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Letter to the Editor

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 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.

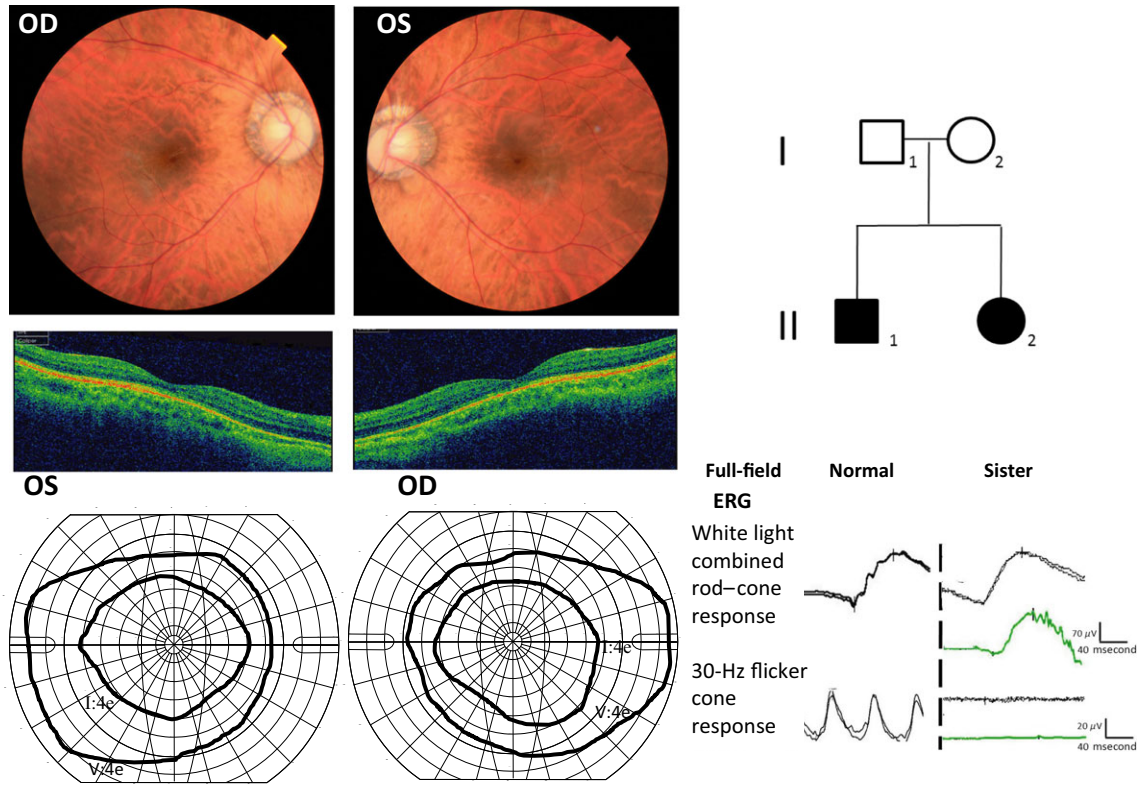

Fig. 1. *Up left*: Ocular fundus of the girl at age 28 with peripapillary atrophy, otherwise normal. Visual acuity was OD 0.25 (−2.0), OS 0.09 (−2.0). Optical coherence tomography demonstrates mainly normal appearance. Up right: Pedigree with the two siblings. *Down left:* Goldmann perimetry demonstrates 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.

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