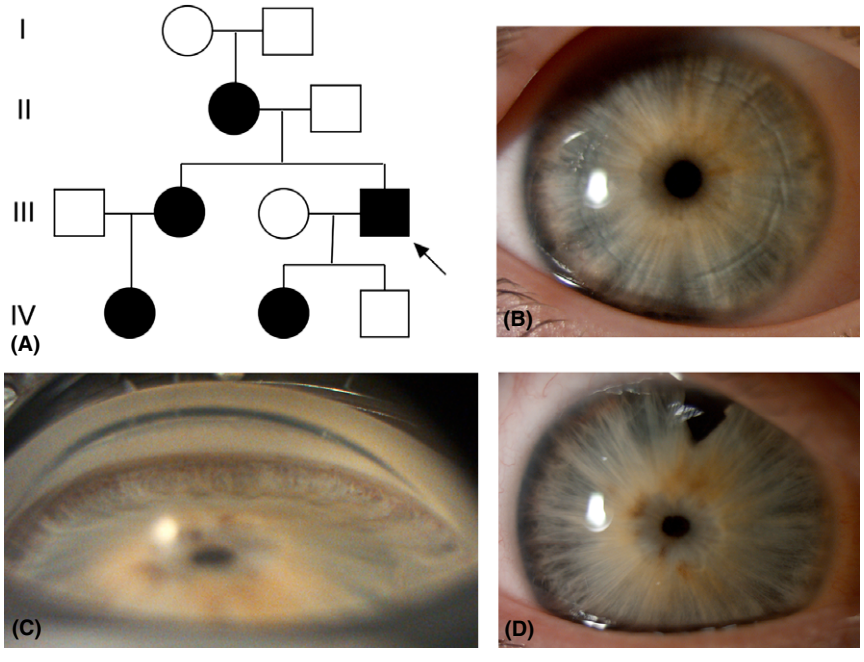

Fig. 1. Pedigree and slit-lamp photographs from a family segregating congenital microcoria. (A) Pedigree showing individuals affected with microcoria in multiple generations. The proband (arrow; subject III: 4) and his mother (subject II: 1) also had glaucoma that required surgery. A heterozygous 69-kb deletion encompassing *TGDS* and *GPR180* was detected in subject III: 4. (B) Colour photography of the anterior segment in a 6-year-old affected girl (subject IV:2) revealing mid-iris folds and a small pupil. (C) Imaging of the inferior iridocorneal angle in the 41-year-old proband (subject III:4) revealing numerous iris processes over the trabecular meshwork. (D) Colour photography of the proband's (subject III:4) anterior segment revealing extensive peripheral iris atrophy, a large peripheral iridotomy and a small pupil.

obtained, a blood sample was tested using clinical genome sequencing. The Complete Genomics (California, USA) platform was used, and bioinformatics analysis was performed using the Complete Genomics pipeline (v2.5) (Carnevali et al. 2012). After excluding mutations in known glaucoma-associated genes, we focused on the 13q32 region, where an autosomal-dominant microcoria gene has been mapped (Fares-Taie et al. 2015). A heterozygous 69-kb deletion (chr13:95219283-95288376) encompassing the entire TGDS and GPR180 genes was detected. The presence and extent of the deletion were confirmed through Sanger sequencing of the deletion breakpoints.

A family with early-onset glaucoma and microcoria, in which genome sequencing identified a large genomic deletion, is reported. It is evident from previous studies that individuals with congenital microcoria are at risk of developing ocular hypertension (Toulemont et al. 1995; Tawara et al. 2005; Fares-Taie et al. 2015). This rarely occurs before the end of the second decade of life, but at least one in three microcoria patients are going to require treatment for glaucoma (Toulemont et al. 1995). It can be speculated that glaucoma in these cases is associated with the iridocorneal angle abnormalities. However, the gonioscopic appearance in the proband of this study was similar to that of his older sister who has microcoria without any signs of glaucoma at age 44. Similar findings have been previously reported (Toulemont et al. 1995) suggesting that the significance of the angle dysgenesis is unclear.

Sequencing of the entire genome for clinical applications has now entered medical practice (Biesecker & Green 2014). The rapid identification of the disease-causing Deoxyribonucleic acid (DNA) sequence alteration in the presented case clearly demonstrates the potential of this approach in the diagnostics of developmental eye disorders.

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Genotype and Phenotype in an unusual form of Laurence–Moon–Bardet–Biedl syndrome

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Dear Editor,

The main purpose of this study was to further investigate the phenotype and genotype in two siblings with atypical retinal degeneration later diagnosed as Laurence–Moon–Bardet–Biedl (LMBB) syndrome. Follow-up visit 22 years later in one of the siblings verified a slowly progressive retinal degeneration.

Two siblings with atypical retinal degeneration underwent complete ophthalmological examination including Goldmann perimetry. Optical coherence tomography (OCT) images were obtained with a Topcon 3D OCT-1000 and full-field electroretinograms.

The two siblings underwent whole-exome sequencing. Details have already been published (Weisschuh et al. 2016).

The study was conducted in accordance with the tenets of the Declaration of Helsinki, and it was approved by the Ethical Committee for Medical Research at Lund University.

Results

Their parents were non-related and one elderly sibling had no symptoms (Fig. 1).

One of the siblings was examined at the age of 6 years (girl) and was re-examined 22 years later. She had since childhood poor motor coordination in daylight and bright sunshine. At the age of 8 years, she had OD 0.2 ($-9.25 = -5.25 \times 15°$) OS 0.1 ($-9.25 = -5.25 \times 140°$), nystagmus, abnormal colour vision and normal night vision. Fundus examination revealed no major retinal changes and no spicular pigments. Full-field ERG during general anaesthesia at the age of 6 years presented subnormal rod response and no measurable cone response.

She was re-examined 22 years later and presented similar visual acuity and essentially normal peripheral visual field. Fundus examination revealed slight macular changes, and OCT, essential normal findings. Full-field ERG showed similar response as previous examination with subnormal rod response and no detectable cone response.

Further medical examinations after the first eye examination revealed that she had problems with obesitas, hirsutism, irregular menstruation and elevated testosterone. She was not born with extra toe or finger.

The other sibling was examined at the age of 12 years (boy). Visual acuity was OD 0.4 ($-2.0 = -2.5 \times 20°$) OS 0.5 ($-2.0 = -3.0 \times 170°$), and he showed poorly defined maculae. Full-field ERG presented subnormal rod response and no measurable cone response. He did not agree to re-examination 20 years later.

Further medical examinations after the first eye examination revealed that he had serious problems with obesitas and underwent gastric bypass surgery and club foot surgery. He was not born with extra toe or finger.

Upon whole-exome sequencing in both siblings, we found rare and potentially disease causing variants following a model of autosomal recessive inheritance only in one gene: a homozygous missense variant was identified in the *BBS5* gene. The c.790G>A (Ref Seq accession number NM_152384.2) nucleotide substitution is predicted to change the glycine residue at position 264 of the protein into an arginine residue (Ref Seq accession number

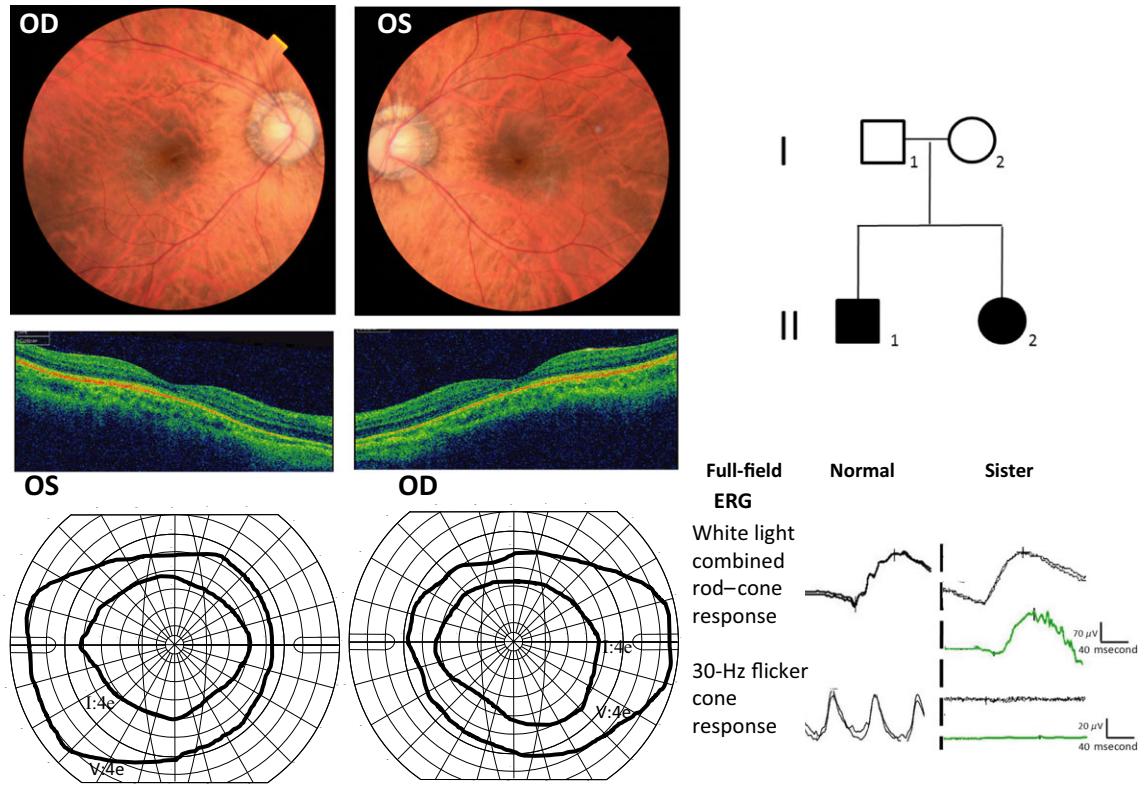

Fig. 1. *Up left*: Ocular fundus of the girl at age 28 with peripapillary atrophy, otherwise normal. Visual acuity was OD 0.25 (−2.0), OS 0.09 (−2.0). Optical coherence tomography demonstrates mainly normal appearance. Up right: Pedigree with the two siblings. *Down left:* Goldmann perimetry demonstrates essential normal peripheral visual field, but slightly reduced visual field with small object I:4e. *Down right:* Full-field electroretinogram from a normal control subject and one of the subjects (girl). Black line at 6 years of age with no cone response and essentially normal rod response. Green line at 28 years of age with similar response.

NP_689597.1). This mutation was confirmed by Sanger sequencing in both affected siblings. Amino acid position 264, which we found to be altered in our patients, is conserved between vertebrates, insects and *C. elegans*. Consequently, *in silico* analyses using various prediction programs such as PolyPhen-2 [http://genetics.bwh.harvard.edu/pph2/] and Mutation Taster [http://www.mutationtaster.org/] predict this variant to affect protein function.

Discussion

Laurence–Moon–Bardet–Biedl syndrome is known to be a progressive retinal disorder mainly presenting as rod–cone degeneration and often with more severe visual handicap in early life (Riise 1998). There are only few reports describing this disorder as cone–rod degeneration, but recently, Scheidecker and colleagues described a rare form of LMBB with cone system dysfunction in a group of patients with molecularly confirmed diagnoses (Azari et al. 2006; Scheidecker et al. 2015).

The two siblings in this study demonstrated an atypical phenotype with almost no residual cone response and subnormal rod response and at early life no medical sign of LMBB.

To our knowledge, unusually or not previously described, full-field ERG demonstrated no significant progression of the retinal degeneration in a patient with the genotype of LMBB. This was verified in one of the siblings, when she was re-examined 22 years later. As recently described, the variability of the phenotype in LMBB can be considerable (Azari et al. 2006). It has also been shown that mutations in BBS genes, such as *BBS1* and *BBS2*, can cause mild forms or even non-syndromic retinal dystrophy (Shevach et al. 2015). This is an atypical form of LMBB with ocular symptoms, with a very slowly progressive form of cone–rod degeneration, and associated with a novel mutation in *BBS5*. The total picture agrees with an atypical form of LMBB.

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Cataract surgery affects the pupil size and pupil constrictions, but not the late post-illumination pupil response

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Editor,

Recent research findings suggest chromatic pupillometry as a novel tool to differentiate between outer and inner retinal diseases. As many patients with retinal diseases undergo cataract surgery, we wanted to investigate whether there was a mechanical effect of unilateral cataract surgery on the pupillary light response.

Bilateral pupil responses to blue light (463 nm, 2 loglux) were recorded in 11 subjects before, 1 day, 3 weeks and 3 months after unilateral cataract surgery using a binocular chromatic pupillometer (DP-2000, NeurOptics). The non-operated eye was illuminated, and the pupil response was measured in both eyes. The outcomes were baseline pupil diameter, maximum pupil contraction and post-illumination sustained pupil responses from 1 to 10 seconds ($PIPR_{010s}$) and 10 to 30 seconds ($PIPR_{1030s}$) after termination of the light. Cataract surgery by phacoemulsification was performed using local anaesthesia. Three patients were not examined at the 3-month follow-up due to the cataract surgery of the fellow eye.

The effect of surgery was investigated by comparing the intereye differences (fellow eye – surgery eye) before and after surgery.

The baseline pupil diameter was transiently affected by surgery, as the pupil was 0.37 mm ($p = 0.003$) smaller on the surgery eye 1 day after surgery but not at any other time-point hereafter (Table 1). Likewise, the maximum contraction was reduced minutely at 1 day ($p = 0.02$) and 3 weeks ($p = 0.01$), but not at the 3-month follow-up ($p = 0.50$). The $PIPR_{010s}$ in the surgery eye was 0.30 ($\pm$0.05) and in the fellow eye 0.31 ($\pm$0.05), and the pupils showed reduced $PIPR_{010s}$ in the eye having undergone surgery at each time-point, but the effect was minor. The $PIPR_{1030s}$ before the surgical intervention was 0.14 ($\pm$0.06) in the surgery eye and 0.13 ($\pm$0.08) in the fellow eye ($p = 0.87$), and there was no significant difference following the surgery.

The reported transient miotic effect of cataract surgery on short term is consistent with one previous study (Hayashi & Hayashi 2004). Yet, other studies have reported decreased pupil size up to 12 months after surgery (Komatsu et al. 1997; Moller et al. 2000; Kanellopoulos & Asimellis 2014). This may be caused by different levels of inflammation, as postoperative inflammation has been shown to vary similarly. Lens thickness may also contribute to the decreased pupil size, as intraocular lens intraocular lens (IOL) is much thinner, thus protruding the iris less than the larger cataractous eye lens.