Predominantly Cone-System Dysfunction as Rare Form of Retinal Degeneration in Patients With Molecularly Confirmed Bardet-Biedl Syndrome

SOPHIE SCHEIDECKER, SARAH HULL, YAUMARA PERDOMO, FOUZIA STUDER, VALÉRIE PELLETIER, JEAN MULLER, CORINNE STOETZEL, ELISE SCHAEFER, SABINE DEFOORT-DHELLEMMES, ISABELLE DRUMARE, GRAHAM E. HOLDER, CHRISTIAN P. HAMEL, ANDREW R. WEBSTER, ANTHONY T. MOORE, BERNARD PUECH, AND HÉLÈNE J. DOLLFUS

• PURPOSE: To describe a series of patients with Bardet-Biedl syndrome (BBS) and predominantly retinal cone dysfunction, a previously only rarely reported association.

• DESIGN: Retrospective observational case series.

• METHODS: Seven patients with clinically proven Bardet-Biedl syndrome had undergone detailed ocular phenotyping, which included fundus examination, Goldmann visual fields, fundus autofluorescence imaging (FAF), optical coherence tomography (OCT), and electroretinography (ERG). Mutational screening in the BBS genes was performed either by direct Sanger sequencing or targeted next-generation sequencing.

• RESULTS: All 7 patients had proven BBS mutations; 1 had a cone dystrophy phenotype on ERG and 6 had a cone-rod pattern of dysfunction. Macular atrophy was present in all patients, usually with central hypofluorescence surrounded by a continuous hyperfluorescent ring on fundus autofluorescence imaging. OCT confirmed loss of outer retinal structure within the atrophic areas. No clear genotype-phenotype relationship was evident.

• CONCLUSIONS: Patients with Bardet-Biedl syndrome usually develop early-onset retinitis pigmentosa. In contrast, the patients described herein, with molecularly confirmed Bardet-Biedl syndrome, developed early cone dysfunction, including the first reported case of a cone dystrophy phenotype associated with the disorder. The findings significantly expand the phenotype associated with Bardet-Biedl syndrome. (Am J Ophthalmol 2015;160(2):364–372. © 2015 by Elsevier Inc. All rights reserved.)

BARDET-BIEDL SYNDROME IS AN EMBLEMATIC CILIOPathy associated with severe and early-onset retinal dystrophy, postaxial polydactyly, early obesity, renal dysfunction, hypogonadism, and learning difficulties.[1] It is genetically heterogeneous, with 20 BBS genes identified (*BBS1* to *BBS20*) to date,[2,3] all of which encode proteins involved in the development and the maintenance of the primary cilium.

The retinal dystrophy associated with Bardet-Biedl syndrome is usually severe but expression can be variable. Electroretinography (ERG) is an important diagnostic investigation and can be abnormal prior to the development of fundus abnormalities. A rod-cone dystrophy is usually present, with initial symptoms of night blindness and constricted peripheral fields with later central retinal involvement.[4] Cone-rod dystrophy has also been reported but is very uncommon.[5]

The present report describes 7 patients with molecularly confirmed Bardet-Biedl syndrome who have predominantly cone dysfunction, contrasting with previous series and expanding the phenotype that can be associated with the disorder.

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From the Service de Génétique Médicale, Institut de Génétique Médicale d'Alsace, Centre de Référence pour les Affections Rares en Génétique Ophtalmologique (CARGO) (S.S., Y.P., F.S., V.P., E.S., H.J.D.), and Laboratoire de Diagnostic Génétique, Institut de Génétique Médicale d'Alsace (J.M.), Hôpitaux Universitaires de Strasbourg, Strasbourg, France; Inherited Eye Diseases, UCL Institute of Ophthalmology, London, and Moorfields Eye Hospital NHS Trust, London, United Kingdom (S.H., A.R.W., A.T.M.); Laboratoire de Génétique Médicale, Institut de Génétique Médicale d'Alsace, INSERM U1112, Faculté de Médecine, Université de Strasbourg, Strasbourg, France (C.S., H.J.D.); Service d'exploration de la Vision et Neuro-ophtalmologie, CHRU de Lille, Lille, France (S.D.-D., I.D., B.P.); Visual Neuroscience, UCL Institute of Ophthalmology, London, and Moorfields Eye Hospital NHS Trust, London, United Kingdom (G.E.H.); Genetic Sensory Diseases, CHU Montpellier, Montpellier, France (C.P.H.); Department of Ophthalmology, University of California, San Francisco Medical School, san Francisco, California (A.T.M.).

Inquiries to Hélène J. Dollfus, Service de Génétique Médicale, Institut de génétique Médicale d'Alsace, CARGO - Laboratoire de Génétique Médicale, INSERM U1112, 11 rue Humann, 67085 Strasbourg Cedex, France; e-mail: dollfus@unistra.fr

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METHODS

THIS IS A RETROSPECTIVE, OBSERVATIONAL CASE SERIES.

Seven patients with Bardet-Biedl syndrome from 6 unrelated families were identified as having cone or cone-rod dystrophy on ERG. Patients in Cases 1 and 2 were examined in the Center for Rare Genetic Ophthalmologic Diseases (CARGO) in the Strasbourg University Hospital (Strasbourg, France); in Cases 3 and 4 at Moorfields Eye Hospital (London, UK); and in Cases 5–7 in the University Hospital of Lille (Lille, France). Ethical approval was obtained from the local ethics committee of Strasbourg University Hospital and Lille Hospital and The Research Management Committee of Moorfields Eye Hospital.

All patients had a standard ophthalmic examination, including best-corrected visual acuity, slit-lamp examination, dilated fundus examination, and ERG. Visual fields were assessed with a Goldmann perimeter in Cases 1, 2, and 5–7. Full-field ERG was recorded according to the guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV) in all centers.[6] Full-field ERG was performed in Cases 1, 3, and 4 with the Espion system (Diagnosys LLC, Lowell, MA, USA), and in Cases 2 and 5–7 with a Metrovision system (Pérenchies, France). The diagnosis of cone dystrophy was based on progressive decline of visual acuity, severe central retinal dysfunction, and reduced and delayed cone responses on full-field ERG with normal rod-mediated responses at the time of diagnosis. Cone-rod dystrophy has both abnormal cone and rod responses on full-field ERG, with cone function being more severely affected. Spectral-domain optical coherence tomography (OCT) and fundus autofluorescence imaging (FAF) were performed for Cases 1–4 with a spectral-domain OCT device (Spectralis OCT; Heidelberg Engineering, Germany) and for Cases 5–7 with Cirrus HD-OCT (Carl Zeiss Meditec, Oberkochen, Germany). FAF in Cases 5–7 was performed by means of a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph; Heidelberg Engineering, Dossenheim, Germany).

The study protocol adhered to the tenets of the Declaration of Helsinki and received approval from the local ethics committee. Written informed consent was obtained from each subject prior to genetic investigation.

• **GENETIC ANALYSIS:** DNA of the patients was extracted from peripheral blood lymphocytes. The analysis was performed in either the research setting of the Medical Genetics Laboratory (Institut de Génétique Médicale d'Alsace, University of Strasbourg, INSERM U1112) or the Genetic Diagnostic Laboratory of the Strasbourg University Hospital. The mutational screening of the BBS genes was different between the patients depending on the strategy used at the time of the analysis, as the duration of the study was more than 8 years. The patient in Case 1 initially underwent homozygosity mapping (GeneChip Human Mapping 250K Nsp Array) (Platform IGBMC) (HomoSNP in house software) identifying a putative locus in which a mutation was detected by Sanger sequencing. Targeted Sanger sequencing of the more frequently involved BBS genes (*BBS1*, *BBS10*, and *BBS12*) allowed the molecular diagnosis for Cases 2 and 4. Cases 3, 5, and 6 were diagnosed by using targeted exome sequencing of the BBS genes.[7] The screening of *BBS1-BBS12* and of other ciliopathy genes (*AHI1*, *NPHP2-NPHP8*, *MKS1*, *MKS3*, *TTC21B*, *ALMS1*) was undertaken for Case 7 by a program performed by the Centre National de Séquençage (Evry, France) in 2009–2010.

RESULTS

THE OPHTHALMOLOGIC AND EXTRAOCULAR FEATURES OF the 7 patients are detailed in Table 1 and the ERG findings in Table 2. Fundus photographs and FAF and OCT images appear in Figures 1 and 2, with ERG imaging appearing in Figure 3.

The patient in Case 1 was born from related Syrian parents (second degree of consanguinity) and has a similarly affected older brother. The patient presented with reduced visual acuity at the age of 6 years. He later developed photophobia and macular atrophy was confirmed at age 10 years. Fundus examination at age 37 years showed central macular atrophy. OCT showed reduced macular thickness and absence of the foveal ellipsoid photoreceptor line. Central abnormal hypoautofluorescence surrounded by a ring of hyperautofluorescence was present in both eyes, whereas the periphery disclosed normal autofluorescence. Goldmann visual fields showed good preservation of peripheral isopters, but there was a failure to detect the I1e stimulus centrally in each eye. The ERG showed abnormal cone responses with mildly abnormal rod function. The patient had scars from surgical removal of hexadactyly, obesity (body mass index 38.6 kg/m^2), learning difficulties, hypogonadism, dyslipidemia, hepatic steatosis, and diabetes. He also suffered from depression and sleep apnea. SNP (single nucleotide polymorphism) analysis showed homozygosity in the *BBS5* region and Sanger sequencing revealed a homozygous p.M1L mutation in *BBS5*.

The patient in Case 2 was born to unrelated parents. He presented at age 45 years with reduced visual acuity. There was bilateral macular atrophy on fundus examination. FAF showed an area of central hypoautofluorescence corresponding to the atrophy, surrounded by a ring of hyperautofluorescence. Goldman visual fields showed good preservation of peripheral isopters. The ERG showed severe cone dysfunction with no detectable responses on flicker stimulation and mildly

TABLE 1. Key Clinical Features and Molecular Results of Bardet-Biedl Syndrome Patients With Predominantly Cone Dysfunction

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Sex	Male	Male	Female	Male	Male	Male	Male
Age at last examination	37 years	45 years	25 years	27 years	54 years	36 years	36 years
Family history	C (2nd degree)	Simplex	Simplex	Simplex	S (Case 6)	S (Case 5)	Simplex
Extraocular features							
Hexadactyly	+	+	+	+	+	+	+
Obesity	+	+	+	−	+	+	+
Learning difficulties	+	+	−	+	−	−	−
Hypogonadism	+	−	−	−	+	+	−
Renal failure	−	+	−	−	−		−
Others	Psychiatric disorders, diabetes, deafness, hyposmia	Imperforate anus	Polydipsia, diabetes, amenorrhea				Hydronephrosis, interatrial communication
Features of onset (age)	Decreased VA (6 y) Photophobia Diagnosis of retinal dystrophy (10 y)	Decreased VA	Decreased VA (8 y) Photophobia Dyschromatopsia	Decreased VA (18 y) Red-green dyschromatopsia	Decreased VA Red-green dyschromatopsia	Red-green dyschromatopsia	Decreased VA (10 y)
VA (Snellen)							
Right eye	6/120	6/9.5	6/9	6/18	20/125	20/100	20/200
Left eye	6/120	6/38	6/9	6/12	20/250	20/100	20/200
Ocular phenotype	Cone-rod dystrophy	Cone-rod dystrophy	Cone-rod dystrophy	Cone-rod dystrophy	Cone-rod dystrophy	Cone-rod dystrophy	Cone dystrophy
Molecular diagnosis	*BBS5* p.[M1L];[M1L]	*BBS12* p.[P159L];[I346T]	*BBS10* p.[R95S];[V707fs*]	*BBS1* p.[M390R(;) G318Vfs*61]	*BBS10* p.[R49W(;) Q139P]	*BBS10* p.[R49W(;) Q139P]	*BBS6* p.[M1I];[Y37C]

C = consanguinity; S = affected sibling; VA =visual acuity.

TABLE 2. Summary of Most Recent Electroretinogram Findings in Bardet-Biedl Patients With Predominantly Cone Dysfunction

Case	Dark-Adapted Responses	Light-Adapted Responses	Phenotype
1	Mildly reduced	Severely reduced and delayed	Severe CORD
2	Mildly reduced	Severely reduced and delayed	Severe CORD
3	Moderately reduced	Very severely reduced and delayed	Severe CORD
4	Mildly reduced	Mildly reduced	Mild CORD
5	Moderately reduced	Undetectable	Severe CORD
6	Moderately reduced	Severely reduced and delayed	Severe CORD
7	Normal	Moderately reduced and delayed	Moderately severe COD

COD = cone dystrophy; CORD = cone-rod dystrophy.
Grade of amplitude reduction for age: Mild, 70%–100%; Moderate, 40%–70%; Severe, 10%–40%; Very severe, <10%; Undetectable.

abnormal rod function. He had a history of imperforate anus, present from birth; hexadactyly; obesity; renal failure; and learning difficulties. Bardet-Biedl syndrome was confirmed by Sanger sequencing of *BBS12*, revealing a compound heterozygote status with the p.P159L and p.I346T mutations.

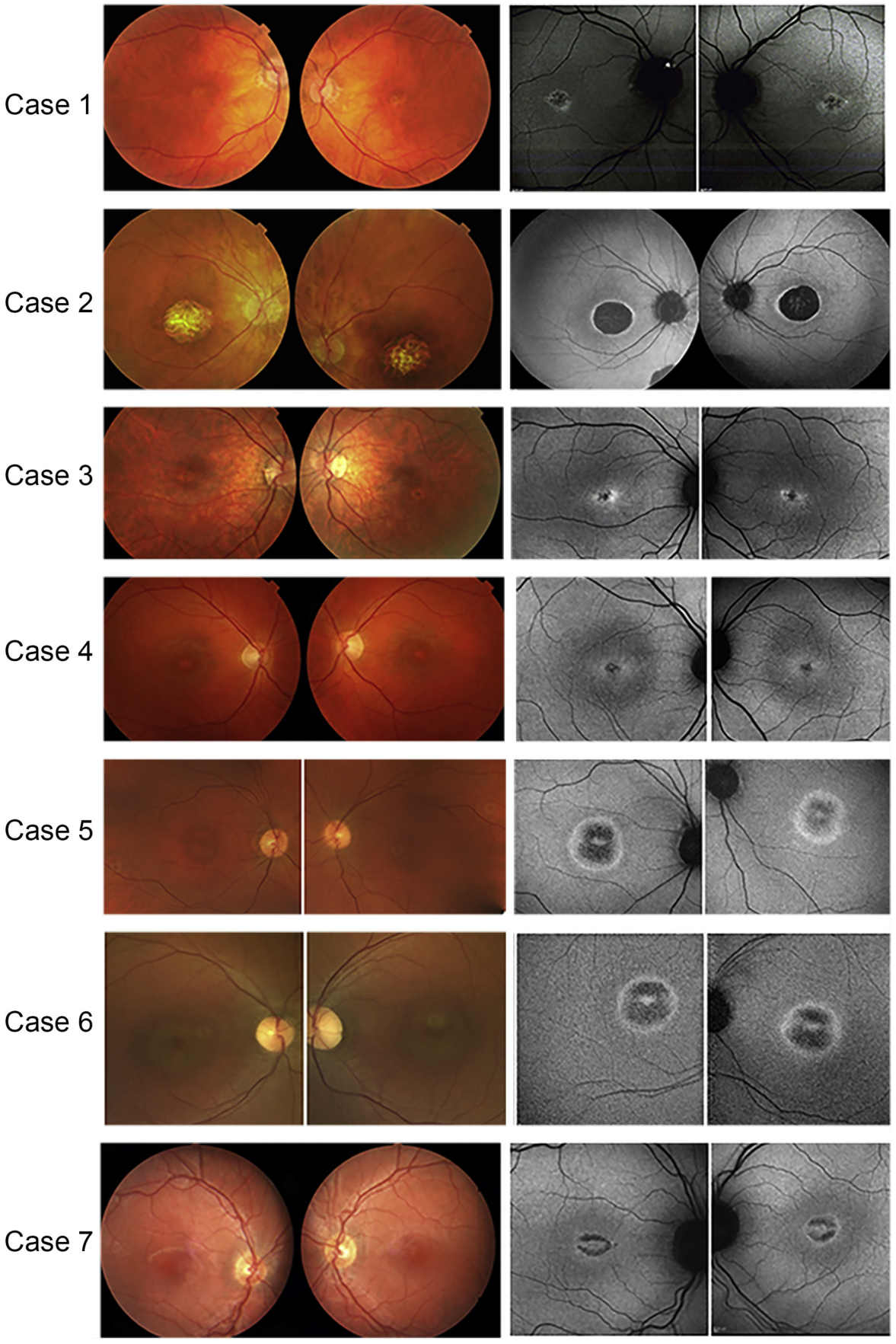
The patient in Case 3 first developed central visual disturbance at age 8, with photophobia and progressive alteration of color vision. Fundus examination at 21 years of age showed macular atrophy. Central FAF showed an area of hypoautofluorescence surrounded by a ring of hyperautofluorescence with disruption of the foveal ellipsoid line on OCT corresponding to the area of reduced autofluorescence. ERG (at age 18 years) showed severely abnormal cone function with milder rod system involvement. There was hexadactyly, obesity (body mass index 48.8 kg/m^2), amenorrhea, polydipsia, and diabetes. Targeted exome sequencing of the BBS genes revealed 2 mutations in *BBS10*, p.R95S and p.V707fs*.

The patient in Case 4 was noted at birth to have an extra digit on each hand and foot. At the age of 18 years, he noticed difficulty with distance vision. By 20 years of age visual acuity was 6/12 in each eye. He had poor color vision (he could only see 3 of the Ishihara color vision plates). Fundus examination showed mild macular atrophy. FAF demonstrated central hypoautofluorescence with a ring of increased autofluorescence in each eye, with OCT again demonstrating a disrupted foveal ellipsoid line corresponding to the reduced autofluorescence. Electrophysiological assessment at age 21 years showed bilateral abnormalities of the pattern ERG, indicating bilateral central macular dysfunction but a normal full-field ERG. A repeat ERG at age 25 years showed an abnormal full-field ERG with cone ERGs showing marked deterioration and the development of mild rod-system abnormalities. There was no subjective deterioration in vision. Bardet-Biedl syndrome was confirmed by Sanger sequencing of *BBS1*, which revealed the recurrent mutation p.M390R and a deep intronic mutation c.951+58C>T in intron 10 creating a cryptic splice donor site, leading to the inclusion of a part of intron 10 and to a premature stop codon (p.G318Vfs*61) (Supplemental Figure, available at AJO.com).

The patients in Cases 5 and 6 were brothers, both of whom had had surgery for postaxial polydactyly. In Case 5, the patient (the older brother) had obesity and oligospermia; his brother, in Case 6, had only oligospermia. The brother in Case 5 was initially examined at the age of 31 years when he presented with reduced vision, photophobia, and color vision disturbance. He had a small central scotoma but peripheral isopter V was normal. The ERG showed abnormal cone responses with normal scotopic responses. After 25 years of evolution, he had developed macular changes on fundus examination. FAF imaging revealed a central hypoautofluorescence with a ring of increased autofluorescence. OCT showed a disrupted foveal ellipsoid line corresponding to the reduced autofluorescence. A repeat ERG showed undetectable cone system responses with moderately reduced rod system responses.

The brother in Case 6 was noted to have reduced visual acuity at the age of 12. He had slight photophobia. Fundus examination showed normal maculae, vessels, and periphery. FAF and OCT revealed changes that were similar to (although less extensive than) his brother. ERG performed at the age of 16 showed absent photopic responses with normal scotopic responses. Fundus examination was normal. At 36 years, the ERG showed severe cone dysfunction with abnormal rod responses. The visual field showed a 10 degree central scotoma. Targeted exome sequencing revealed 2 mutations in *BBS10*, p.R49W and p.Q139P, in each brother.

The patient in Case 7 had a history of polydactyly, obesity, hydronephrosis, and interatrial communication. He presented with decreased visual acuity at age 7 years. The examination of the fundus was normal apart from an absence of the foveal reflex. Color vision testing was abnormal and Goldmann visual fields showed a central scotoma with normal peripheral isopters (III and V). When last examined (at age 36 years), he showed cone dystrophy with a mildly decreased visual acuity and photophobia. FAF demonstrated central macular abnormalities with increased foveal autofluorescence surrounded by hypoautofluorescence, with a further ring of increased autofluorescence surrounding this. OCT demonstrated a disrupted foveal


Case 1
Case 2
Case 3
Case 4
Case 5
Case 6
Case 7

ellipsoid line corresponding to the reduced autofluorescence. ERG showed abnormal cone function with no significant rod system involvement. Sequencing of *BBS6* revealed 2 mutations, p.M1I and p.Y37C.

DISCUSSION

BARDET-BIEDL SYNDROME IS ASSOCIATED WITH A RETINAL photoreceptor dystrophy, which is usually a rod-cone dystrophy (eg, retinitis pigmentosa [RP]). Moreover, it can be the only manifestation found in patients having retinal-specific mutations in the *BBS3* and *BBS8* genes or the recurrent p.M390R mutation in *BBS1*.[8–10] The present series of 7 molecularly confirmed Bardet-Biedl syndrome patients all have cone-rod or cone dystrophy and thus the series expands the existing phenotypic descriptions. One novel mutation is described.

Visual acuity loss was the initial complaint and was more severe at presentation compared to that seen in most patients with Bardet-Biedl syndrome, where the more typical RP has initial preservation of central visual acuity. Retinal imaging in all patients confirmed macular involvement. The patients show a perifoveal ring of increased FAF surrounding a central area of hypoautofluorescence, atypical for RP, in which more commonly a ring of increased FAF surrounds a preserved central zone.

Full-field ERG showed predominant cone dysfunction in all patients. Case 7 involved a cone dystrophy phenotype with severe cone dysfunction but rod responses in the normal range. The remaining 6 cases involved abnormal rod responses accompanying marked cone dysfunction, a cone-rod dystrophy phenotype. Two brothers, in Cases 5 and 6, initially presented a cone dystrophy phenotype but subsequently developed rod involvement.

The diagnosis of Bardet-Biedl syndrome and of other ciliopathies may be difficult owing to the genetic and phenotypic heterogeneity and the overlap existing between the different ciliopathies. The main differential diagnosis is Alström syndrome, another ciliopathy, characterized by infantile-onset retinal dystrophy associated with obesity, childhood-onset diabetes, and deafness.[11] The retinal dystrophy in Alström syndrome is an early-onset cone-rod dystrophy accompanied by nystagmus and photophobia in the first months and abnormal cone ERGs before the age of 6 months. The rods are initially preserved, with progressive degeneration. Legal blindness usually develops during the second decade.[12] Phenotypic variability in age of onset and in the disease progression has been described,[13] but the retinal dystrophy is typically of earlier onset, with severe infantile cone system involvement and more rapid and more severe progression than the retinal dystrophy usually associated with Bardet-Biedl syndrome.[13,14] The present series of patients also had early cone dysfunction, but disease progression was slower than that in Alström syndrome. Other than the atypical ERG data, all 7 patients had clinical features in keeping with Bardet-Biedl syndrome, including polydactyly, frequently present in Bardet-Biedl syndrome but not a feature of Alström syndrome. The unusual predominantly cone dysfunction retinal phenotype in the present series of Bardet-Biedl patients adds further complexity to the differential diagnosis.

The molecular biology shows mutations in different BBS genes, involved in the 2 BBS protein complexes, the BBSome and the chaperonin complex. Interestingly, 5 of the 7 patients have mutations in genes encoding the chaperonin complex. However, no phenotype/genotype correlation can be established owing to the limited number of patients. One novel mutation is reported; the others have previously been described. The novel mutation is the deep intronic mutation c.951+58C>T in *BBS1* and illustrates the importance of seeking intronic variants when biallelic mutations are not found on analysis of the coding sequence.[15]

Bardet-Biedl syndrome is a well-known example of oligogenic inheritance, as some patients carry 3 mutations in 2 distinct BBS loci, which potentially interact and thus modify the phenotype.[16] It can be hypothesized that patients with this atypical retinal phenotype could have a common modifying variant or variants that result in this unusual phenotype. A third mutation in other known BBS genes has not been detected in the 3 patients (Cases 3, 5, and 6) who benefited from a targeted exome sequencing on known BBS genes (*BBS 1–16*). The involvement of such modifying factors and their role(s) is difficult to identify and warrants further molecular studies in larger numbers of Bardet-Biedl patients.

To conclude, Bardet-Biedl syndrome is associated with marked phenotypic and genotypic variability, which complicates diagnosis and genetic counseling. The present series of patients with cone or cone-rod dystrophy significantly expands the phenotype spectrum. Recognition of these unusual phenotypes and an understanding of the underlying pathophysiological mechanisms are crucial to the diagnosis and management of these patients and the development of future therapies.

FIGURE 1. Fundus photographs and autofluorescence (FAF) showing macular involvement in Bardet-Biedl syndrome patients. (Left two columns) Fundus photographs (respectively, right eye, left eye) show macular atrophy. (Right two columns) FAF (respectively, right eye, left eye) contains variably sized regions of reduced autofluorescence at the central macula surrounded by a ring of increased autofluorescence for all cases and, for Cases 5, 6, and 7, an additional central foveal hyperautofluorescent spot.

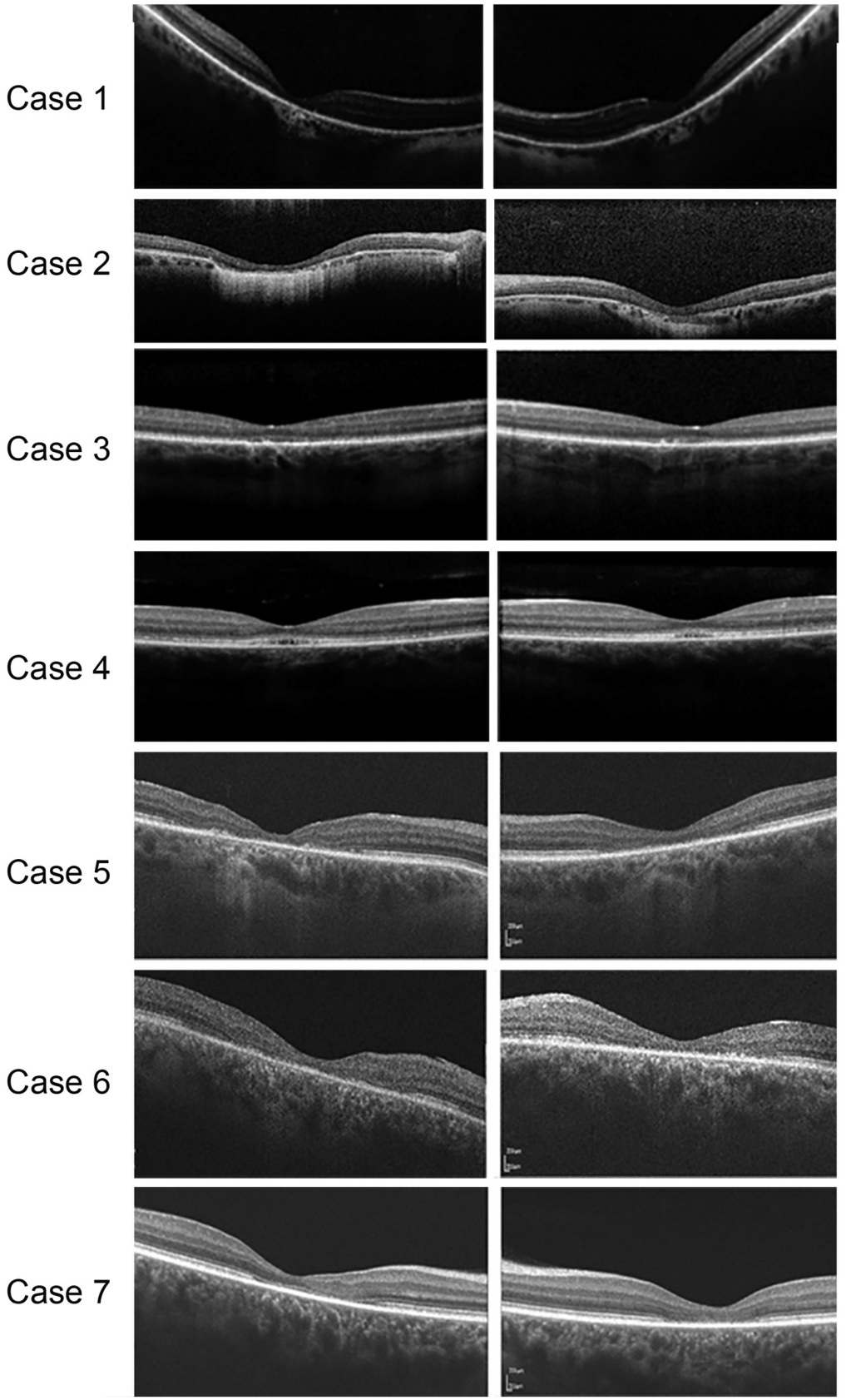


FIGURE 2. Optical coherence tomography (right eye, left eye) showing disruption or loss of the foveal ellipsoid line in Bardet-Biedl syndrome patients.

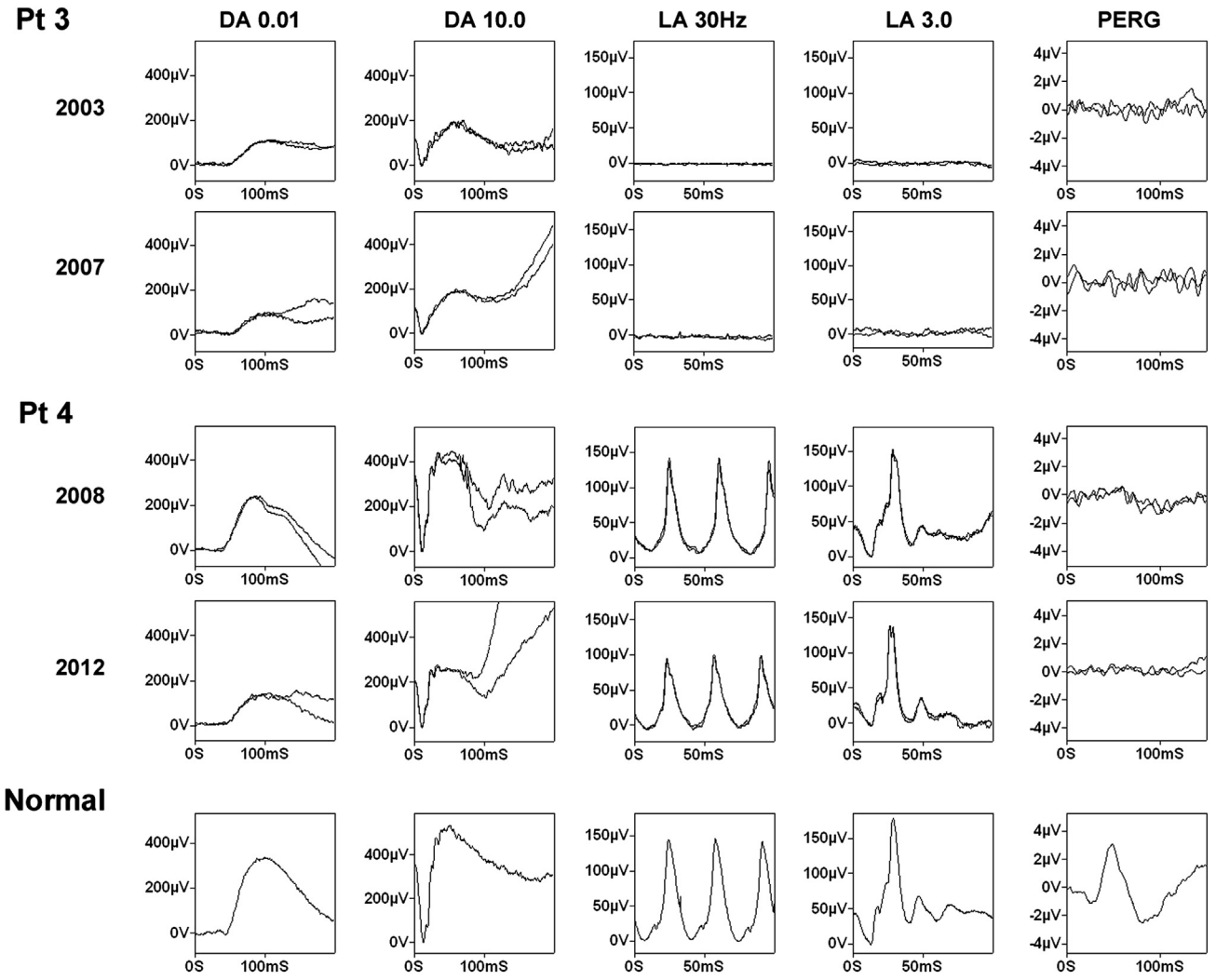


FIGURE 3. International Society for Clinical Electrophysiology of Vision (ISCEV) Standard full-field and pattern electroretinograms (PERG) showing predominant cone dysfunction in Bardet-Biedl patients (from 1 eye each of patients in Cases 3 and 4). There is no significant interocular asymmetry in either patient. Case 3 shows undetectable PERG and full-field cone electroretinograms (ERGs) (light-adapted [LA 3.0 and LA 30 Hz]) with subnormal dark-adapted (DA 0.01 rod specific) and bright flash dark-adapted (DA 10.0) ERGs, which were stable over a 4-year follow-up period. Case 4 demonstrates severely abnormal PERG with normal ERG in 2008. There was deterioration in both cone and rod function when tested in 2012. Data from a representative normal control subject are shown for comparison.

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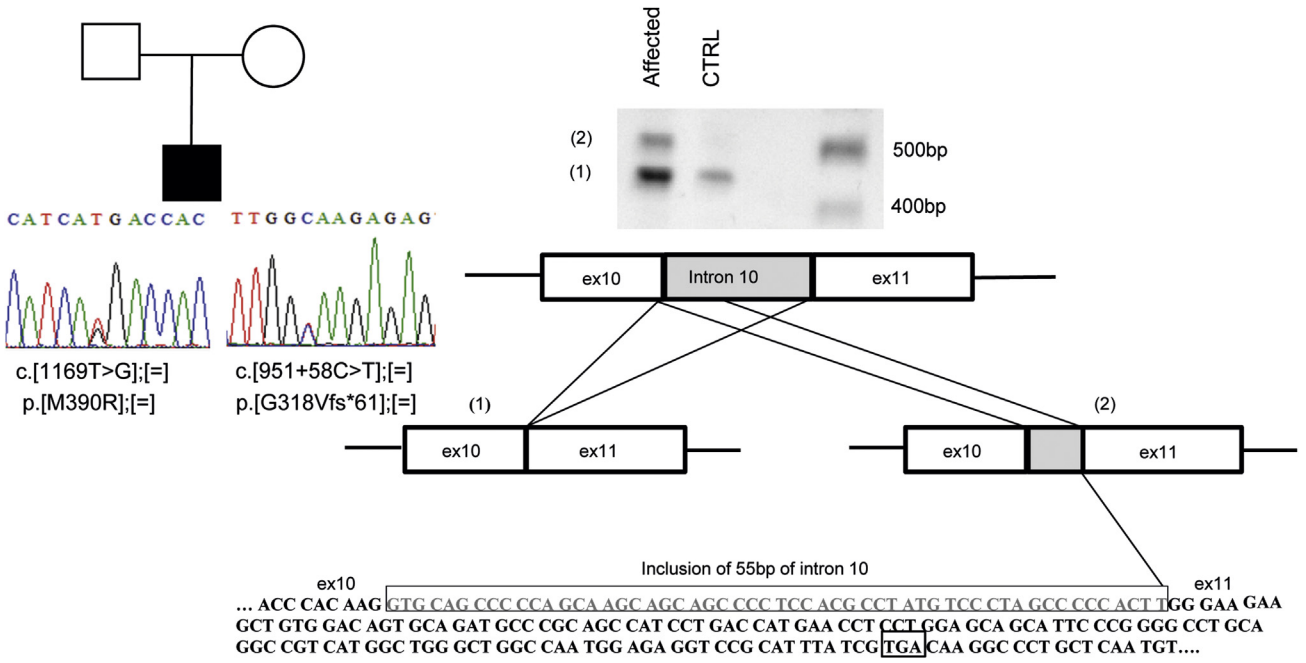
REPORTING VISUAL ACUITIES

The AJO encourages authors to report the visual acuity in the manuscript using the same nomenclature that was used in gathering the data provided they were recorded in one of the methods listed here. This table of equivalent visual acuities is provided to the readers as an aid to interpret visual acuity findings in familiar units.

Table of Equivalent Visual Acuity Measurements

Snellen Visual Acuities				
4 Meters	6 Meters	20 Feet	Decimal Fraction	LogMAR
4/40	6/60	20/200	0.10	+1.0
4/32	6/48	20/160	0.125	+0.9
4/25	6/38	20/125	0.16	+0.8
4/20	6/30	20/100	0.20	+0.7
4/16	6/24	20/80	0.25	+0.6
4/12.6	6/20	20/63	0.32	+0.5
4/10	6/15	20/50	0.40	+0.4
4/8	6/12	20/40	0.50	+0.3
4/6.3	6/10	20/32	0.63	+0.2
4/5	6/7.5	20/25	0.80	+0.1
4/4	6/6	20/20	1.00	0.0
4/3.2	6/5	20/16	1.25	−0.1
4/2.5	6/3.75	20/12.5	1.60	−0.2
4/2	6/3	20/10	2.00	−0.3

From Ferris FL III, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol 1982;94:91–96.



SUPPLEMENTAL FIGURE. Mutation analysis of a Bardet-Biedl syndrome patient (Case 4). Pedigree of patient in Case 4 shows the recurrent mutation p.M390R and a deep intronic mutation c.951+58C>T in intron 10 in the *BBS1* gene (on the left). Electrophoresis gel shows the polymerase chain reaction (PCR) amplification of cDNA and a schematic representations of the 2 PCR products, 1 with normal size and 1 bigger with the inclusion of 55 bp of intron 10 owing to the creation of a cryptic splice donor site with the c.951+58C>T mutation (on the right).