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Relatively mild blue cone monochromacy phenotype caused by various haplotypes in the L- and M-cone opsin genes

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Purpose: Blue cone monochromacy (BCM) is an X-linked retinopathy caused by mutations in the red and green cone opsin genes. The aim of this study was to establish the clinical, genetic, and electrophysiological characteristics of a specific form of BCM.

Methods: Patients harboring mutations in the *OPN1LW/OPN1MW* genes underwent a full clinical examination, including ocular examination, color vision, full-field electroretinography, color fundus and autofluorescence photography, and optical coherence tomography. Genetic analysis was performed using whole-exome sequencing, duplex PCR, PCR/restriction fragment length polymorphism, and Sanger sequencing. IBM SPSS Statistics v. 21.0 was used for the data analysis.

Results: Twenty-five patients harboring various haplotypes in exon 3 of the *OPN1LW/OPN1MW* genes were recruited. They showed a milder incomplete phenotype of BCM than the typical BCM control group. They presented significantly better visual acuity (logarithm of the minimum angle of resolution [logMAR] 0.48 ± 0.26 vs. 1.10 ± 0.54; $p < 0.0001$) and a highly myopic refraction (−7.81 ± 5.81 D vs. −4.78 ± 5.27 D; $p = 0.0222$) compared with the BCM control group. The study group had higher 30-Hz cone flicker responses (28.60 ± 15.02 μv; $n = 24$), whereas the BCM group had none (0.66 ± 2.12 μv; $n = 21$; $p < 0.0001$). The Lanthony 15-HUE desaturated test was variable for the exon 3 haplotype group, with a tendency toward the deutan-protan axis.

Conclusions: The present study included genetic and clinical data from the largest cohort of patients with exon 3 haplotypes that were previously shown to cause missplicing of the *OPN1LW* and *OPN1MW* genes. Analysis of the clinical data revealed better best-corrected visual acuity, more severe myopia, and higher 30-Hz cone flicker responses in the patients with exon 3 haplotypes than in those with typical BCM.

Blue cone monochromacy (BCM; OMIM 303700) is an X-linked retinopathy caused by mutations in the *OPN1LW* (OMIM 300822)/*OPN1MW* (OMIM 300821) gene cluster, encoding the red (long wavelength-senstitive [L]) and green (middle wavelength-sensitive [M]) cone opsins [1-3]. The most common mutations reported to cause BCM are large deletions at the *OPN1LW/OPN1MW* gene cluster, affecting the locus control region in most cases, and the p.C203R missense mutation [2,4]. Genes that express blue cone opsin (short wavelength-sensitive [S]) and the rod pigment are autosomal and normal in BCM [5,6].

The estimated BCM prevalence is 1 in 100,000 individuals [7]. The clinical presentation of BCM can be variable and is similar to that of achromatopsia (rod monochromacy), and the blue-yellow filtered glass test can differentiate between the two entities [8]. Male patients with BCM usually present with myopia, reduced visual acuity (VA) ranging from 20/80 to 20/400, severely abnormal color vision, photophobia, and mild to severe nystagmus [3,9]. Typically, patients with BCM show numerous errors along the protan-deutan axis, as can be seen in the Farnsworth D-15 panel test. Electroretinography (ERG) recordings show diminished cone and retained rod responses [3]. The disease is considered stationary with minimal fundus changes such as granularity within the macular area, but recent studies have shown progressive macular atrophic changes among old patients [10,11]. In addition, thinning of the photoreceptor outer nuclear layer within the foveal region and shortening of the cone outer segments, which led to a lack of umbo, and residual L/M-cones that were presumably non-functional within the central 1.5 mm of the retina were observed [6].

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Besides the set of mutations that cause the classic BCM phenotype, a group of haplotypes (a combination of specific amino acid residues) based on common single nucleotide variants residing in exon 3 has recently received special attention [12-21]. By using in vitro splicing assays, certain combinations of these variants have been shown to lead to the complete or partial skipping of exon 3 or other missplicing events [13,15,22].

Herein, we report the clinical and molecular genetic findings from the largest reported cohort of patients harboring various *OPN1LW/OPN1MW* exon 3 haplotypes and compare them with those of patients with typical BCM-causing variants. The phenotype of the group harboring haplotype variants was milder than that of the typical BCM group.

METHODS

Patient recruitment: The tenets of the Declaration of Helsinki were followed in the conduct of this study. Prior to blood sample donation, all individuals who participated in this study provided written informed consent after receiving an explanation of the nature and possible consequences of the study. The research was approved by the institutional review boards of Hadassah Medical Center and Rambam Health Care Campus. In this study, we included male patients who were clinically diagnosed with BCM (or mild BCM) suggested as the major phenotype or as one of the possible phenotypes (usually when young male patients were clinically tested and unequivocally determining whether the phenotype was indeed BCM or another cone-dominated disease was challenging).

Clinical evaluation: Ocular evaluation was performed with a full ophthalmological examination, including family history, ocular and systemic histories, best-corrected visual acuity (BCVA) tested for both distance and proximity (from a reading distance), Goldmann perimetry, full-field ERG (ffERG), color vision test using the Ishihara 38-panel and Farnsworth-Munsell D-15 tests, color and infrared fundus photography, spectral domain optical coherence tomography (SD-OCT), and fundus autofluorescence imaging. ffERG responses were recorded in accordance with the International Society for Clinical Electrophysiology of Vision standard using corneal electrodes and a computerized system (UTAS 3000, LKC Technologies, MD) as previously described [23]. Clinical data are presented as mean ± standard deviation (SD).

Genetic analyses: DNA samples were extracted from the index patients and other affected and unaffected family members by using the FlexiGene DNA kit (QIAGEN, Hilden, Germany). Genetic analysis included whole-exome sequencing as previously detailed [24] and Sanger sequencing using specific primers designed using the Primer3 software and University of California Santa Cruz website, as detailed in Appendix 1.

In addition, the basic structure and integrity of the *OPN1LW/OPN1MW* gene cluster were analyzed using PCR and PCR/restriction fragment length polymorphism, and the BCM-causing point mutations and exon 3 haplotypes of the *OPN1LW/OPN1MW* genes were screened with Sanger sequencing as previously described [9,15]. For the subjects with a structurally intact array, *OPN1LW*- or *OPN1MW*-specific long-distance PCRs were performed and used for the reamplification of exon 3 followed by Sanger sequencing [15].

RESULTS

Identification of patients harboring mutations in the cone opsin cluster: We identified two groups of patients with pathogenic sequence variants in the *OPN1LW/OPN1MW* gene cluster: 25 patients (from 14 unrelated families) with various exon 3 haplotypes (exon 3 group; see below for more details and Appendix 2) and 21 patients (from three unrelated families) with other pathogenic variants (the BCM group). The genetic and clinical information of some of the patients was reported in our previous studies [12,25]. Of the 21 patients from the BCM group, 20 had a large deletion removing most exons of the red and green opsin genes (Table 1), and one harbored a single hybrid gene with the previously reported p.C203R mutation. Patients who belonged to the exon 3 group had various combinations of sequence variants within exon 3, as detailed in Table 1.

Visual acuity and refraction: Detailed clinical information for each participating subject is presented in Appendix 2. BCVA ± SD data are available for all patients in the exon 3 group, who were examined at a mean age of 13.83 ± 12.64 years (range, 4–61 years) and presented a mean BCVA of Snellen of 0.369 ± 0.172 (logMAR, 0.48 ± 0.26). The mean BCVA of Snellen of 0.14 ± 0.19 (logMAR, 1.10 ± 0.54) is available for 17 patients in the BCM group, who were examined at a mean age of 18.44 ± 15.33 years (range, 3.5–51 years; Table 2). The study group had significant better BCVA than the BCM group ($p < 0.0001$). The patients in the exon 3 group were also more myopic than the patients with BCM (mean spherical equivalent, −7.81 ± 5.81 D [range, 9.875 to −15.75 D; n = 21] vs. −4.78 ± 5.27 D [range, 0.25 to −18.0 D], n = 13; $p = 0.0222$; Table 2).

Near VA was available for 11 patients, most of whom demonstrated a good near VA, which was usually better than the distance VA for the same patients. Nine of the 11 patients had Jager 1 (J1) in at least one eye (Appendix 2).

Table 1. Information regarding the participating families and their genetic results.

OPN1LW/OPN1MW mutation/ exon 3 haplotype*	Gene	Genetic method	Family No.
Blue cone monochromacy (BCM)			
chrX:g.153409766_153455982del	Cone opsin cluster	Sanger Sequencing	MOL0110
p.C203R	*OPN1LW/OPN1MW* single hybrid gene	Sanger sequencing	MOL0432
chrX:g.153409766_153455982del	Cone opsin cluster	Sanger sequencing	MOL01405
Exon 3 haplotype blue cone monochromacy			
G-C-G-A-T-C-G-G (R**L**V**IAVA**) A-A-C-G-G-T-G-G (R**M**V**V**V**VA**)	*OPN1LW* *OPN1MW*	WES and PCR, PCR/ RFLP, LD-PCR, Sanger sequencing	MOL0048
G-C-G-A-T-C-G-G (R**L**V**IAVA**)	*OPN1LW/OPN1MW* single hybrid gene	Sanger sequencing	MOL0057
G-C-G-A-T-C-G-G (R**L**V**IAVA**) A-A-C-G-G-T-G-G (R**M**V**V**V**VA**)	*OPN1LW* *OPN1MW*	Sanger sequencing	MOL0152
G-C-G-A-T-C-G-T (R**L**V**IAVS**)	*OPN1LW*	Sanger sequencing	MOL0267
G-C-G-G-G-C-G-G (R**L**V**VAVA**) A-A-C-G-G-T-G-G (R**M**V**V**V**VA**)	*OPN1LW* *OPN1MW*	PCR, PCR/RFLP, LD-PCR, Sanger sequencing	MOL0298
G-C-G-G-G-C-G-G (R**L**V**VAVA**) A-A-C-G-G-T-G-G (R**M**V**V**V**VA**) A-A-C-G-G-C-G-G (R**M**V**VAVA**)	*OPN1LW* *OPN1MW* *OPN1MW*	PCR, PCR/RFLP, LD-PCR, Sanger sequencing	MOL0961
G-C-G-A-T-C-G-G (R**L**V**IAVA**) A-A-C-G-G-T-G-G (R**M**V**V**V**VA**)	*OPN1LW* *OPN1MW*	PCR, PCR/RFLP, LD-PCR, Sanger sequencing	MOL1215
G-C-G-G-G-C-G-G (R**L**V**VAVA**) A-A-G-G-G-T-G-G (R**M**V**V**V**VA**)	*OPN1LW* *OPN1MW*	WES and Sanger sequencing	MOL1231
G-C-G-A-T-C-G-G (R**L**V**IAVA**) A-A-G-G-G-T-G-G (R**M**V**V**V**VA**)	*OPN1LW* *OPN1MW*	PCR, PCR/RFLP, LD-PCR, Sanger sequencing	MOL1383
G-C-G-A-T-C-G-G (R**L**V**IAVA**) G-C-G-A-T-C-G-G (R**L**V**IAVA**) A-A-C-A-T-T-G-G (R**M**V**I**V**VA**)	*OPN1LW* *OPN1MW OPN1MW*	Sanger sequencing	MOL1434
G-C-G-A-T-C-G-G (R**L**V**IAVA**) A-A-G-G-G-T-G-G (R**M**V**V**V**VA**)	*OPN1LW* *OPN1MW*	PCR, PCR/RFLP, LD-PCR, Sanger sequencing	MOL1459
G-C-G-G-G-C-G-G (R**L**V**VAVA**) A-A-C-G-G-C-A-G (R**M**V**VAIA**)**	*OPN1LW* *OPN1MW*	PCR, PCR/RFLP, LD-PCR, Sanger sequencing	MOL1611
G-C-G-A-T-C-G-T (R**L**V**IAVS**)	*OPN1LW*	WES and Sanger sequencing	MOL1654
G-C-G-A-T-C-G-T (R**L**V**IAVS**)	*OPN1LW*	Sanger sequencing	MOL1736

*- The haplotype in exon 3 is composed of the following variants: c.453A/G (p.151R/R), c.457A/C (p.153M/L), c.465C/G (p.155V/V), c.511G/A and c.513G/T (p.171V/I), c.521C/T (p.174A/V), c.532A/G (p. 178I/V), c.538G/T (p.180A/S). Based on this order, nucleotides are presented as "G-C-G-A-T-C-G-G" that corresponds to the protein haplotype that is shown in parenthesis "(R**L**V**IAVA**)"- the amino acids in bold represent the five missense variants that are part of the haplotype. **- This haplotype is not considered pathogenic, but cosegregates in a family that includes 3 distantly related affected individuals.

Table 2. Visual acuity, refraction and electrophysiological responses of Exon 3 and BCM-control groups included in this study.

Blue -wave rod response [µv] (n)	b-wave mixed response [µv] (n)	a-wave mixed response [µv] (n)	Time [msec] (n)	Cone Flicker- 30 Hz [µv] (n)	Spherical Equivalent [D] (n)	Snellen VA±SD (n)	Variables and study group
18.24±14.05			14.372±13.25		13.83±12.64		**Age at examination ± SD [years]**
236.32±104.37 (17)	320.03±100.68 (17)	148.97±74.02 (17)	34.10±3.84 (22)	28.60±15.02 (24)	−7.81±5.81 (21)	0.369±0.172 (24)	**Incomplete BCM**
22.76±16.71	22±16.31		16.39±15.52		18.44±15.33		**Age at examination ± SD [years]**
216.03±44.66 (13)	290.92±57.44 (14)	162.46±49.48 (14)	39.5±5.65 (2)	0.66±2.12 (21)	−4.78±5.27 (13)	0.14±0.19 (15)	**Complete BCM**
0.8128	0.3358	0.29	0.28	**<0.0001**	**0.0222**	**<0.0001**	**p-value**

GraphPad prism 7.0 was used for statistical analysis. Non-parametric Mann–Whitney test was used to compare between two groups. Data represent average between both eyes. Full-field ERG results include the following details: Dark-adapted mixed cone-rod a- and b-wave amplitudes (in µV, normal a-wave 90–350 µV, normal b-wave 380–630 µV). Light-adapted cone flicker amplitude (Amp., in µV, normal 60–144 µV) and implicit time (IT, in ms, normal 27–33 ms); Dark-adapted rod response b-wave amplitude (in µV, normal range 200–500 µV). Age is provided for the detailed clinical tests.

Color vision: The color vision tested using the Lanthony 15-HUE desaturated test was performed for 10 of the 25 patients included in this study. Four patients showed deuteranopic color vision deficit, two presented with protanopia, and two had normal results. In another two patients, the exact dyschromatopsia profile was difficult to determine (Appendix 2). None of the subjects had tritanopic axis errors.

ERG responses: ffERG data were collected for both groups of patients in relation to the age at which the test was performed. The cone flicker responses at a mean of 30 Hz and the implicit time of the exon 3 group were 28.60 ± 15.02 µv (n = 24) and 34.10 ± 3.84 ms (n = 22), respectively, at a mean age of 14.372 ± 13.25 years. However, the patients with BCM who underwent ffERG at a similar mean age of 16.39 ± 15.52 years showed significantly diminished cone responses of 0.66 ± 2.12 µv (n = 21) and a longer response time of 39.5 ± 5.65 (n = 2). In line with these findings, 92% (22/24) of the patients with exon 3 haplotypes had measurable cone responses compared with 10% (2/21) of the patients with typical BCM. These findings are compatible with the BCVA findings and highlight the fact that the patients with exon 3 haplotypes presented with milder retinal phenotypes. The mixed cone-rod and rod responses were reduced but not significantly different between the two groups of patients (Table 2).

Ocular findings: The anterior segments were within the normal limits in all the patients with BCM in this study, except one patient (aged 57 years) who presented with a cataract; all the other patients had clear lenses. Around half of the patients presented with mild changes of the retinal pigment epithelium in the fovea at an early age (12/25), and two patients had foveal atrophy (MOL1459–1 and MOL1736–1; aged 37 and 57 years, respectively). In addition, most of the patients were highly myopic, presenting myopic fundus characteristics, including peripapillary atrophy (13/25), tilted optic disc (5/25), and myopic appearance (7/25; Figure 1 and Appendix 2).

Spectral domain OCT: SD-OCT scans were available for 12 of the 25 patients, five of whom demonstrated SD-OCT scans within the normal limits, whereas the remaining seven patients showed a variable extent of ellipsoid zone disruption, which led to foveal thinning (Figure 1 and Appendix 2). No choroidal neovascularization or cystoid macular edema was evident. However, retinal "cavitation" secondary to atrophy (MOL1654–2 and MOL1736–1) and subretinal fluid secondary to a dome-shaped macula (MOL0057–3) were observed (Figure 1).

Short-wavelength fundus autofluorescence: Short-wavelength fundus autofluorescence images were available for nine of the 25 patients in the study group. Four patients demonstrated a normal autofluorescence pattern, whereas five had variable disrupted autofluorescence without a characteristic pattern (Figure 1).

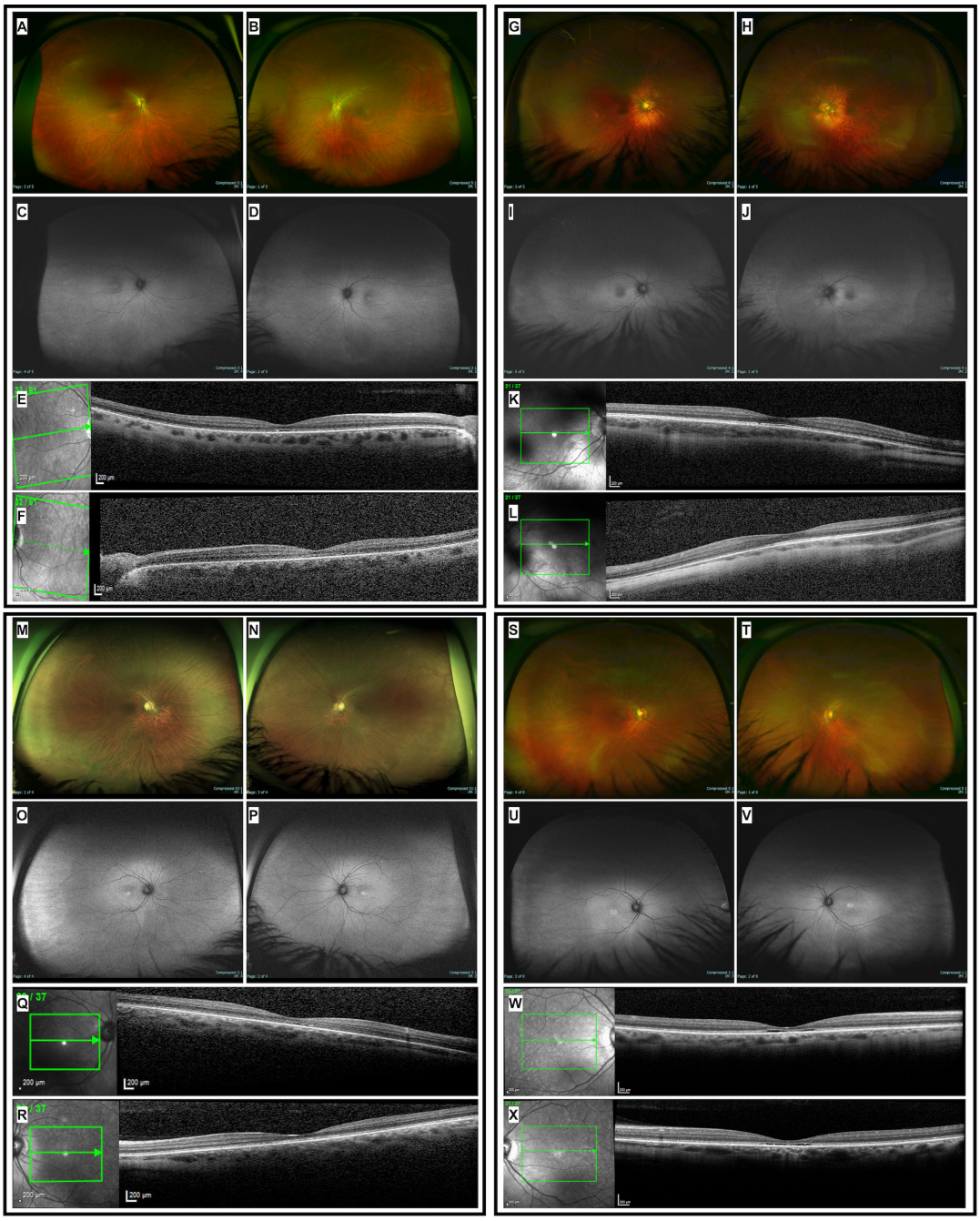

Figure 1. Color fundus, fundus autofluorescence (FAF), and spectral-domain optical coherence tomography (SD-OCT) images of the patients with exon 3 haplotype blue cone monochromacy. (**A–F**) MOL0057–3, (**G–L**) MOL1383–1, (**M–R**) MOL1434–1, and (**S–X**) MOL1736–1. (**A, B, G, H, M, N, S, and T**) Color fundus photos showing peripapillary atrophy, temporal pallor of the optic disc, normal-looking peripheral retina, and disrupted foveal reflex, except MOL1383–1. The parallel FAF images (**C, D, O, P, U,** and **V**) demonstrate a hyperfluorescent foveal reflex complementary with foveal ellipsoid zone atrophy in the SD-OCT horizontal cross-sections (**E, F, Q, R, W, and X**). (**I, J**) Normal FAF reflex for MOL1383–1 reflecting the preserved ellipsoid zone in the SD-OCT cross-sectional images (**K, L**).

DISCUSSION

Sequence variants in the X-linked *OPN1LW/OPN1MW* gene cluster can cause various ocular phenotypes. The milder form presents with color vision deficiency of either the red (less commonly protan) or green (more commonly deutan) cone function and is usually caused by deletions of either the *OPN1LW* or *OPN1MW* gene, with or without the formation of hybrid genes due to a non-homologous recombination [26]. The most severe phenotype related to alterations and mutations at the *OPN1LW/OPN1MW* gene cluster is BCM, in which both genes are nonfunctional. The classic BCM phenotype is described as a congenital disease with a severely reduced VA, severely impaired color discrimination, nystagmus, photophobia, and no detectable cone function by ERG testing [9]. BCM is caused by one of three types of mutations: (1) deletion of the locus control region upstream of the *OPN1LW/OPN1MW* gene array [1]; (2) deleterious point mutation in a single gene or in all genes of the array, including the common missense variant c.607T>C;p.C203R [13,27]; and (3) exon 3 haplotypes leading to exon skipping of exon 3 [15,22]. However, other phenotypes such as Bornholm eye disease (OMIM 300843) [17], X-linked cone dysfunction, and X-linked cone dystrophy (COD5; OMIM 303700) have been described. All phenotypes result from sequence variants in the *OPN1LW/OPN1MW* genes.

The specific combinations of the common sequence variants (termed “haplotypes”) in exon 3 have been reported to cause milder BCM. In minigene studies on cell lines, these haplotypes were shown to affect the correct splicing of exon 3 [13,15,22].

We report a large cohort of patients with various combinations of exon 3 haplotypes who demonstrated high myopia, relatively preserved VA, and decreased but not extinguished 30-Hz cone flicker responses. Other authors and we have previously suggested a correlation between this group of haplotypes and the unique phenotype that partially resembles BCM [12-17,22]. By analyzing the largest cohort of patients with exon 3 haplotypes, we provide further and more comprehensive evidence of a distinct clinical entity. Although the present study did not contain follow-up data (mainly because of the young age of the patients), no indications of a progressive disease were found. Additional studies with long-term follow-up are needed to determine whether the disease progresses with age. The exon 3 group shows a milder BCM phenotype on average, similarly to milder forms of other inherited retinal diseases such as incomplete achromatopsia [28] and incomplete congenital stationary night blindness [29]. A previous study [17] suggested that most analyzed cases of Bornholm eye syndrome had rare exon 3 haplotypes in *OPN1LW*.

Most (25/45, 56%) of the patients with *OPN1LW/OPN1MW* gene cluster mutations included in our cohort (with more than 2,000 inherited retinal disease families) had a milder BCM phenotype due to exon 3 haplotypes. To better characterize this phenotype, we compared its clinical features with those of typical BCM. Our analysis revealed that the most efficient parameter for distinguishing between the two groups is cone flicker ERG responses, which were measurable in 92% of the exon 3 cases and in only 10% of the typical BCM cases. The value was reduced to approximately 50% of the normal value in the exon 3 group and practically extinguished in the typical BCM group. Moreover, the combination of relatively better VA, higher myopia, and higher 30-Hz cone flicker responses strongly indicates an exon 3 haplotype. However, rod function was reduced in both groups to similar levels.

The color vision test results were variable among the patients with exon 3 haplotypes with a tendency toward deuteranopia-protanopia deficit. This information was available for the older patients with BCM in our cohort but missing for the younger patients. The Mollon-Reffin minimal test is expected to be more useful in the characterization of the color deficit in patients with exon 3 haplotypes than in patients with BCM who failed the protan-deutan axes but retained good discrimination on the tritan axis in the Mollon-Reffin test [3]. Fundoscopic findings were similar between the two groups and included tilted optic disc and peripapillary atrophy, reflecting the high myopic refraction of the patients together with minimal retinal pigment epithelium changes in the fovea [14]. SD-OCT and FAF imaging were consistent in showing the fundoscopic changes as an ellipsoid zone disruption and disrupted foveal autofluorescence, respectively.

To conclude, the exon 3 variant haplotypes of the *OPN1LW/OPN1MW* genes might cause a milder variant of the BCM phenotype. The indications of this group are male patients (isolated cases or with a family history of X-linked inheritance) with congenital high myopia, low VA, and reduced (but detectable) 30-Hz cone flicker ERG amplitudes. As whole-exome sequencing is not a good tool for BCM analysis (owing to the high intragenic and intergenic sequence conservation and possible large number of opsin genes in the cluster), long-range PCR distinguishing between *OPN1LW* and *OPN1MW* exon 3 should be used for PCR and Sanger sequencing.

APPENDIX 1. PRIMERS USED IN THIS STUDY.

To access the data, click or select the words “Appendix 1.”

APPENDIX 2. CLINICAL DATA OF EXON 3 HAPLOTYPE PATIENTS INCLUDED IN THIS STUDY.

To access the data, click or select the words "Appendix 2."

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