Late Onset Is Common in Best Macular Dystrophy Associated with VMD2 Gene Mutations

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Purpose: To perform a detailed morphologic and functional evaluation of Best macular dystrophy (BMD) associated with mutations in the VMD2 gene.

Design: Retrospective study.

Participants: The records of 16 patients with BMD and heterozygous VMD2 mutations (group 1) and 5 patients with Best-like lesions with no detectable disease-associated alterations in the VMD2 gene (group 2) were evaluated retrospectively.

Methods: The data were reviewed regarding visual acuity (VA), color vision, perimetry, autofluorescence of the retinal pigment epithelium (RPE), fluorescein angiography, electro-oculography (EOG), and full-field electroretinography (ERG) and multifocal ERG (mfERG).

Main Outcome Measures: VMD2 mutations, age at onset of BMD, RPE autofluorescence, EOG, ERG, and mfERG.

Results: The mean age of the patients in group 1 was 47.1 years (range, 16.7–86.5), and age at onset varied between 5 and 58 years (median, 42.0). Visual acuity ranged between 20/16 and 20/400 (median, 20/40). No association existed between the specific nature of the VMD2 mutation and disease onset or expressivity. Retinal pigment epithelium autofluorescence was increased corresponding to ophthalmoscopically visible yellow material, whereas it was decreased in the atrophic stage of BMD. Electro-oculography light rise was reduced in 18 of 19 eyes. Electroretinography amplitudes were normal in 3 patients and reduced in 6 patients. Multifocal ERG revealed in 10 of 20 eyes a central amplitude reduction and in 7 eyes a generalized one. There were no marked differences in clinical and functional findings between the patients in groups 1 and 2, except that the mean age of the patients in group 2 was higher (64.0 years [range, 45.7–80.6]) and the median VA lower (20/50 [range, 20/32–20/320]).

Conclusions: The onset of BMD is highly variable and occurred in the majority of patients after the second decade of life. Best-like lesions may develop in older patients without associated VMD2 mutations. Those manifestations may be related to a specific form of age-related macular degeneration. *Ophthalmology 2005;112: 586–592 © 2005 by the American Academy of Ophthalmology.*

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Best macular dystrophy (BMD) is a relatively frequent vitelliform dystrophy of the central retina with autosomal dominant inheritance but highly variable penetrance and expressivity.[1–3] Best macular dystrophy is characterized by an egg yolk–like macular lesion larger than 1 disc diameter. Multiple lesions or sparing of the fovea is less frequent. Visual function can remain good despite ophthalmoscopic visible manifestations; however, progressive visual loss usually occurs when the vitelliform lesions change to the pseudohypopyon stage, followed by vitelliruptive changes and finally resulting in atrophic lesions. Reduction or absence of the light rise in the electro-oculogram (EOG) has been considered as the most distinctive feature besides the macular lesions.[4] The full-field electroretinogram (ERG) is usually normal,[1,2,5,6] whereas multifocal electroretinography (mfERG) reveals variable central functional loss depending on the stage of the disease.[5–7]

Best macular dystrophy is associated with mutations in the VMD2 gene,[8–10] which can be identified in the vast majority of patients with a positive family history.[11] Genetically, BMD is a homogeneous disorder, in that mutations in other genes do not cause the disease. Conversely, mutations in the VMD2 gene have also been associated with a fraction

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of cases of bull's-eye maculopathy[12] and of adult vitelliform macular dystrophy (AVMD).[12–15] Adult vitelliform macular dystrophy is characterized by vitelliform foveal lesions, smaller than 1 disc diameter and usually containing a small pigmented spot. Adult vitelliform macular dystrophy has been described with later onset and usually normal EOGs.[16]

The purpose of the present study is to assess retrospectively the clinical and functional findings in patients with BMD and identified mutations in the VMD2 gene. In addition, we compare these data with patients diagnosed with Best-like vitelliform lesions but without disease-associated alterations in the VMD2 gene.

Materials and Methods

All 21 patients were seen at the Department of Ophthalmology at the Charité, Campus Benjamin Franklin, between May 1996 and October 2003. The clinical diagnosis was confirmed by one observer (UK). Clinical examinations and blood withdrawal for genetic analysis were conducted after explanation of the procedures and obtaining informed consent. The research adhered to the tenets of the Declaration of Helsinki, and investigational review board approval was obtained. The diagnosis of BMD was based on the presence of large vitelliform or vitelliruptive lesions, a reduced light rise in the EOG, or a positive family history of the disease. Mutational analysis in the VMD2 gene was done in all patients, and disease-associated mutations were identified in 16 of 21 patients by direct sequencing of the 10 coding exons of the VMD2 gene.[8] In the remaining 5 patients who tested negative for VMD2 mutations, the peripherin/RDS gene was analyzed by direct DNA sequencing with polymerase chain reaction (PCR) primers and conditions as described previously.[17] All patients underwent a complete eye examination, including best-corrected visual acuity (VA), slit-lamp examination, ophthalmoscopy, and fundus photography. Color vision was tested with the desaturated Panel D 15 test (n = 17). Visual field (VF) testing was performed with Goldmann (n = 13) or automatic (n = 5) perimetry. Fluorescein angiography was done in 12 patients. Autofluorescence imaging of the fundus was performed on 5 patients. The in vivo measurement of autofluorescence of the retinal pigment epithelium (RPE) was carried out with a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph, Heidelberg Engineering, Dossenheim, Germany). Argon laser light (488 nm) was used to excite RPE autofluorescence. A wide band-pass filter with a cutoff at 500 nm was inserted in front of the detector. A 30° field-of-view mode was used. The image resolution was 512×512 pixels. The maximal illumination of a 10×10° field of view was approximately 2 mW/cm^2. Six pictures per second were recorded, and between 4 and 12 single images were averaged, depending on the fixation of the patient.

Electrophysiologic testing included EOG (n = 13), ERG (n = 9), and mfERG (n = 17). All examinations were recorded by the same technician. The recording equipment remained the same during all evaluations. Recording of EOG and ERG was done according to the International Society for Clinical Electrophysiology of Vision standard,[18,19] and mfERG was done according to the International Society for Clinical Electrophysiology of Vision's guidelines.[20] The recording protocols have been described in detail elsewhere.[21,22] The EOG was recorded with a ramp test method.[23] Electroretinography recordings were done with maximally dilated pupils using a Nicolet Spirit and Ganzfeld (Nicolet, Madison, WI). Stimulus duration was 0.1 milliseconds. After 30 minutes of dark adaptation, 4 stimuli with increasing intensity (maximum light intensity, 10 candelas · second per square meter) were used for recordings in the dark. Light-adapted recordings were performed after 10 minutes of light adaptation in the presence of white background light of 30 candelas per square meter with white stimuli of maximum light intensity. No averaging was done. For comparison, age-related normal ranges for amplitudes and implicit times were determined by calculation of the median values and the 95% confidence intervals (CIs) from single eyes of 70 probands. Multifocal ERGs were recorded and analyzed with the VERIS system.[24] Recording was performed with maximally dilated pupils after the ERG using a Jet contact lens electrode (Microcomponents SA, Division Universo Plastique, Le Crêt-du-Locle, Switzerland). Refractive errors were corrected. For stimulation, a black-and-white pattern of 61 or 103 hexagons was presented on a monitor (200 candelas per square meter for white, 99.3% contrast). Duration of data acquisition was 4 minutes, divided into 8 sessions of 30 seconds. Data analysis (first-order kernel) was performed with the VERIS system. The response elicited by the central hexagon (ring 1) and summated responses elicited by concentric rings of hexagons surrounding the center (rings 2–5) were evaluated. Based on manually controlled cursor placement, amplitudes and implicit times were determined for the first positive component (P1) of each trace. Amplitudes were expressed relative to their respective area (nanovolts per square degree). The normal ranges for these amplitudes and implicit times were defined by calculation of the median values and the 95% CIs in one eye of 50 age-similar probands. The mfERG stimuli location and anatomical areas correspond roughly as follows: ring 1 to the fovea, ring 2 to the parafovea, ring 3 to the perifovea, ring 4 to the near periphery, and ring 5 to the central part of the middle periphery.

Results

Group 1: Best Macular Dystrophy with Identified Disease-Associated VMD2 Mutations

There were 10 males and 6 females ranging from 16.7 to 86.5 years of age (mean, 47.1±17.6; median, 53.4) at the time of their first visit. Seven patients were family members of 3 unrelated families: families W, F, and B (additional online-only Table 1 available at http://www.ophsource.org/periodicals/ophtha). Nine patients were sporadic cases. Of these, 5 had an unremarkable family history, and 4 reported complaints of visual disturbances from additional family members, although further information or results of eye examinations of these family members were not available. Thirteen of 16 patients complained of reduced VA and, furthermore, decreased reading vision (n = 3), photophobia (n = 2), impaired night vision (n = 1), and metamorphopsia (n = 1). The remaining 3 patients had no symptoms. Of these, 1 (no. 1346) had parafoveal lesions, 1 (no. 1080) had a central vitelliform lesion on the left eye detected during an eye examination when a posterior uveal melanoma became symptomatic on the right eye, and the third patient (no. 808) was a nonmanifesting carrier of a VMD2 mutation in family W.

The age at onset varied (range, 5–58 years; mean, 36.1±18.0; median, 42.0). In 2 unrelated families (W and F), the same VMD2 gene mutation, D301E, was present. In both families, affected individuals differed in age at onset as well as in progression of the disease. In family W, all affected members had a late onset, at approximately 45 years. The loss of VA was rather rapid within a few years after the first signs were noted. Considering the late onset in her relatives, the nonmanifesting carrier (no. 808) remains at risk for developing clinical signs at a later age. Her brother (not included in our series) had a normal fundus and normal EOG and did not inherit the mutation. In family F, all affected family members had an early onset in childhood, at approximately 5 years

Table 2. Full-Field Electroretinography (ERG): b-Wave Amplitudes at First Eye Examination

Full-Field ERG	Standard Combined Response	Single Cone Response	30-Hertz Flicker Response
	With VMD2 gene mutation (16 eyes of 8 patients)		
Reduced in no. of eyes	6 (37.5%)	6 (37.5%)	9 (56.3%)
Range of reduction to %*	76.7–61.4	79.7–49.1	80.5–43.5
Mean of reduction to %	68.9 ± 6.1	62.3 ± 11.3	65.1 ± 14.7
Median of reduction to %	68.0	58.7	72.2
	Without VMD2 gene mutation (2 eyes of 1 patient)		
Reduced in no. of eyes	0	2	2
Right eye/left eye reduced to %*		73.6/66.7	83.0/85.5

*Values are given in percentage of the median of the corresponding age-related norm.

of age. The progression of the disease was rather slow. The siblings reported that they have a further sister (not included in our series) who has a similar age of onset and severity of visual function loss. In family B, the A243V mutation was found. The onset of BMD in the daughter was almost 20 years earlier than that in her father.

Most of the patients had a central single lesion, and a vitelliruptive lesion was most frequent (Fig 1, additional online-only Table 1 [available at http://www.ophsource.org/periodicals/ophtha]). Two patients presented with additionally peripheral lesions, and 1 patient had only parafoveal lesions. In 9 patients, the lesions were similar in both eyes, and in 6 patients, the fundus findings differed between both eyes, representing various stages of BMD. Families W and F, both having the D301E mutation, presented with bilateral vitelliruptive lesions (except no. 808), although BMD in family W had manifested at a later age and approximately 10 years before our examination and BMD in family F manifested at an earlier age and approximately 25 years before our examination. However, the single patient (no. 1908) with the same mutation and an onset 10 years earlier than family W showed atrophic lesions after 20 years of BMD.

Visual acuity varied between 20/16 and 20/400 (median, 20/40). Thirteen patients were hyperopic (from +0.5 to +7.5 diopters [D]), 1 showed mild myopia, and 2 showed emmetropia. The age at onset did not seem predictive for the course of VA. Patients like members of family F with early onset retained good VA for >2 decades, and patients like members of family W with late onset showed a faster visual loss. Color vision disturbances seen in 11 patients were moderate to severe and without any typical axis of confusion. Most of the scotomas seen in 11 patients were relative (additional online-only Table 1 available at http://www.ophsource.org/periodicals/ophtha). Fluorescein angiography carried out in 8 of 16 patients showed, in 6 of them, the typical blockade of the choroidal fluorescence by vitelliform material or RPE window defects in atrophic areas. However, both members of family B with the A243V mutation presented with a pattern configuration, although one had vitelliruptive lesions and the other had atrophic lesions. Retinal pigment epithelium autofluorescence imaging of the fundus was performed in 4 patients (nos. 1911, 1908, 1659, and 916). An increased or decreased autofluorescence correlated with clinically visible yellow material or atrophic areas (Fig 1).

An EOG was recorded in 19 eyes of 11 patients. A normal light rise (≥160%) was present in only 1 eye (163%); however, the light rise of the fellow eye was reduced (153%) (additional online-only Table 1 available at http://www.ophsource.org/periodicals/ophtha). The most severe light rise reduction was observed in patient no. 916, with a R92S mutation and multiple vitelliform lesions but normal VA. In contrast, the eye with a normal light rise showed a single central atrophic lesion and VA of 20/200. In this patient (no. 1164), a Q58L mutation was detected. In patients with a D301E mutation, moderate and strong reductions of the light rise could be found. An ERG was recorded in 8 of 16 patients (additional online-only Table 1 [available at http://www.ophsource.org/periodicals/ophtha], Table 2). In family B (A243V mutation) and patient no. 1659 (624G>A mutation), the b-wave amplitudes in the standard combined and single flash cone responses as well as the 30-Hertz (Hz) flicker amplitude were reduced. In 2 other patients, only the amplitude of the 30-Hz flicker response was reduced, and in the remaining 3 patients, the ERG was normal. There was no association between mutation and ERG findings, except that both members of family B had similar ERG reductions. Multifocal ERGs were recorded in 20 eyes of 13 patients (additional online-only Table 1 [available at http://www.ophsource.org/periodicals/ophtha], Table 3). Seven eyes presented a generalized reduction of the P1 amplitude in all rings. In 10 other eyes, the reduction of the P1 amplitude was predominantly in the center. In only 3 eyes of 2 patients was the mfERG normal. One of these patients had only parafoveal vitelliform lesions. The second patient had a central vitelliform lesion without symptoms. An increased implicit time was found in the majority of the patients in the center of the retina and in about a third of the patients generalized.

Five patients were observed over 0.4 to 6.8 years. Four of these patients were seen once for a reexamination (follow-up range, 0.4–2.1 years), and 1 patient was seen on several occasions during 6.8 years. Almost no functional or fundus changes were detected in patients no. 1149 (A243V mutation) and no. 780 (D301E mutation) after 0.75 and 1.25 years, respectively. In contrast, patient no. 1911 (R41S mutation) was reexamined after 5 months because of increasing photophobia, reading and night vision difficulties, and repetitive phenomena of flicker light. Although VA was unchanged, ophthalmoscopy revealed on the right eye the development of a small central RPE and choriocapillaris atrophy (Fig 1). In patient no. 1659 (624G>A mutation), who had a 2.1-year follow-up, reduced VAs of 20/32 (right eye) and 20/100 (left eye) were found, in addition to a progression of the lesions to vitelliruptive (right eye) and atrophic (left eye) stages and a development of a relative central scotoma in both eyes. Patient no. 916 (R92S mutation) was seen 11 times during 6.8 years and presented a very unusual course, with a rapid variation of multifocal lesions (Fig 1). At the first visit (age 51.6 years), a central vitelliform lesion and multifocal vitelliform lesions around the upper temporal vascular arcade, in some cases with a pseudohypopyon, were seen on both eyes. The lesions changed rapidly in size and filling status. Over the years, the lesions became more filled and larger; some of the lesions were confluent, and other lesions decreased in size. The large confluent lesions changed to vitelliruptive lesions. New small lesions developed. At the latest examination (age 58.3 years), the patient reported an ongoing loss of VA and color and night vision, an increase of photophobia, and the requirement of magnifying reading glasses. Visual acuities were 20/100 (right eye) and 20/63 (left eye). On both

Table 3. Multifocal Electroretinography (mfERG) (61 Hexagons) of Patients with Best Macular Dystrophy and VMD2 Gene Mutations

mfERG	Ring 1	Ring 2	Ring 3	Ring 4	Ring 5
	61 hexagons (13 eyes of 8 patients)				
P1 amplitude					
Reduced in no. of eyes	11 (84.6%)	10 (76.9%)	7 (53.8%)	5 (38.5%)	5 (38.5%)
Reduction to %*	44.4–12.7	57.0–26.3	55.7–34.9	55.6–41.4	54.0–44.2
Mean	27.1 ± 10.8%	36.7 ± 8.2%	50.4 ± 7.5%	49.3 ± 5.9%	48.6 ± 4.6%
Median	26.7%	35.6%	54.6%	47.9%	46.3%
P1 implicit time					
Increased in no. of eyes	7 (53.8%)	6 (46.2%)	5 (38.5%)	5 (38.5%)	4 (30.8%)
Increased to %*	114.0–131.2	117.7–135.3	115.3–130.2	115.3–133.5	114.8–132.5
Mean	117.4 ± 6.3%	123.2 ± 6.2%	122.5 ± 6.9%	123.1 ± 7.9%	123.7 ± 7.6%
Median	114.0%	120.9%	124.4%	124.4%	123.7%

P1 = first positive component of each trace.
Data are from the first eye examination. In further 7 eyes of 5 patients, mfERGs with 103 hexagons were recorded (for simplicity not illustrated here).
*Values are given in percentage of the median of the corresponding age-related norm.

eyes, a sharply delineated central choriocapillaris atrophy and multiple small vitelliform lesions above the macula were seen.

Group 2: Vitelliform Lesions without VMD2 Mutations

This group included 1 male and 4 female patients, ranging in age from 45.7 to 80.6 years (mean, 64.0±13.8; median, 68.6) at the time of their first visit. All patients were sporadic cases and had an unremarkable family history. They complained of slowly progressive visual loss, with a duration ranging from 6 months to 5 years. Additional symptoms were decreased reading vision (n = 2) and photophobia (n = 2). All patients had a single central lesion in each eye similar to different stages of BMD (Fig 1, additional online-only Table 1 available at http://www.ophsource.org/periodicals/ophtha). Visual acuity varied between 20/32 and 20/320 (median, 20/50). Three patients were hyperopic (from +1.5 to +3.5 D). Color vision disturbances were moderate to severe and without any typical axis of confusion. Visual field testing revealed relative central scotomas. Fluorescein angiography carried out in 4 patients presented the typical blockade of the choroidal fluorescence or RPE window defects, depending on the stage of BMD-like lesions. Autofluorescence imaging of the fundus was performed in patient no. 1820, who had bilateral vitelliruptive lesions and showed centrally an increased RPE autofluorescence corresponding to the clinically visible yellow material.

The EOG light rise recorded in 2 patients was reduced (additional online-only Table 1 available at http://www.ophsource.org/periodicals/ophtha). The ERG recorded in 1 patient revealed a reduced b-wave amplitude of the single flash cone response and a 30-Hz flicker amplitude reduction (Table 2). Multifocal ERGs were recorded in 6 eyes of 4 patients and showed in all eyes a reduction of the central P1 amplitudes. A detailed evaluation of P1 amplitude and implicit time is given in Table 4.

Patient no. 853 was seen for a reexamination after 1 year. Visual acuities were reduced to 20/200 (right eye) and 20/125 (left eye), and both eyes now presented with vitelliruptive lesions.

In all group 2 patients, the peripherin/RDS gene was analyzed by direct sequencing of the 3 coding exons. No disease-associated changes could be detected.

Discussion

Best macular dystrophy is known to present with variable expressivity and reduced penetrance.[1–3] This fact is emphasized by the clinical and functional findings in our series. The age at onset of BMD in the patients with a VMD2

Table 4. Multifocal Electroretinography (mfERG) (61 Hexagons) of Patients with Best-like Lesions without VMD2 Gene Mutations

mfERG	Ring 1	Ring 2	Ring 3	Ring 4	Ring 5
	61 hexagons (5 eyes of 4 patients)				
P1 amplitude					
Reduced in no. of eyes	4 (80.0%)	4 (80.0%)	2 (40.0%)	1 (20.0%)	0
Reduction to %*	46.8–12.6	62.0–27.2	57.3–45.2	48.4	
Mean	25.9 ± 15.3%	43.9 ± 14.4%	51.2 ± 8.5%		
Median	22.2%	43.2%	51.2%		
P1 implicit time					
Increased in no. of eyes	3 (60.0%)	3 (60.0%)	3 (60.0%)	1 (20.0%)	0
Increased to %*	114.0–119.9	114.8–120.9	115.3–118.2	115.3	
Mean	117.0 ± 2.9%	117.8 ± 3.0%	116.2 ± 1.7%		
Median	117.1%	117.7%	115.3%		

P1 = first positive component of each trace.
Data are from the first eye examination. In further 1 eye of 1 patient, a mfERG with 103 hexagons was recorded (for simplicity not illustrated here).
*Values are given in percentage of the median of the corresponding age-related norm.

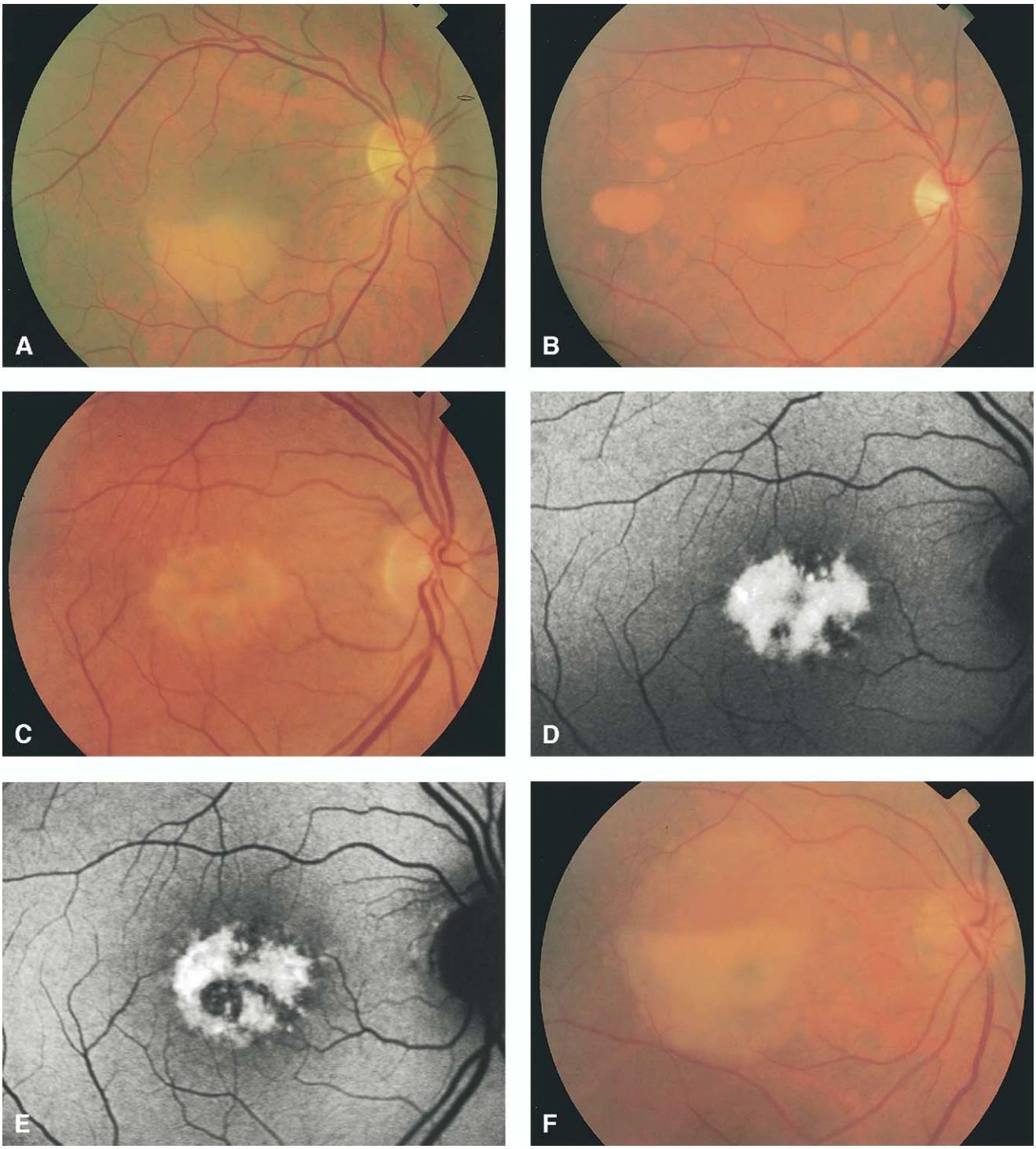

Figure 1. **A**, Fundus photograph of patient no. 1640 with Best macular dystrophy (BMD) at 59.6 years of age and visual acuity (VA) of 20/25. The right eye presented with a pseudohypopyon. **B**, Fundus photograph of patient no. 916 with BMD at 52.1 years of age and 20/25 VA. The right eye presented with a central vitelliform lesion and peripheral vitelliform lesions. **C–E**, Fundus photograph and retinal pigment epithelium (RPE) autofluorescence of patient no. 1911 with BMD. At the first visit (age, 54.5 years), the right eye (20/160 VA) presented with a vitelliruptive lesion (C). The increased RPE autofluorescence was correlated to the clinically visible yellow material (D). After 5 months (age, 54.9; 20/160 VA), a small central RPE and choriocapillaris atrophy was now visible and correlated in the RPE autofluorescence to a small central area of reduced autofluorescence (E). **F**, Fundus photograph of patient no. 853 with a Best-like pseudohypopyon and no VMD2 or peripherin/RDS gene mutation (age, 70.4; 20/40 VA).

mutation (group 1) varied between 5 and 58 years. The median of 42 years indicates that BMD does not necessarily present as juvenile vitelliform macular dystrophy, as it is often described. Previous genetic studies on VMD2 mutations in BMD families reported great variability in age of onset[2] as well as a diagnosis after 40 years of age as more common than earlier.[3] Eksandh et al[5] concluded from their data that patients with a V89S mutation frequently present with a late-onset visual loss. In our series, a V89S mutation was not detected; however, there were several other VMD2 mutations found in patients with a late onset as well (D301E, R92S, A243V, Q58L, F298S, W102R, and R41S). However, even with the same mutation, the age at onset and the progression of visual function loss was highly variable (1) interfamilially (families W and F, D301E mutation), although, within these families, the expression of the disease was less variable, and (2) intrafamilially (family B, A243V mutation).

The great range in age of onset and the different stages of BMD can make it more difficult to diagnose BMD in elderly patients, in whom age-related macular degeneration is common. Furthermore, the vitelliform phase of BMD in elderly patients can be confused with AVMD, RPE detachment, or chronic serous retinopathy.[5] A positive family history and bilateral symmetrical fundus findings, present in the majority of our patients, suggest an inherited macular disease. In our experience, a confusion with AVMD is unlikely because all of our patients with AVMD seen in our clinic had a vitelliform lesion smaller than 1 disc diameter.[16] A progressed stage of BMD, however, can be similar to geographic lesions in age-related macular degeneration.

In 5 older unrelated patients (group 2) with an unremarkable family history, bilateral lesions resembling BMD were observed. Relative to BMD patients, the mean age at onset was higher and the VA was lower, but there were no differences between the patients in either group regarding fundus findings, color vision, VF, fluorescein angiography, and EOG results. Full-field ERG and mfERG abnormalities tended to be less severe in group 2 patients. Besides VMD2, additionally the peripherin/RDS gene tested negative for disease-related changes. This is of interest because mutations in the peripherin/RDS gene have been associated with approximately 18% of AVMD cases.[17] The Best-like lesions in this patient group could have been caused by mutations in thus far unknown genes. Alternatively, one of the genes, VMD2 or peripherin/RDS, harbors a disease-related alteration but could not be detected by the PCR-based sequencing techniques used in the present study. These patients may also represent a different entity of vitelliform lesions. A symmetry of fundus findings is a typical sign for an inherited disorder. However, as these patients are all single cases, and no mutations have been detected so far, an inheritance is not automatically conclusive. These patients may also constitute a certain subgroup of age-related macular degeneration. Lotery et al[11] screened 39 unrelated probands with familial BMD and 57 unrelated probands with the ophthalmoscopic findings of BMD but no family history for the disease. They concluded that patients with the clinical diagnosis of BMD are significantly more likely to have a VMD2 mutation if they also have a positive family history. Of our 16 patients with a VMD2 mutation, 11 had a positive family history.

To distinguish clinically BMD from RPE detachment or chronic serous retinopathy, the fast and noninvasive measurement of RPE autofluorescence may be of advantage. This autofluorescence is derived from lipofuscin in the RPE,[25] and in vivo recording of RPE autofluorescence provides information about the levels and distribution of lipofuscin of the RPE. Autofluorescence imaging was performed in 5 patients in this study. The areas with increased autofluorescence corresponded to the ophthalmoscopically visible areas with the yellow material, in vitelliform as well as vitelliruptive lesions. Patients with a central atrophic lesion showed a reduced autofluorescence within the atrophic areas. Measurement of autofluorescence seems to be a very sensitive method for recording changes in lipofuscin accumulation in the lesions, the progression of the disease, and development of RPE atrophy in patients with BMD.[26]

For years, the EOG has been considered the main functional test to define BMD. It was used especially for detection of nonmanifesting carriers of the mutated gene. In this series, the EOG light rise was reduced in 18 of 19 eyes. It seems that a normal EOG may not unequivocally exclude nonmanifesting carriers and that molecular genetic testing is mandatory for adequate counseling of the families.[27] In addition, the EOG light rise was also reduced in patients with BMD-like lesions and without VMD2 mutations, and may indicate an inherited disorder in patients with no risk of affected family members.

The ERG is considered to be normal in BMD, although previous studies reported only limited numbers of patients.[1,2,5,6] In the present series, the ERG was normal in 3 of 8 BMD patients. Two patients had a reduced 30-Hz flicker response, and 3 patients had a reduction of all amplitudes of the ERG. Patient no. 1908, with a D301E mutation, had a normal ERG. In patient no. 1066, having the same mutation, the 30-Hz flicker response was reduced in one eye. However, both members of family B with an A243V mutation had a reduced ERG. There were 3 patients (nos. 823, 1066, and 1149), unrelated and with distinct VMD2 mutations, all having vitelliruptive lesions, but each patient had a different ERG abnormality. In contrast to the ERG, the mfERG allows the evaluation of macular function. Only 2 patients had normal findings. The remaining patients had a central or generalized reduction of the P1 amplitude. Eksandh et al[5] recorded mfERGs in a patient and a carrier with a V89A mutation, and in both, they found centrally a minor reduction of the P1 amplitudes. A central reduced mfERG was reported as well from Palmowski et al[6] testing 3 patients. They measured a normal implicit time. However, a VMD2 mutation (A195V) was reported in only a single patient. Scholl et al[7] recorded mfERGs in 18 eyes of 18 BMD patients (only 1 patient screened for a VMD2 mutation) and also found that central amplitude decreases, most frequently for ring 1. The implicit times were slightly but significantly increased in more eccentric groups. They also reported a considerable interindividual variability, even between patients at the same clinical stage. Although the EOG has been regarded as the main diagnostic tool in the diagnosis of BMD, the use of ERG and mfERG should be

reconsidered. The ERG may define patients with more widespread retinal abnormalities, and the mfERG may allow conclusions as to the severity of posterior pole involvement. Further studies and long-term follow-up are necessary to evaluate the prognostic value of both methods.

In conclusion, BMD manifests frequently after the second and up to the sixth decade of life. Electro-oculographies may be normal in BMD patients with VMD2 mutations. Molecular genetic testing should be part of the diagnostic evaluation in patients who are suspected to have BMD due to fundus findings resembling BMD or a family history of BMD. This is especially important for genetic counseling of BMD families, particularly those families with late onset of the disease.

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Table 1. Functional and Molecular

Patient Identification No., Family	VMD2 Mutation	Age (yrs)	Gender	Age of Onset	Lesions,* Right Eye/Left Eye
780,‖ W–brother	D301E	55.4	M	45	Single, vr/vr
806, W–sister	D301E	52.9	F	45	Few, vr/vr
808 (B-1), W–sister's child	D301E	16.7	F	—	None
1065 (B-17), F–sister	D301E	31.5	F	5	Single, vr/vr
1066 (B-16),‖ F–brother	D301E	29.4	M	5	Single, vr/vr
1149 (A-4), B–daughter	A243V	54.3	F	35	Single, vr/vr
1150 (A-5), B–father	A243V	86.5	M	54	Single, atr/atr
823 (PAT14)	V9M	56.4	M	21	Single, vr/vr
916 (B-15)	R92S	51.6	M	51	Multiple, vf/vf
1080 (B-13)	R218S	30.8	M	30	Single, −/vf
1164 (B-28)	Q58L	57.3	F	56	Single, atr/vf
1346 (G99-0273)	F298S	42.7	M	42	Parafoveal, 2 vf/vf
1640 (G01-1102)	W102R	59.6	M	58	Single, ps/vr
1659 (G01-1378)	624G > A¶	20.5	F	18	Single, ps/vr
1908 (G03-1810)	D301E	53.9	M	34	Single, atr/atr
1911 (G03-2001)	R41S	54.5	M	53	Single, vr/vf
1680 (G01-1406)	None	68.6	M	66	Single, vf/vf
1820 (G02-1828)	None	80.6	F	—	Single, vr/vr
1535 (G00-1090)	None	45.7	F	40	Single, atr/vr
853 (B-14)	None	70.4	F	69	Single, ps/vr
1421 (G99-1201)	None	54.7	F	53	Single, ps/ps

abs = absolute; atr = atrophic lesion; EOG = electro-oculogram; ERG = electroretinography; F = female; Hz = hertz; M = male; mfERG = multifocal liruptive lesion.
*Single, one central lesion; few, central lesion and 2–3 midperipheral lesions; multiple, several lesions at the posterior pole.
†Standard combined, single cone flash, and 30-Hz flicker responses are reduced.
‡61/103 are the numbers of hexagons of the mfERG.
§Values are light rise (%). The normal value of the light rise is ≥160%.
‖Left eye amblyopia.
¶Pathogenic effect unknown.

Data of All Patients

VA, Right Eye/ Left Eye	Color Vision	Visual Field	Full-Field ERG†	mfERG‡	EOG§ Right Eye/Left Eye
20/50 20/200	Errors	Scotoma[rel]	—	R1-4 (103) reduced	147/147
20/63 20/32	Errors	—	—	—	—
20/20 20/16	Normal	Normal	—	—	139/140
20/40 20/50	Errors	Normal	—	R1-5 (103) reduced	123/118
20/63 20/200	Errors	Scotoma (left eye)	Right eye: 30-Hz flicker reduced	R1-4 (103) reduced	—
20/32 20/40	Errors	Scotoma[rel]	Reduced	R1-2 (61) reduced	141/155
20/400 20/400	Errors	Scotoma[abs]	Reduced	All rings (61) reduced	—
20/100 20/63	Errors	Scotoma[rel]	Normal	—	149/141
20/25 20/20	Errors	Scotoma[rel]	—	All rings (103) reduced	118/115
20/50 20/25	—	Normal	—	Normal	−/118
20/200 20/32	Errors	Scotoma[abs/rel]	Normal	R1-2 (61) reduced	163/153
20/20 20/40	—	Scotoma[abs]	—	Normal	−/126
20/25 20/63	Errors	Scotoma[rel]	—	All rings (61) reduced	—
20/25 20/32	Normal	Normal	Reduced	All rings (61) reduced	—
20/100 20/100	Normal	Scotoma[rel]	Normal	R1-3 (61) reduced	152/−
20/160 20/25	Errors	Scotoma[rel]	30-Hz flicker reduced	Right eye: R1-2 (61); left eye: all rings (61) reduced	132/154
20/63 20/200	Normal	Scotoma[rel]	—	R1-4 (61) reduced	—
20/63 20/320	—	—	—	—	—
20/200 20/50	Errors	Scotoma[abs/rel]	Single cone and 30-Hz flicker reduced	R1-3 (61) reduced	145/145
20/40 20/40	—	—	—	R1-2 (61/103) reduced	146/134
20/32 20/40	Errors	Scotoma[rel]	—	Right eye: R2 (61); left eye: R1 (61) reduced	—

ERG; ps = pseudohypopyon; R = ring of ringwise analysis of mfERG; rel = relative; VA = visual acuity; vf = vitelliform lesion; vr = vitel-