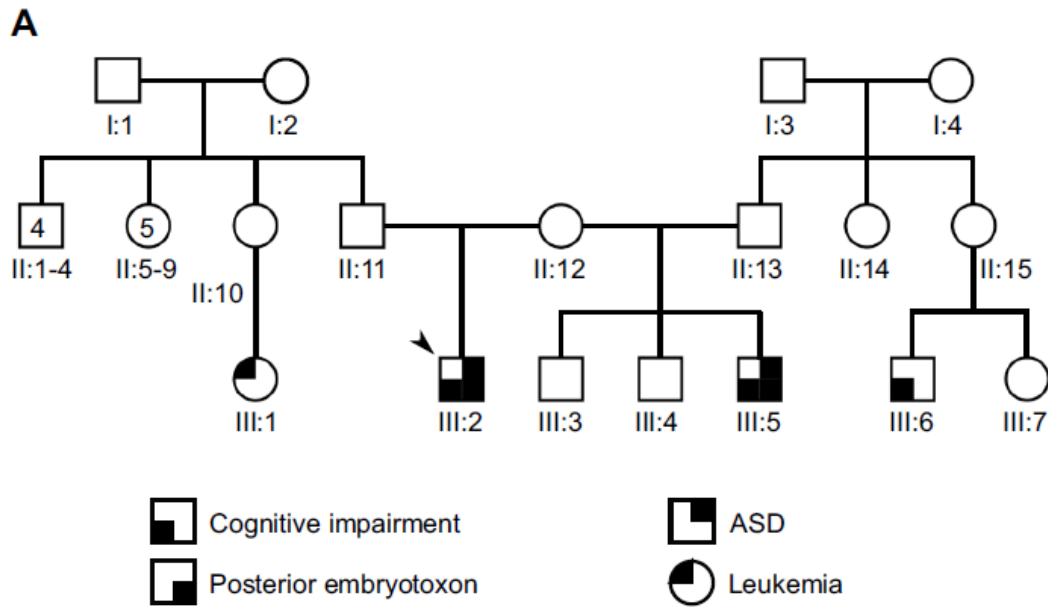


Figure 2. A. Pedigree of cases 4 and 5; B. Pedigree of case 7; C. Pedigree of case 12

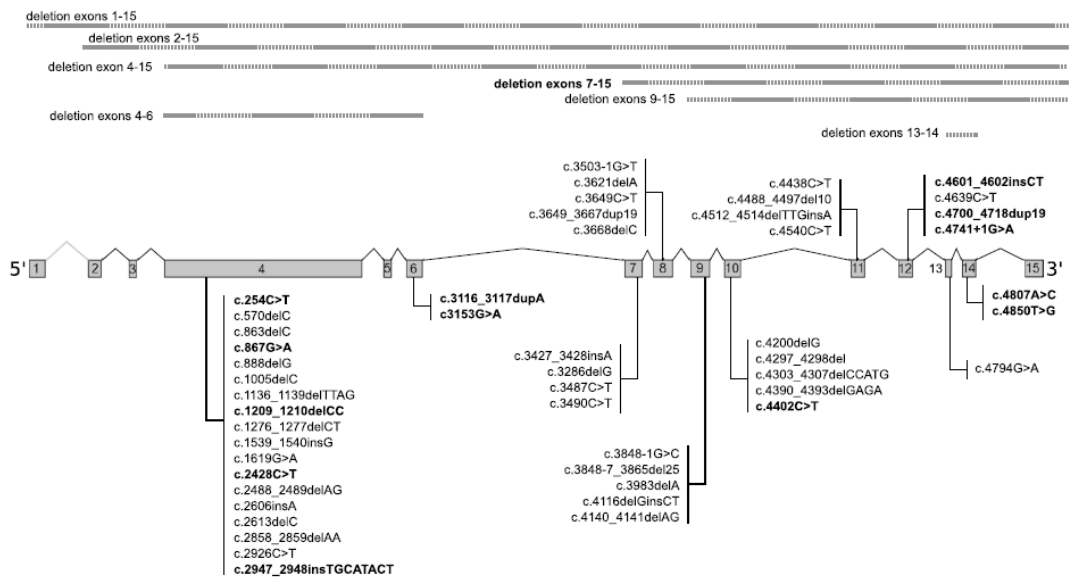


Figure 3: Summary of the described and new (in bold) variants in *BCOR*

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



**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
<i>BCOR</i> 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_2948insTGCAT ACT 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	<i>de novo</i>	mat	<i>de novo</i>	mat	mat	<i>de novo</i>	mat	mat	mat	<i>de novo</i>	NK	mat	<i>de novo</i>	mat	NK	<i>de novo</i>
affected family members				brother (case 5)	brother (case 4)		mother; gmother; aunt	mother						mother		
<b>growth</b>																
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)	2 <sup>nd</sup> (11y)	9 <sup>th</sup> (9y); 0.4-2 <sup>nd</sup> (21y)	50 <sup>th</sup> (3y)	80 <sup>th</sup> (birth)	-1 SD (4y 6m)	50 <sup>th</sup> (17y)	+0.5 SD (15y)	+2 SD (6y 6m)	50 <sup>th</sup> (27y)	91 <sup>st</sup> (8y)	NK	+1.5 SD (birth)	NK	13 <sup>th</sup> (3m), 2 <sup>nd</sup> (3y)	NK	NK
weight centile (age)	< 0.4 <sup>th</sup> (11y)	0.4-2 <sup>nd</sup> (9y); <3 <sup>rd</sup> (21y)	60 <sup>th</sup> (3y)	25 <sup>th</sup> (birth)	0 SD (4y 6m)	90 <sup>th</sup> (17y)	10 <sup>th</sup> (15y)	+3 SD (6y 6m)	91 <sup>st</sup> (27y)	98-99.6 <sup>th</sup> (8y)	NK	60 <sup>th</sup> (birth)	NK	6 <sup>th</sup> (3m), 23 <sup>rd</sup> (3y)	NK	NK
HC centile (age)	50 <sup>th</sup> (11y)	25 <sup>th</sup> (9y); 9 <sup>th</sup> (21y)	NK	28 <sup>th</sup> (birth)	-2.5 SD (4y 6m)	95 <sup>th</sup> (17y)	+0.5 SD (15y)	+1 SD (6y 6m)	75 <sup>th</sup> -91 <sup>st</sup> (27y)	> 99 <sup>th</sup> (8y)	NK	+1 SD (birth)	NK	96 <sup>th</sup> (3m)	NK	NK
<b>ocular</b>																
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 heterochromia	nystagmus	B Mo, nystagmus, high myopia	nystagmus			iris rubeosis, flat anterior chambers
<b>craniofacial</b>																
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, exophthalmos, glabellar naevus flammeus,			ptosis, macrocephaly, alveolar cleft	square shaped face, upslanting PF
<b>cardiac</b>																
ASD				+	+		+			+	+	+		+		+
VSD												+		+		+

other		triple heart sounds								dysplastic pulmonary valve	PDA	PDA, persistent L vena cava			cardiac defect
<b>dental</b>															
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	
<b>skeletal</b>															
hands	long Fi	5 <sup>th</sup> Fi clin, long Fi	long Fi	long Fi, 4-5 Cam	cam all Fi	5th Fi Clin	long Fi		long Fi	4 <sup>th</sup> fi Poly-syn, 5/6 fi poly-syn		long Fi short metacarpals, 5 <sup>th</sup> Fi Bra			
feet	SG, 2 <sup>nd</sup> 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	
<b>developmental</b>															
ID				+	+							+			
motor delay	+	+		+	+					+		+			
speech delay		+		+	+							+			
AuSD		+													
<b>MRI findings</b>															
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
<b>other findings</b>															
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

## Conflict of Interest Statement

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

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